



A Practical Guide to **Diabetes Mellitus**

Editors

Nihal Thomas

Nitin Kapoor

Jachin Velavan

Senthil Vasan K

7 TH EDITION



Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore, India



The Health Sciences Publisher

A Practical Guide to Diabetes Mellitus



Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore - 632004, INDIA



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Seventh Edition

Editors

Nihal Thomas

MBBS MD MNAMS DNB (Endo)
FRACP (Endo) FRCP (Edin) FRCP (Glasg)
Professor and Head
Department of Endocrinology
Vice Principal (Research)
Christian Medical College
Vellore, Tamil Nadu, India

Nitin Kapoor

MBBS MD (Med) DM (Endo)
ABBM (USA) Post-Doctoral Fellowship (Endo)
Assistant Professor
Department of Endocrinology,
Diabetes and Metabolism
Christian Medical College
Vellore, Tamil Nadu, India

Jachin Velavan

MBBS DNB (Fam Med) MRCGP (Int)
Coordinator
Department of Distance Medical Education
Christian Medical College
Vellore, Tamil Nadu, India

Senthil Vasan K

MBBS PhD
Post-Doctoral Researcher
Center for Molecular Medicine
Karolinska Institute
Stockholm, Sweden



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Jaypee Brothers Medical Publishers (P) Ltd

Headquarters

Jaypee Brothers Medical Publishers (P) Ltd.
4838/24, Ansari Road, Daryaganj
New Delhi 110 002, India
Phone: +91-11-43574357
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Overseas Offices

J.P. Medical Ltd.
83, Victoria Street, London
SW1H 0HW (UK)
Phone: +44-20 3170 8910
Fax: +44(0)20 3008 6180
E-mail: info@jpmepub.com

Jaypee Medical Inc.
The Bourse
111 South Independence Mall East
Suite 835
Philadelphia, PA 19106, USA
Phone: +1 267-519-9789
E-mail: jpmepub.us@gmail.com

Jaypee Brothers Medical Publishers (P) Ltd.
Bhotahity, Kathmandu, Nepal
Phone: +977-9741283608
E-mail: kathmandu@jaypeebrothers.com

Jaypee-Highlights Medical Publishers Inc.
City of Knowledge, Bld. 237, Clayton
Panama City, Panama
Phone: +1 507-301-0496
Fax: +1 507-301-0499
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Jaypee Brothers Medical Publishers (P) Ltd.
17/1-B, Babar Road, Block-B, Shaymali
Mohammadpur, Dhaka-1207
Bangladesh
Mobile: +08801912003485
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Advisory Board

Asha HS DNB (Med) DNB (Endo)

Associate Professor

Department of Endocrinology

Diabetes and Metabolism

Christian Medical College, Vellore, Tamil Nadu, India

Dukhabandhu Naik MD (Med) DM (Endo)

Associate Professor

Department of Endocrinology

Diabetes and Metabolism

Christian Medical College, Vellore, Tamil Nadu, India

Mahesh DM MD (Med) DM (Endo)

Assistant Professor

Department of Endocrinology

Diabetes and Metabolism

Christian Medical College, Vellore, Tamil Nadu, India

Thomas V Paul MD DNB (Endo) PhD (Endo)

Professor

Department of Endocrinology, Diabetes and Metabolism

Christian Medical College, Vellore, Tamil Nadu, India

Simon Rajaratnam MD MNAMS PhD (Endo) FRACP (Endo)

Professor and Head Unit-II

Department of Endocrinology, Diabetes and Metabolism

Christian Medical College, Vellore, Tamil Nadu, India



The Health Sciences Publisher

Contributors

Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore, Tamil Nadu, India

Authors

Asha HS DNB (Med) DNB (Endo)
Bharathi S BSc (N) RN
Dukhabandhu Naik MD DM (Endo)
Mahesh DM MD DM (Endo)
Nihal Thomas MD MNAMS DNB (Endo) FRACP (Endo) FRCP (Edin) FRCP (Glasg)
Nitin Kapoor MD DM (Endo) ABBM (USA) Post Doc. Fellowship (Endo)
Ruth Ruby Murray BSc (N) RN
Sunitha R RN
Thomas V Paul MD, DNB (Endo), PhD (Endo)

Contributors from other Departments
in Christian Medical College, Vellore, Tamil Nadu, India

Abraham OC MD MS
Anna Simon MD DCH
Bobeeena Rachel Chandy MD (PMR) DNB (PMR)
Edwin Stephen MS
Elizabeth Tharion DO MD (Physio)
Flory Christina RN
Geethanjali Arulappan MSc PhD
George M Varghese MD DNB DTMH FIDSA
Georgene Singh MD (Anes)
Hasna Rajesh BE
Inian Samarasam MS FRCS FRACS
Judy Ann John MD (PMR) DNB (PMR)
Mercy Jesudoss MSc (N)
Niranjan Thomas MD (Ped)
NV Mahendri MSc MHRM
Padma Paul DO MS Ophthal MPH
Ravikar Ralph MD (Med)
Saban Horo MS (Ophthal)
Samuel Vinod Kumar BPT
Sanjith Aaron MD DM (Neuro)
Santosh Varghese MD DM (Nephro)
Solomon Sathish Kumar MD
Subhrangshu Dey MD DM (Cardio)
Suceena Alexander MD DM (Nephro)
Viji Samuel MD DM (Cardio)

National Authors

- Abraham Joseph** MD DCH MS (Epid)
G Sai Mala PhD
Jubbin Jagan Jacob MD DNB (Endo)
Kishore Kumar Behera MD DNB (Endo)
Leepica Kapoor BSc MSc (Food and Nutrition) BEd.
Mathew John MD DM DNB (Endo)
Philip Finny MD DNB (Med) DNB (Endo)
Premkumar R PhD
Rajan P BOT
Ron Thomas Varghese MBBS
Ruchita Mehra Srivastava Hon (Psy) MSW (TISS)
Sudeep K MD Dip Diab DNB (Endo)
Veena V Nair MD PDCC (Ped Endo)
Vinod Shah MS MCh

International Authors

- Charles Stephen** MSc PhD
Hari Krishna Nair MD OSH (NIOSH) OHD (DOH) CMIA (MAL) CHM (USA) ESWT (Austria, Germany)
Kanakamani Jeyaraman MD DM (Endo) DNB (Endo)
Rahul Baxi MBBS MD PDF Diabetes (CMC, Vellore)
Ross Kristal
Senthil Vasan K MBBS PhD

Department of Endocrinology, Diabetes and Metabolism
Christian Medical College, Vellore, Tamil Nadu, India

Resource Persons

- Aaron Chapla** MSc (Bio-Chem)
Anil Satyaraddi MD
Chaitanya Murthy MBBS
Divya RN
Ezhilarasi RN
Felix Jebasingh MD
Haobam Surjitkumar Singh MBBS
Jansi Vimala Rani RN
Kaushiki Kirty MD
Kripa Elizabeth Cherian MD
Mercy Inbakumari BSc
Mini Joseph MSc (Diet) PhD
Padmapriya RN
Praveen MBBS
Riddhi Das Gupta MD

Sahana Shetty MD

Samantha MD

Sandip Chindhi MD

Shirley Jennifer RN

Shrinath Pratap Shetty MD

Simon Rajaratnam MD DNB (Endo) MNAMS PhD (Endo) FRACP (Endo) FRCP (Edin)

Vijayalakshmi BSc

Foreword

Copenhagen

Obesity and type 2 diabetes have become global epidemics affecting not only Western populations, but indeed to a highly worrying degree, the Asian populations including those of the Indian citizens. As for type 2 diabetes, there are currently an estimated number of more than 62,000,000 people suffering from this disease in India. Type 2 diabetes is associated with more than a two-fold excess mortality from cardiovascular disease, devastating microvascular complications affecting the eyes, kidneys and nerves, as well as with significant comorbidities including cancer, infections and psychosocial stress. If left untreated, the microvascular complications will ultimately lead to blindness, overt kidney failure, foot ulcers and amputations. There is an enormous challenge for the society and the healthcare system to organize treatment and management of people with diabetes to reduce its serious impact on health of the individual, as well as to reduce the otherwise extreme expenditure of society to compensate for lost working years as well as for managing blindness, dialysis, amputations, etc. Many landmark achievements within diabetes care have been obtained during recent years, including definitive knowledge that multifactorial pharmacological as well as nonpharmacological intervention targeting physical inactivity, overeating, smoking, reduction of blood pressure and lipids, as well as lowering glucose, significantly improves the most important clinical outcome variables in people with diabetes. Many novel drugs have been introduced targeting different distinct defects of metabolism in diabetes patients, leaving the clinical diabetes specialist with much better tools to tailor a more optimal and individualized treatment strategy in different diabetes patients. The fast generation of knowledge within the field of diabetes, as well as its significant quantitative impact on health within the society, makes it extremely important to have medical doctors with a proper and constantly updated scientific training in diabetes research, to lead the implementation of novel, better and more (cost-effective) treatment and care programs for patients with diabetes. I have had the great pleasure of working together with Professor Nihal Thomas and his team on clinical matters, as well as on important translational scientific projects, and in all of our interactions. I have been indeed very impressed about the dedication, level of knowledge as well as enthusiasm in general of Nihal Thomas and his team. I am therefore extremely happy hereby and with great confidence—to be able to give the doctors, councilors teams and patients associated with international community, the most sincere recommendations provided in this book, that would help in leading the fight against diabetes with the Seventh Edition of 'A Practical Guide to Diabetes Mellitus'.

Allan Vaag MD PhD
Professor and Head
Department of Endocrinology
Riggs Hospital Copenhagen, Denmark
Adjunct Professor of Clinical Diabetes Research
Lund University, Sweden

Foreword

New York

Diabetes mellitus has reached an astounding global prevalence of 343 million, according to recent estimates. While staggering, these numbers fall short of conveying the full magnitude of the problem. The human impact of diabetes includes devastating complications, economic hardships and reduction in the most creative and productive years of life. Though challenging to implement, optimal diabetes management has been proven to reduce the complications of diabetes. This underscores the vital need for training healthcare professionals in comprehensive diabetes management, particularly in settings that provide care to the poor.

Under the visionary leadership of Professor Nihal Thomas, Christian Medical College, Vellore, has developed a large-scale comprehensive diabetes education program. More than a hundred hospitals in rural and semi-urban parts of India have now been instructed in the medical management of diabetes. This program has promoted the creation of integrated diabetes clinics with an emphasis on close cooperation between diabetes nurse educators and doctors, thus favoring a very effective multidisciplinary approach to diabetes management.

Recently, in conjunction with the Global Diabetes Initiative of the Albert Einstein College of Medicine, New York, USA, this program has expanded its reach to over thirty countries, including many parts of Asia and Sub-Saharan Africa. The Seventh Edition of 'A Practical Guide to Diabetes Mellitus' offers a unique combination of rigorous pathophysiology with very practical approaches to diabetes prevention and control. This outstanding textbook will equip a cadre of doctors and other healthcare professionals to deliver high quality care to vulnerable populations around India and far beyond.

An ounce of practice is worth more than tons of preaching.

—Mahatma Gandhi

Meredith Hawkins MD MS FRCP (C)

Professor of Medicine

Endocrinology and Geriatrics

Director, Global Diabetes Initiative

Albert Einstein College of Medicine

New York, USA

Foreword

Copenhagen

Diabetes mellitus is an emerging global health problem, not just in India. Fortunately, Indian physicians and researchers are also increasingly taking the lead, when it comes to doing something practical to stem the epidemic and to manage diabetes. Millions are affected by this chronic and potentially life-threatening disease. More than 3 million patients die from the disease on an annual basis. In some urban Indian societies, one out of five adults has diabetes.

The devoted team, editing the present as well as the previous editions of this important book, is headed by Professor Nihal Thomas. He and former Professor Abraham Joseph were partners in the renowned World Diabetes Foundation, and supported project entitled "Prevention and Control of Diabetes Mellitus in rural and semi-urban India through an established network of Hospitals," which has successfully trained key-staff from more than 100 hospitals, many of these are situated in areas which are not easily accessible. The course material from this project makes up this book. Admirably, new versions are constantly evolving, including most recent knowledge on how to prevent, diagnose, care for and rehabilitate patients with diabetes. This book is soundly based on research as well as clinical practice, and it is a privilege and honor to write the foreword, while looking much forward to future editions from, and collaboration with Professor Nihal Thomas and his team.

Ib Chr. Bygbjerg MD DSc

Professor of International Health

University of Copenhagen and

National University Hospital

Copenhagen, Denmark

Board Member of World Diabetes Foundation

From Womb to Tomb: The Diabetes Cataclysm and Solutions Beyond

In the year 1995, when King et al, published an article in what is at times thought to be the clinical bible of diabetes (*Diabetes Care* 1998)—he articulated for the very first time that India would house the largest number of patients with diabetes approaching around 20 million. The article had also prophesied that the number of diabetics in the country would stand at 57 million by the year 2025.

The prediction has not been false, but proven to be an underestimate. Today, in 2015, we stand at the precipice of reckoning and the predictions of Dr King have outlasted his own life. According to the findings of the ICMR sponsored INDIAB study, published in *Diabetologia* 2011, India is faced with a galloping diabetes epidemic which is progressing at a speed which challenges the meanest and fastest on the F-1 circuit in a figurative sense. There are now an estimated 62 million patients with diabetes in India and this number is projected to explode beyond 85 million by the year 2030.

While diabetes in urban areas, with places like Cochin having figures in excess of 20% and Chennai at 17%, the epidemic is sweeping like a typhoon across the subcontinent and engulfing rural areas as well, and across terrains which were previously perceived as untouched. A study done by our group from rural Tripura, the first of its sort in the North-East part of the country and published in *Journal of the Association of Physicians in India* 2007, demonstrated that a part of rural Tripura on the Indo-Bangladesh border, had a prevalence of diabetes of 9%. This was in contrast to parts of Himachal Pradesh which had a prevalence of 0.4% in the early 1990s. Similar trends have been shown in the state of Arunachal Pradesh, just South of China, published by our group (*Ind J Endocrinol* 2012). The changing patterns of disease in a country which still has a major proportion of the population in rural areas may be predictors of stories which may foretell a gloomy future.

The explosive growth of diabetes from across the country from the 1980s to till now is essentially multi-factorial which is very real and large. The real reasons would be inclusive of: (a) cable television, (b) economic liberalization (c) more processed food and fast food (d) increased academic competitiveness (thereby reducing physical activity) (e) mobile phones and computers (f) increased life expectancy—69 years for males now as opposed to 56 in 1980 and 66 for females, at present. I am indeed particularly fond of calling the jump in the prevalence of diabetes in the 1990s and their subsequent impact on teenage obesity in this millennium as the ‘Murdoch phenomenon,’ thanks to Rupert Murdoch for giving us cable television, which has perpetuated our populace to sit on their backsides for umpteen hours in a day adding to the catapult effect with regards to blood sugars. The hours of cricket being viewed on television, perpetuated unashamedly by mega-circuses like the Indian Premier League, not only serve to fatten the purses of those who run the industry, but also broaden the backsides and the waistlines of youngsters and elderly enhancing their propensity to develop diabetes! Surely our haloed film stars instead of munching bags of potato chips in voluminous quantities can show us how they manage to keep their figures trim and attractive by demonstrating methods of pumping iron or performing sessions of aerobics!

In the year 1998, wise men put their heads together and decided by consensus that the cut-off point for diabetes with regards to the fasting sugar should be reduced from 140 mg/dL to 126 mg/dL. This was a decision taken based on the fact that it appeared that 'microvascular disease' as generally gauged by diabetic involvement of the retina was present at much lower levels. From a scientific perspective, the decision was correct. However, many epidemiologists were not open about this fact when they published studies and data after 1998, mentioning the increasing prevalence of diabetes. In an ideal setting, they should have declared this in their publications—but they did not. They should have published 'corrected' figures taking into account the new definition. In any case, for the public, the 'virtual effect' added to the fuel provided for non-communicable disease awareness stakes, though some scientists gained a little extra mileage on the value of their publications.

There is an over representation of the phenomenon of impaired fasting glycemia and impaired glucose tolerance (measures of prediabetes) in screening surveys which does not necessarily indicate subsequent progression of disease. The newer cut-off of 100 mg/dL (well not so new!—instituted in 2002) for impaired fasting glycemia leads to earlier detection of the disease and enhancing the long-term prognostic outcome of pre-diabetes falsely causing another bias in the form of 'lead time bias'.

Well—all in all, the disease is no doubt on the increase in geometric proportions, despite scientific interpretations that analyzing the situation. The evolution of the epidemic is a 'womb to tomb' phenomenon. Low birth weight is a precipitating factor for diabetes, cardiovascular disease, obesity, schizophrenia, osteoporosis and cancer, and perhaps more unperceived pestilences. This was a hypothesis proposed by Barker in the 1980s, which is no longer a hypothesis but a practical reality. Maternal malnutrition and the deficiency of micronutrients *per se* are responsible for the problem. The additive effect of poor lifestyle in childhood through adulthood therefore increases the chance of a low-birth weight child in subsequently developing diabetes. The mechanisms of this problem include a reduced secretion of insulin by the pancreas, increased peripheral resistance to insulin and an inability to burn calories when compared to the metabolism in a normal birth weight individual. Since low birth weight is present in almost 26% of the Indian population and in a larger proportion in rural areas, the impact is self-explanatory. From a scientific perspective, epigenetic changes or chemical changes in the uterus lead to changes in the genomic material which the child is born with.

The solutions are not simple, and essentially would involve proper counseling of the mothers and families of those children who are born low birth weight or preterm as to how over enthusiastic attempts to make the growth curve more steep in these children is probably likely to increase childhood obesity and lead to adverse consequences in adulthood. The ultimate solution of optimum feeding of mothers in pregnancy can be debated, but what is optimum and when? Research is on but the answer is unclear, and concepts are still evolving. Certainly, economic equity is a solution in improving birth weights, but is much more easily said than done.

So poverty may beget low birth weight and low birth weight begets diabetes. Unfortunately, to add to the complexity, when these children grow older they may have diabetes in pregnancy which may be inadequately treated due to poor awareness, finances or substandard medical care. This subsequently increases the risk of their offspring getting diabetes, particularly if

the diabetes in pregnancy is uncontrolled. Therefore, diabetes in pregnancy ends up being a continuous and depressing transgenerational phenomenon.

Thankfully, it appears that the effects of low birth weight can be blocked to a large extent by a healthy habitus, as suggested in our publication in *Eur J Endocrinol* 2012 and may indeed ameliorated by exercise interventions as simple as cycling (*J Dev Health and Dis* 2014), which are generally easily accessible and part of childhood recreation.

To add to the woes of those who are most affected by inflation, here is another quirk of fate which will increase the subsequent chances of the lower middle class and the poor in getting diabetes. Drewnowski and Specter in the *American Journal of Clinical Nutrition* 2004 have stated, that amongst subjects who belonged to the lower socioeconomic group, that there was a tendency to take more carbohydrate and fat rich food in greater abundance since it was cheaper than that of the food which was lower in calories and contained a larger quantum of free radicals and vitamins. Hence, the socioeconomically deprived, may in fact have a greater propensity to develop weight gain through the food which they eat, rather than those who are well-off. In other words, certainly cheaper oils are abundantly available and are not expensive compared to fresh fruits and vegetables. This lends further credence to the statement: 'An apple a day keeps the doctor away'.

Vitamin D which is termed the 'sunshine vitamin', has its deficiency being associated with insulin resistance (the body's own lack of ability to respond to insulin). There is more evidence nowadays that though not entirely always with controversy, that since vitamin D deficiency has been shown by several groups including ours (*Endocrine Practice* 2008) to be fairly common owing to our propensity to avoid the sun for occupational and cosmetic reasons that this in itself may pose an added risk factor for the increasing prevalence of diabetes.

The magnitude of the disease in terms of its prevalence and the potential causes for the problem has now been discussed *ad nauseum!* The subsequent consequences of the disorder, with its impact on quality of life and even its economic impact cannot be overstated. Take for instance just one complication—the damage to the nerves (peripheral neuropathy). It is awfully common—according to an earlier study done in 4 centers across the country published in the *Journal of Association of Physicians in India* in 2005. Nerve damage was present in 15% of those who had diabetes who attended the outpatient clinics at these centers. What was probably more eerie is the fact that 3–4% of those patients with diabetes also had the amputation of at least a single toe, if not a whole limb.

Now try and visualize a situation that at least 1.5 million of your 70 million patients with diabetes have at least a toe or a limb that has been removed. This would impair not only their morale, but also their physical balance when attempting to walk and would lead to a number of those in the agrarian or laborer classes to be totally ineffective in their day-to-day work, without extensive rehabilitative therapy and prostheses.

The fact is that, as early as 2000, Lucini et al, pointed out in a study that was published in *Pharmacoeconomics* that if a patient with diabetes has one microvascular complication (that is peripheral nerve damage, retinal damage in the eye or early kidney disease) the cost of treatment goes up by 1.5 times. If a patient has one macrovascular complication (heart disease or stroke) the cost goes up by twice the amount that would normally be spent. However, if a patient has both 1 microvascular and 1 macrovascular complication, the cost of treatment goes up 3.5 times. This is totally unacceptable for the lower socioeconomic class in this country.

A study conducted at Vellore published in *Journal of Diabetes* 2011, has shown that the commonest cause of death is cardiovascular disease (in general, a heart attack) or a stroke in 38% of the total number of hospitalized patients with diabetes. Urinary tract infections as a cause for death are far more common amongst the population with diabetes when compared to the non-diabetic population. There is an important public health message for administrators and also for the primary care physicians.

Indeed the number of pharmacological agents, on the other hand, that have emerged in the market over the last decade are significant, as opposed to the 1980s, when there were just 5 oral tablets for the management of diabetes, there are 18 at present! They may be used in a number of permutations and combinations. If used properly and up to maximal doses, the potential for delaying the usage of injectable products is certainly there. For the majority of the population in rural areas and amongst the lower socioeconomic classes, cost is a significant deciding factor. The harsh reality of incomplete and suboptimal therapy is a combination of the patient's financial inadequacy and at times the inability of the healthcare system to meet with the growing demands of and increasing patient load.

Going by the fact that prevention of complications is far more important than ultimately trying to treat or cure them, it brings us to a position where we would question ourselves as to where should we target our strategies, and who should we work on to improve the overall impact with regards to the prevention and treatment of diabetes in the community.

An editorial from the *Lancet* 2011 and some work from our center quoted in *Heart Asia* 2011 have both highlighted the fact that prediabetes, as documented as a fasting blood sugar of more than 100 mg/dL is present in 20% or more of high school children. They have a greater amount of subcutaneous fat (thicker skin) than their peers who do not have blood sugar or cholesterol problems. This is a strong signal that school programs are of primary importance in preventing obesity, diabetes and abnormalities of cholesterol which will wreck havoc on the individual and society later on as these children become adults.

Both at the central and state government levels, educational regulatory bodies should highlight the importance of compulsory physical training and games during school hours. There should be a compulsory assessment of physical fitness and period, self-assessment of physical abilities, weight and flexibility as a pre-requisite to pass before going to the next academic level. Radical thinking no doubt, but what if it were to help in preventing 80 million people or more from falling sick in the ensuing 40 years from now?

No doubt the growing number of endocrinologists and diabetologists appears to be a promising factor on the horizon. However, are they the ultimate solution for a disease that is going to affect 1 in 10 of the population of the country and 1 in 6 above the age of 20 years of age? Attempting to train large numbers of endocrinologists and diabetologists would be a time consuming, economically demanding and difficult to achieve solution for such a common disorder—an estimated 30,000 of them would be needed in our country—there are hardly 1,000 present at this point of time, almost all of them concentrated in urban areas. The concept of a competent family physician that has a better understanding of problems like diabetes, obesity, hypertension and other non-communicable problems are the way to go forward in tackling the problems of numerous clients with diabetes and prediabetes.

The role of councillors and educators who could be nurses, dieticians, physiotherapists and even school teachers in large numbers would be important in disseminating information

and supporting the role of public health physicians and family physicians in handling this pandemic. However, to sort out the problem of diabetes on a large-scale basis will require a megalithic vision spearheaded and encouraged by the government to develop teams to enhance physical activity and discourage unhealthy eating habits. It should involve a public health policy targeting schools, with primary health caregivers playing an important supplementary role.

There are other factors which play a role in the evolution of diabetes in India, and indeed, the genetic patterns do vary. Our recent studies in Maturity Onset Diabetes of the Young (MODY), have shown that the genetic forms which appear to be common in India (*Clin Endocrinol* 2015), differ from the patterns that are seen in the West. Moreover, it raises a possibility of other forms of diabetes also existing amongst the young, besides type 1 and type 2 diabetes. It also sets the foundation for a greater propensity of pharmacogenomic interventions in the years to come.

The current book is now into its 7th edition and has gone through a process of evolution starting with the World Diabetes Foundation Program which was initiated in 2004 to train doctors, nurses, foot care technicians and cobblers in the management of diabetes and set up integrated diabetes centers. Beyond that, what has resulted are comprehensive training programs for primary care doctors in diabetes and councillors in every corner on India, and parts of South-Asia and Africa as well.

Our role in handling the epidemic is to teach and to train those who can do their best in the periphery to handle diabetes to the extent they may be able to do well.

I would like to thank the number of authors who have performed their job so well to the extent that the current edition may be able to provide much more than what previous editions have for healthcare givers in both India as well as other parts of the world. I would like to specially thank Dr Nitin Kapoor, who has played a major role in the process of compiling the current edition of the book which has several new chapters including the ones on obesity, wound care, the elderly and epidemiology.

We are here to serve our patients directly, and in more ways than one through education of others to play their role better in countering the diabetic pestilence.

Nihal Thomas MBBS MD MNAMS DNB (Endo)
FRACP (Endo) FRCP (Edin) FRCP (Glasg)
Professor and Head
Department of Endocrinology
Vice Principal (Research)
Christian Medical College
Vellore, Tamil Nadu, India

Acknowledgments

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CHAPTER

1

Physiology

Solomon Sathish Kumar

*“Insulin the peptide—it is the true tonic,
Islets they pump them, it is quite anabolic,
A quaint homeostasis it provides all along,
Courtesy: in combo with GLP-glucagon.”*

Pancreas, the source of insulin production, is an essential organ responsible for both digestion and glucose homeostasis. Historically, insulin is associated with “blood sugar” and true enough, insulin has profound effects on carbohydrate metabolism. Besides, it also plays a very vital role in fat and protein metabolism. Absolute or relative insulin deficiency causes diabetes mellitus, which is characterized by abnormalities in carbohydrate, protein and fat metabolism. The hormones of particular importance in glycemic regulation are insulin, glucagon and more recently glucagon-like peptide-1.

PANCREAS

Functional Anatomy

The adult human pancreas is made up of numerous collections of cells called islets of Langerhans. There are about 1–2 million islets, and which make up only about 2% of the volume of the pancreas, while the rest of it is constitute by ducts, blood vessels and the larger exocrine portion of the pancreas made up of acini which secrete digestive juices.

There are four major cell types in the islets of Langerhans based on staining characteristics and appearance. They are as follows (Fig. 1.1):

α cells: These cells produce glucagon. It increases plasma glucose by increasing hepatic glycogenolysis and gluconeogenesis; increases lipolysis.

β cells: The majority of cells in the islets of Langerhans are β cells, i.e. about 60–70%. They produce insulin, which is anabolic in nature. The effects of insulin are discussed further along in this chapter.

Δ cells: These cells produce somatostatin, which acts locally in a paracrine manner and inhibits secretion of pancreatic polypeptide, insulin and glucagon.

***F* (or *PP*) cells:** These cells produce pancreatic polypeptide, which slows absorption of food, but its physiological significance is uncertain.

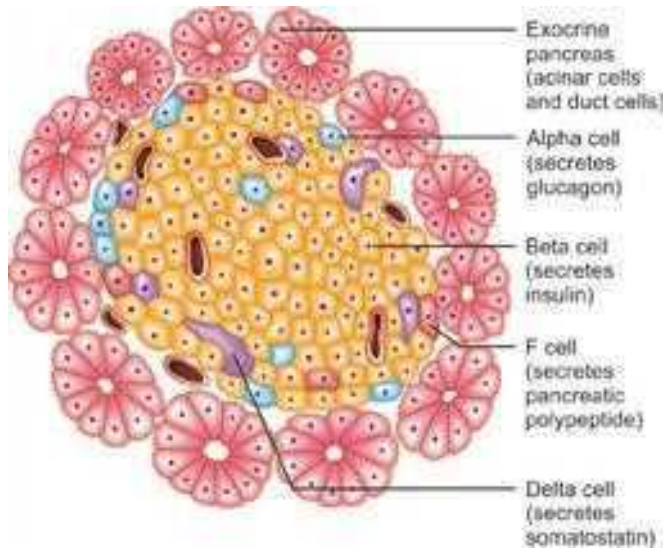


Fig. 1.1: Islets of Langerhans in the pancreas surrounded by exocrine acinar cells.

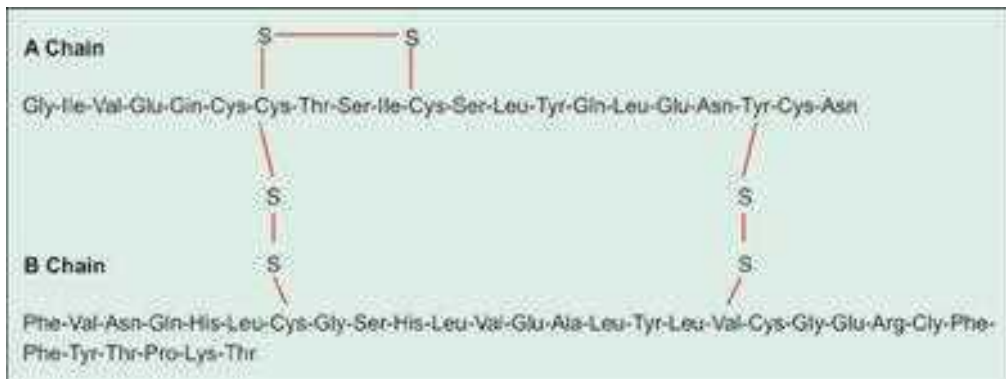


Fig. 1.2: Structure of human insulin.

Insulin is a polypeptide/small protein made of two chains of amino acids connected by disulfide linkages or bridges (Fig. 1.2).

The amino acid sequence of insulin molecule varies very little from species to species (cows, pigs, etc.). These differences do not affect the biological activity if insulin from one species is given to another species, but they are definitely antigenic and induce antibody formation against the injected insulin when given over a prolonged period of time. Human insulin is now used to avoid this problem.

Synthesis of Insulin

Insulin is synthesized in the rough endoplasmic reticulum of the β cells. It is then packed into secretory granules in the Golgi apparatus and released by exocytosis.

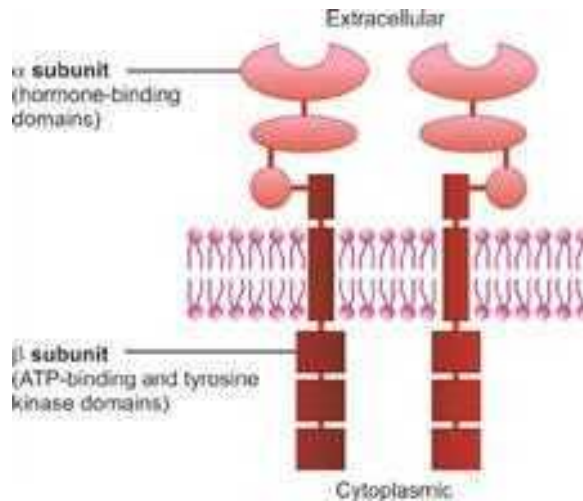


Fig. 1.3: Structure of insulin receptor.

Source: Taken with permission from R Bowen.

Insulin is synthesized from a single long chain of amino acids called preproinsulin. This chain gets cleaved, i.e. 23 amino acid signal peptide is removed from it and the remaining portion folds on itself with the formation of disulfide bonds, to form proinsulin.

The connecting peptide or C-peptide facilitates in the folding and connects the A and B chains. The C-peptide gets detached and insulin is formed. C-peptide level is an indicator of β cell function in patients who receive exogenous insulin.

Insulin Receptor

Insulin receptors are present in almost all cells of the body. It is a glycoprotein made of 2α and 2β subunits linked by disulfide bridges (Fig. 1.3).

The α subunit which binds insulin is extracellular, while the β subunit extends from the cell membrane into the cell. The part of the β subunit, which extends into the cell has tyrosine kinase activity.

The number and affinity of insulin receptors is affected by various factors like insulin levels, exercise and food. An increased concentration of insulin decreases the number of insulin receptors called downregulation and decreased concentrations of insulin increases the affinity of the insulin receptors. The number of insulin receptors is decreased in obesity and increased in times of starvation.

Mechanism of Action of Insulin

Insulin binds to the α subunit of its receptor. This binding triggers tyrosine kinase activity in the β subunit and causes autophosphorylation of the β subunit. This in turn causes either phosphorylation or dephosphorylation of certain proteins and enzymes in the cytoplasm, activating some and inactivating other, thus bringing about the actions of insulin. One of the

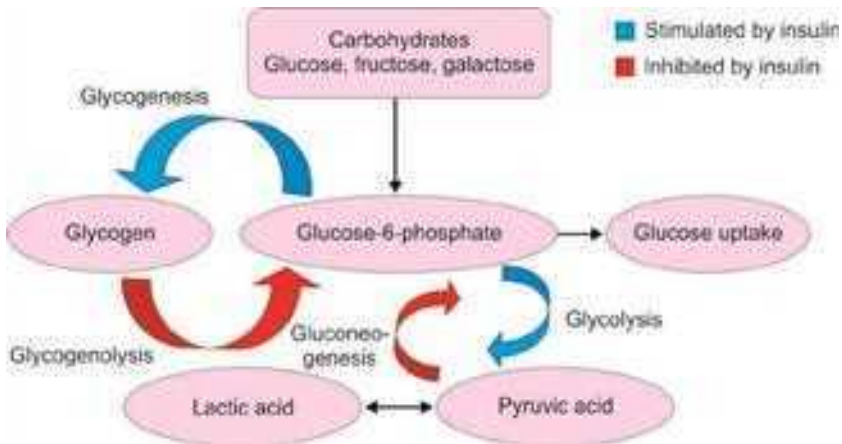


Fig. 1.4: Actions of insulin on carbohydrate metabolism.

cytoplasmic substrates for insulin action is the insulin receptor substrate or IRS-1. Protein synthesis and growth promoting actions of insulin are mediated through phosphoinositol 3-kinase (PI3K) pathway.

Effects of Insulin

Effect on Carbohydrate Metabolism (Fig. 1.4)

- Insulin increases glucose uptake into all cells sensitive to insulin, particularly adipose tissue and muscle. It does not affect glucose uptake in the brain cells.
- Insulin reduces the rate of hepatic glucose output by inhibiting glycogenolysis and gluconeogenesis, while at the same time stimulating glycogen synthesis, glucose uptake and glycolysis.
- Insulin causes increase in glycogenesis in the muscle.

Effect on Lipid Metabolism

- Increases lipid synthesis.
- Stimulates fatty acid synthesis in the liver and adipose tissue, and thus provides the substrate for increased lipid synthesis.
- Stimulates increased formation of triglycerides in adipose tissue.
- Acts on adipose tissue and reduces the rate of release of free fatty acids.
- Inhibits the hormone-sensitive lipase in adipose tissue.
- Activates lipoprotein lipase.

Effect on Protein Metabolism

- Insulin stimulates protein synthesis and inhibits breakdown.
- It also increases the transport of amino acids across the plasma membrane in liver and muscle cells.

Effect on Potassium Transport

Insulin increases movement of potassium into cells, which is probably due to activation of sodium potassium ATPase. The sodium potassium ATPase, which is present on the cell membrane, pumps out sodium and pumps potassium into the cells. Diabetic ketoacidosis, when treated vigorously with insulin can cause hypokalemia due to movement of potassium into cells. Thus, potassium levels need to be monitored in addition to the blood glucose levels, and potassium supplements should be given, if necessary. Insulin is used in the treatment of hyperkalemia but glucose needs to be supplemented simultaneously due to the hypoglycemic effect of insulin.

Effect on General Growth and Development

- Insulin plays an important role in the synthesis of proteins which is essential for growth
- Experiments have shown that growth hormone and insulin have a synergistic effect on growth and growth is retarded if either one of the hormone is lacking.

The effects of insulin can occur within seconds to several hours:

- Immediate actions which occur within seconds include:
 - Insulin has immediate effects such as an increase in transport of potassium, amino acids and glucose into cells.
 - The fact that insulin not only transports glucose but also potassium into cells needs to be monitored while treating patients with diabetic ketoacidosis.
- Intermediate actions which take minutes include:
 - Insulin brings down blood glucose levels by
 - Increasing glycogenesis by activating the enzyme glycogen synthase
 - Decreasing gluconeogenesis by inhibiting the enzymes involved
 - Inhibiting glycogenolysis by inhibiting the enzyme phosphorylase
 - Insulin increases protein synthesis and inhibits its breakdown.
- Late actions which take hours:
 - It increases lipogenesis. It does so by increasing the formation of mRNAs for enzymes involved in lipogenesis.

Glucose Transporters

The entry of glucose into cells is by the process of facilitated diffusion with the help of glucose transporters, GLUT 1 to GLUT 7. The glucose transporter in muscle and adipose tissue, which is stimulated by insulin, is GLUT 4 (Fig. 1.5). Glucose transportation into the intestines and kidneys is by secondary active transport via SGLT 1 and SGLT 2 (sodium dependent glucose transporters).

GLUT 1 deficiency in infants leads to ineffective transport of glucose across the blood brain barrier. Therefore, the CSF glucose level is low when compared with plasma glucose levels, and this causes seizures and developmental delay.

Exercise is an important component in the treatment of diabetes as it causes an insulin-independent increase in the number of glucose transporters (GLUT 4) on the muscle cell membranes, and thus causes an increase in glucose uptake into skeletal muscles.

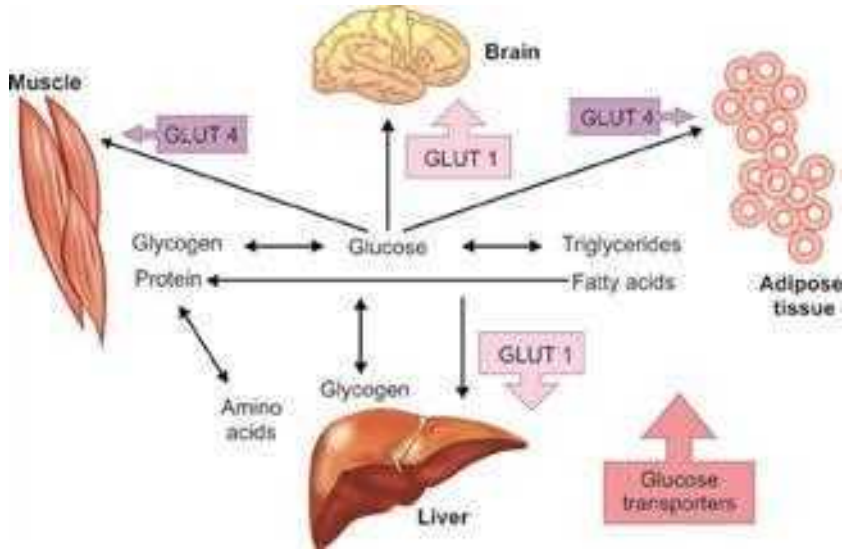


Fig. 1.5: Glucose transporters.

Major Factors Regulating Insulin Secretion

The most important regulator of insulin secretion is the direct feedback of plasma glucose on the β cells.

The glucose transporter on β cells is GLUT 2 (which is not insulin dependent for activation). The glucose, which enters the β cell via GLUT 2, is metabolized by glucokinase. This results in ATP formation and closure of the ATP-sensitive K^+ channels. The resultant decrease in potassium efflux causes the depolarization of cell membrane. This leads to opening of voltage gated calcium channels and rapid entry of calcium into the cell. The increased intracellular calcium triggers the release of insulin by exocytosis from the granules in the β cells, into the islet capillaries. C-peptide is also released but has no physiological function. During fasting, glycogenolysis occurs in the liver to produce glucose for energy. As fasting prolongs over a period of time, the glycogen stores get exhausted and gluconeogenesis occurs to obtain energy from amino acids and glycerol (Fig. 1.6).

Tolbutamide and other sulfonylurea derivatives bind to the ATP cassette protein of the ATP-sensitive K^+ channels on the β cell membrane, thereby inhibiting the K^+ channel activity. Thus, the β cells depolarize and increased Ca^{2+} influx triggers insulin release. Metformin reduces blood glucose by reducing hepatic gluconeogenesis and thus reduces glucose output from the liver. Thiazolidinediones (rosiglitazone, pioglitazone) reduce the insulin resistance or increase the insulin sensitivity (insulin stimulated glucose uptake) by activating peroxisome proliferator-activated receptors (PPAR γ) in the cell nucleus.

Sympathetic nerve stimulation to the pancreas causes an inhibition of insulin secretion and parasympathetic stimulation to the pancreas causes an increase in insulin secretion.

Increased insulin secretion also occurs when there is a stimulus that can cause increased levels of cAMP in the β cells. This is perhaps due to the increase in intracellular calcium levels.

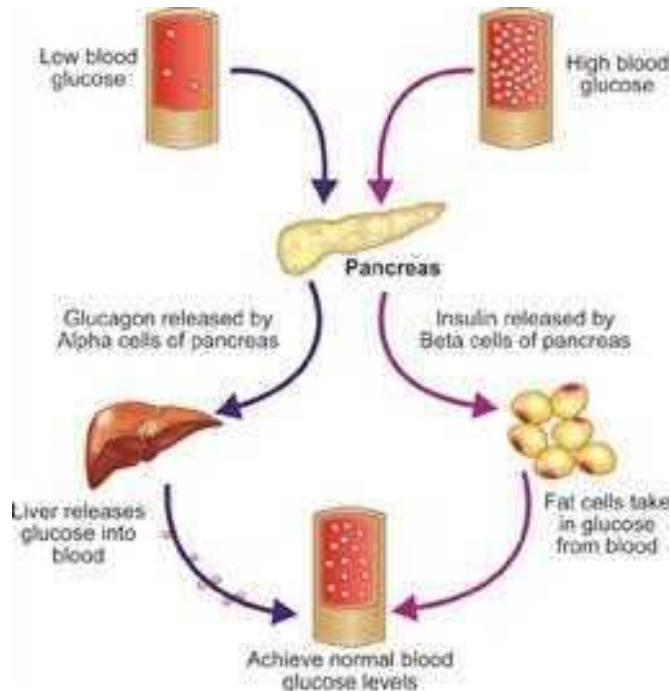


Fig. 1.6: Normal regulation of blood glucose.

It was observed that oral administration of glucose caused a greater insulin stimulatory effect when compared to intravenously administered glucose. This effect was due to substances secreted by the gastrointestinal mucosa, which stimulated insulin secretion like secretin, cholecystokinin, glucagon, glucagon derivatives and gastric inhibitory peptide.

The Incretin Effect

Glucagon-like peptide-1 (GLP-1) is a gut hormone that stimulates insulin secretion, gene expression and β -cell growth. Together with the related hormone, glucose-dependent insulintropic polypeptide (GIP), it is responsible for the incretin effect, the augmentation of insulin secretion by oral as opposed to intravenous administration of glucose.

Incretin effect is the ratio between the integrated insulin response to oral glucose and an isoglycemic IV glucose infusion (Fig. 1.7). Incretin effect for oral glucose is ~20-60%. Total incretin quantity as well as incretin effect is decreased in patients with diabetes.

The two most important incretin hormones are GIP, formerly known as gastric inhibitory polypeptide, and GLP-1. Both are potent insulintropic hormones released by oral glucose as well as ingestion of mixed meals.

GIP

GIP is a peptide of 42 amino acids belonging to the glucagon-secretin family of peptides, the members of which have pronounced sequence homology, particularly in the NH₂-terminus.

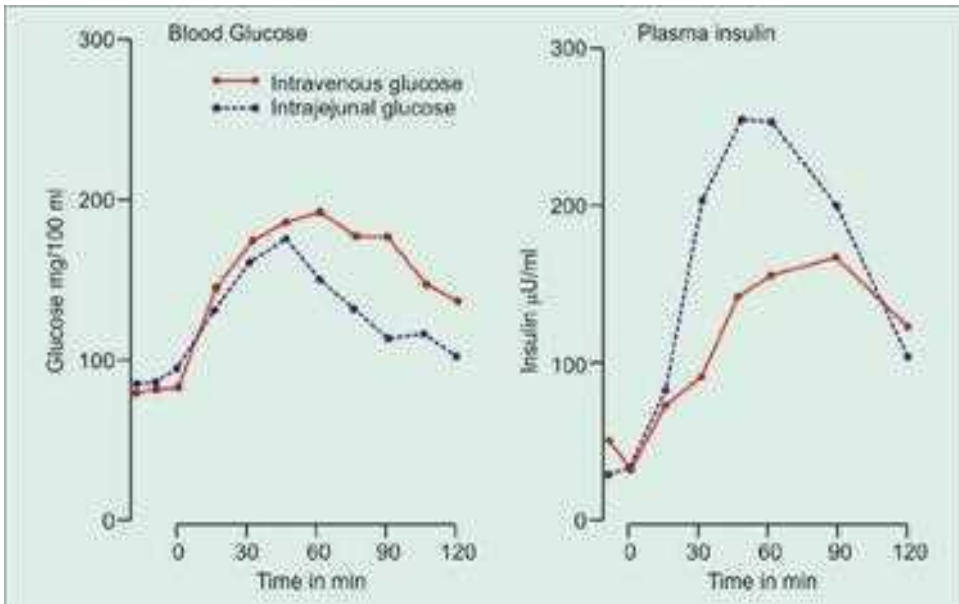


Fig. 1.7: Effect of incretin hormones.

It is processed from a 153 amino acids precursor, but specific functions for other fragments of the precursor have not been identified. It is expressed in the islets and also in the gut, adipose tissue, heart, pituitary, adrenal cortex and several regions of the brain. GIP is secreted from specific endocrine cells called K cells, with highest density in the duodenum but also found in the entire small intestinal mucosa. Secretion is stimulated by absorbable carbohydrates and by lipids. GIP secretion is, therefore, greatly increased in response to meals, resulting in, 10–20 fold elevations of the plasma concentration.

Interaction of GIP with its receptor on the β cells causes elevation of cAMP levels, which in turn increases the intracellular calcium concentration and enhances exocytosis of insulin-containing granules by a mechanism distal to the elevation of calcium.

GLP-1

Glucagon-like peptide (GLP-1) is one of the most potent incretin hormone produced by the L-cells of the intestinal mucosa. Its insulin-releasing property exceeds that of GIP. It is produced by tissue-specific post-translational processing of the glucagon gene, which is expressed not only in the islet cells but also in the L-cells, one of the most abundant endocrine cells of the gut. Unlike in the islets where proglucagon is cleaved to form glucagon (Fig. 1.8), in the L-cells, the COOH-terminal part is cleaved to give rise to GLP-1 and GLP-2, both showing 50% sequence homology with glucagon.

GLP-1 has two important forms GLP-1 (7–36) and GLP-1 (7–37) amide in circulation. Approximately 80% of the circulatory active GLP-1 is GLP-1 (7–36) amide and to a smaller extent in the duodenum and jejunum. It is also expressed in the hypothalamus and brain stem.

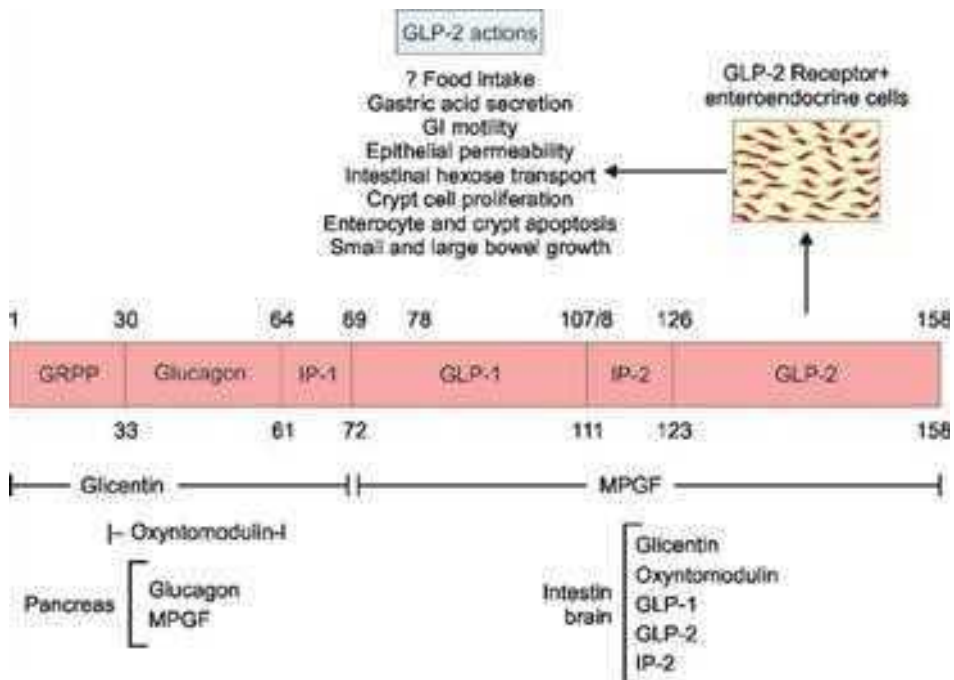


Fig. 1.8: The preproglucagon molecule which is the parent molecule for glucagon and GLP-1.

Source: Abridged from <http://www.med.unibs.it/~marchesi/pephorm.html>

Nutrients, including glucose, fatty acids, and dietary fiber, are all known to upregulate the transcription of the gene encoding GLP-1, and they can stimulate the release of this hormone. Although, the majority of L-cells are located in the distal ileum and colon, the levels of GLP-1 rise rapidly upon food ingestion. Sugars and fats in the diet, liberate GLP-1 and GLP-1 releasing factors, including GIP, gastrin-releasing peptide, and selective neural regulators that also stimulate GLP-1 secretion.

The β cells have got GLP-1 receptors which are G-protein coupled receptors linked to adenylate cyclase. GLP-1 acts via the second messenger cAMP. GLP-1 probably stimulates insulin secretion by causing increased calcium entry via the voltage gated calcium channels.

Within few minutes after food ingestion, the level of GLP-1 rapidly increases. Upon its release, GLP-1 affects multiple target tissues throughout the body, actions thought to be mediated by a single G-protein coupled receptor isoform. GLP-1 receptor transcripts and/or protein have been identified in several tissues, including pancreatic islets, lung, gastrointestinal (GI) tract, and the central nervous system (CNS). GLP-1 stimulates glucose-dependent insulin secretion by the β cells. It increases transcription of the insulin gene. It maintains the function of β cells, and also increases the mass of β cells. It increases the sensitivity to insulin, suppresses glucagon secretion by the α cells, slows down the process of gastric emptying, increases glucose disposal and reduces quantity of food intake. GLP-1 infusion has a glucose lowering effect in type 2 diabetic patients, and there is a rapid rise in blood glucose levels after termination of the GLP-1 infusion.

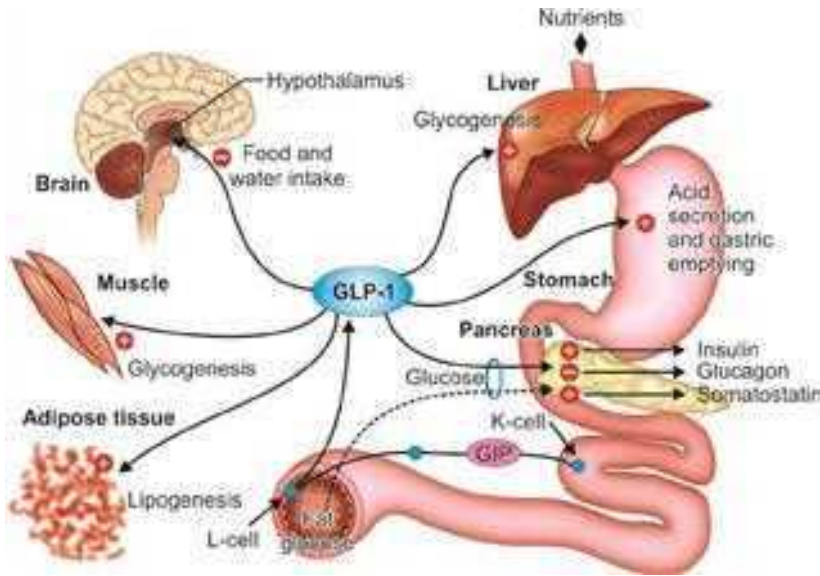


Fig. 1.9: The impact and actions of glucagon-like peptide-1 (GLP-1).
 Source: Adapted from Kieffer & Habener (1999): Endocrine Reviews

GLP-1 in the Pancreas: Insulin Secretion and β cell Mass

GLP-1 rapidly and potently stimulates insulin secretion. GLP-1 also stimulates insulin gene transcription, islet cell growth and neogenesis, additional potentially important functions that may be clinically relevant for the treatment of diabetes.

GLP-1 in the Periphery: Gut Motility and Insulin Sensitivity

GLP-1 decreases gastric motility via direct effects on gastric smooth muscle and also inhibits postprandial acid secretion. It also decreases small intestinal movement through inhibition of smooth muscle activity, resulting in an overall reduction in the absorption of nutrients from the gastrointestinal tract. It is more likely that reduced motility causes less severe postprandial glucose fluctuations and reduces the need for a large and rapid postprandial insulin response.

GLP-1 also appears to improve insulin sensitivity and glucose uptake (Fig. 1.9).

GLP-1 in the CNS: Control of Appetite and Weight

GLP-1 has profound effects on feeding behavior. Although these actions of GLP-1 could be partly related to its effects on intestinal motility, they also appear to directly affect the hypothalamic feeding centers as GLP-1 receptors are found in specific nuclei within the hypothalamus. Studies have shown that acute administration of GLP-1 induces satiety and decreases calorie intake. In humans with type 2 diabetes, short-term GLP-1 or exendin-4 administration curbs appetite and food intake in addition to its insulinotropic actions,

suggesting in long-term; this will promote weight loss in these patients. The ability of GLP-1 analogs to promote weight loss and improve β cell function has made these agents useful for the treatment of type 2 diabetes.

Properties and Biological Actions of GIP and GLP-1

In a nutshell, antidiabetic potential of GLP-1 is mediated by the following mechanisms:

- Glucose-dependent insulinotropic actions;
- Glucagonostatic actions;
- A reduction in appetite/promotion of satiety leading to reduced food intake and weight reduction;
- The deceleration of gastric emptying; and
- The stimulation of islet growth, differentiation and regeneration.

The plasma enzyme dipeptidyl peptidase-IV (DPP-IV) cleaves GLP-1 very quickly and thus GLP-1 has a half-life of only 2 minutes. Thus, GLP-1 has a short duration of action. The glucagon-like peptide 1 receptor (GLP-1R) agonists are resistant to degradation by DPP-IV and presently used for treating type 2 diabetes. Inhibition of DPP-IV also programs the action of endogenous GLP-1, and DPP-IV inhibitions are liked as therapeutic agents.

Substances with Insulin-like Activity

Substances with insulin-like activity include *IGF I and IGF II* (insulin-like growth factors) also called somatomedins. They are synthesized and secreted by liver, cartilage and other tissues in response to growth hormone. The IGF receptor and the insulin receptor are very similar. Their activity is weak when compared with insulin and cannot replace insulin. The insulin-like growth factors are mainly concerned with growth.

DIABETES MELLITUS

Diabetes mellitus is a chronic disorder characterized by fasting and/or postprandial hyperglycemia with plasma glucose levels that are above defined limits during oral glucose tolerance testing or random blood glucose measurements as defined by established criteria.

Type 1 Diabetes

There is absolute insulin deficiency due to autoimmune destruction of β cells. There is also a genetic susceptibility to the disease. The main genetic abnormality is in the major histocompatibility complex on chromosome 6. This usually presents at a younger age.

Type 2 Diabetes

This occurs due to insulin resistance or insensitivity of tissues to insulin and relative insulin deficiency (and may later lead to absolute insulin deficiency).

Obesity is a major risk factor for the disease. The insulin resistance seems to be caused by the toxic effects of increased lipid accumulation, which interferes with insulin signaling

processes between receptor activation and cellular effects. Some studies have shown that obese individuals have less number of insulin receptors in muscle, adipose tissue and liver. They usually show an improvement in glucose tolerance with exercise.

Consequences of Disturbed Carbohydrate Metabolism

Decreased entry of glucose into insulin-sensitive cells and also increased release of glucose from the liver leads to *hyperglycemia*. Glucose is a major source of energy in the cell and due to deficient intracellular glucose, protein and fat reserves are used for energy. The increased breakdown of fat leads to ketosis. Polyuria, polydipsia and polyphagia are seen in some diabetic patients. The *renal threshold* for glucose is 180 mg%, i.e. if the plasma glucose value is raised above 180 mg%, the ability of the kidney to reabsorb glucose is exceeded and glucose will start appearing in urine (*glycosuria*). Thus, as glucose is lost in the urine, water is osmotically dragged along with it (*osmotic diuresis*), leading to an increased urine output (*polyuria*). Since lot of water is lost in the urine, it leads to dehydration and this triggers the processes regulating water intake and causes increased thirst (*polydipsia*). Electrolytes are also lost in the urine. The quantity of glucose lost in urine is enormous and thus to maintain energy balance the patient takes in large quantities of food. Reduced glucose utilization by the ventromedial nucleus of hypothalamus (satiety center) is also possibly the cause for the *polyphagia*.

The plasma glucose levels can get elevated to such an extent that the hyperosmolarity of plasma can cause coma called *hyperosmolar coma*.

Consequences of Disturbed Lipid Metabolism

There is increased breakdown of lipids and decreased formation of fatty acids and triglycerides. Increased fat breakdown leads to increased formation of ketone bodies, which leads to ketosis and acidosis. The ketone bodies include acetoacetate, acetone and β -hydroxybutyrate. The hydrogen ions formed from acetoacetate and β -hydroxybutyrate are buffered to a great extent, beyond which metabolic acidosis occurs. The pH drops due to the acidosis and the increased hydrogen ion concentration stimulates the respiratory center causing the characteristic rapid and regular deep breathing called *Kussmaul breathing*.

The acidosis and dehydration can lead to *coma* and even *death*. The hormone-sensitive lipase converts triglycerides to free fatty acids (FFAs) and glycerol. Insulin has an inhibitory effect on this hormone. In the absence of insulin, the FFA levels greatly increase. The FFA is catabolized to acetyl CoA in the liver and other tissues and the excess acetyl CoA is converted to form ketone bodies.

Consequences of Disturbed Protein Metabolism

There is decreased protein synthesis and increased protein breakdown leading to protein catabolism and muscle wasting. There is increased plasma amino acids and nitrogen loss in urine. All this leads to negative nitrogen balance and protein depletion. Protein depletion causes poor resistance to infections. There is increased gluconeogenesis in the liver since the amino acids are converted to glucose.

Table 1.1: Consequences of disturbed metabolism in diabetes.

<i>Metabolic defect</i>	<i>Chemical abnormality</i>	<i>Clinical abnormalities</i>
<i>Carbohydrate metabolism</i>		
<ul style="list-style-type: none"> • ↓↓ Glucose uptake by tissues (muscle, adipose tissue, liver) • ↑↑↑ Glucose production 2° to Glycogenolysis and glyconeogenesis in liver 	Hyperglycemia ↓ Glycosuria ↓ Osmotic diuresis	<ul style="list-style-type: none"> • Polyuria, Polydipsia, Polyphagia • Blurred vision • Diminished mental alertness • Dehydration (→ death)
<i>Protein metabolism</i>		
<ul style="list-style-type: none"> • ↓ Uptake of amino acids • ↓ Protein synthesis • ↑ Proteolysis 	<ul style="list-style-type: none"> • Negative nitrogen balance • ↑ Levels of branch chain amino acid • ↑ Blood urea nitrogen level • ↑ K⁺ level 	<ul style="list-style-type: none"> • Weakness • Poor resistance to infections • Muscle wasting
<i>Lipid metabolism</i>		
<ul style="list-style-type: none"> • ↑ Lipolysis • ↓ Lipogenesis • ↑ Triglycerides, FFA production • ↑ Ketone production • ↓ Ketone excretion • ↑ Production of LDL and VLDL 	<ul style="list-style-type: none"> • ↑ Plasma FFA • ↑ Plasma glycerol • Hypertriglyceridemia • ↑ Plasma and urine ketone • ↑ Plasma LDL and VLDL 	<ul style="list-style-type: none"> • Loss of adipose tissue → Weight loss • Pancreatitis • Metabolic acidosis → Hyperventilation → Kussmaul breathing → death • Atherosclerotic vascular disease

Consequences of Disturbed Cholesterol Metabolism

Diabetics are more prone for myocardial infarctions and stroke because the cholesterol levels are elevated causing atherosclerosis. This is due to an increase in LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein) levels in the plasma, probably because of either augmented production of VLDL in the liver or decreased removal of LDL and VLDL from the blood stream (Table 1.1).

Further Complications

Long standing uncontrolled diabetes can lead to:

- Microvascular complications like retinopathy, nephropathy and neuropathy involving the peripheral nerves and autonomic nervous system.
- Macrovascular complications like stroke, peripheral vascular disease and myocardial infarction due to increased atherosclerosis caused by increased amounts of LDL (as discussed above).

The microvascular complications are related to both duration of diabetes and uncontrolled plasma glucose levels. Increased intracellular glucose levels (in cells such as endothelial cells that are unable to downregulate glucose transport in the presence of increased extracellular

glucose) cause formation of sorbitol due to activation of the enzyme aldose reductase. Sorbitol decreases sodium potassium ATPase activity. The increased intracellular glucose also nonenzymatically attaches to protein amino groups to form amadori products. The amadori products form advanced glycosylation end-products (AGEs) which cause cross-linkage of matrix proteins and, thus, cause damage to blood vessels. There is also increased accumulation of sorbitol and fructose in Schwann cells due to hyperglycemia. This can interfere with its structure and function.

Causes for delay in wound healing and gangrene in diabetes include:

- Circulatory insufficiency due to atherosclerosis
- Neuropathy
- Protein depletion causes poor resistance to infections
- AGEs cause a decrease in leukocyte response to infection.

SUGGESTED READING

1. Combettes MM. GLP-1 and type 2 diabetes: physiology and new clinical advances. *Curr Opin Pharmacol.* 2006;6(6):598-605.

SELF-ASSESSMENT

1. Which one of the following is the most important source of blood glucose during the last hour of 48 hours fast?

- (a) Muscle glycogen
- (b) Acetoacetate
- (c) Liver glycogen
- (d) Amino acids
- (e) Lactate

2. An obese individual with type 2 diabetes mellitus:

- (a) Usually shows a normal glucose tolerance test
- (b) Usually has a lower plasma insulin than a normal individual
- (c) Usually shows marked improvement in glucose tolerance if body weight is reduced to normal
- (d) Usually benefits from receiving insulin about 6 hours after a meal
- (e) Usually has lower plasma levels of glucagon than a normal individual

3. Which one of the following is most found in untreated patients with type 1 and type 2 diabetes?

- (a) Hyperglycemia
- (b) Low levels of insulin synthesis and secretion
- (c) Synthesis of insulin with abnormal amino acid sequence
- (d) Microangiopathy
- (e) All of the above

4. Insulin causes:

- (a) Increased gluconeogenesis
- (b) Increased glycogenolysis
- (c) Increased glycogenesis
- (d) Lipid breakdown

5. Somatostatin:

- (a) Stimulates insulin and glucagon (b) Inhibits both insulin and glucagon
(c) Inhibits only glucagon (d) Lipid breakdown

6. During diabetes there is “Starvation in the midst of plenty” because:

- (a) Increased intracellular glucose and decreased extracellular glucose
(b) Decreased intracellular and extracellular glucose
(c) Increased extracellular and decreased intracellular glucose
(d) Increased intracellular and extracellular glucose

7. Kussmaul’s breathing seen in diabetes is due to:

- (a) Hyperglycemia (b) Ketosis
(c) Metabolic acidosis (d) Polydipsia

8. The following acid base disturbance is a complication of diabetes:

- (a) Metabolic acidosis (b) Metabolic alkalosis
(c) Respiratory acidosis (d) Respiratory alkalosis

9. Polydipsia in diabetes is due:

- (a) Electrolyte depletion (b) Osmotic diuresis
(c) Decreased water intake (d) Decreased urine output

10. Renal threshold for glucose is:

- (a) 150 mg% (b) 180 mg%
(c) 200 mg% (d) 220 mg%

CHAPTER

2

Introduction and Overview of Glycemic Disorders

PART A: EPIDEMIOLOGY AND PATHOGENESIS

Nihal Thomas, Senthil Vasan K

*“They say its genes not the blue variety,
Environs have a role, and the lack of satiety,
Epigenetics, low birth (weight) babies—problems for poor,
Dwindling secretion and resistance for sure.”*

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by hyperglycemia. Regardless of its etiopathology, diabetes progresses through several clinical stages during its clinical history. It may present with characteristic symptoms or individuals may remain asymptomatic for a very long time. Consequently, diabetes is often diagnosed by an abnormal routine blood test and by then some complication has already set in.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized of hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia is associated with long-term damage, dysfunction and organ failure especially of eyes, kidneys, nerves, heart and blood vessels.

EPIDEMIOLOGY AND EVOLUTION

According to the findings of the Indian Council of Medical Research sponsored INDIAB study, published in 2011, India is faced with a galloping diabetes epidemic which is progressing at a speed which challenges the meanest and fastest on the Formula-1 circuit in a figurative sense. There are now an estimated 70 million patients with diabetes in India and this number is projected to explode beyond 100 million by the year 2030.

While diabetes in urban areas, with places like Cochin having figures in excess of 20% and Chennai at 17% (both cities in Southern India), the epidemic is sweeping across the sub-continent and engulfing rural areas as well, and across terrains which were previously

perceived as untouched. A study which had been done by our institution [Christian Medical College, Vellore (CMC), Tamil Nadu, India] and organized in rural Tripura, the first of its sort in the North East part of the country, adjacent to the Bangladesh border demonstrated that a part of rural Tripura had a prevalence of diabetes of 9%. This was in contrast to parts of Himachal Pradesh a state in the Northern part of the country south of the Kashmir Valley, which had a prevalence of 0.4% in the early 1990s.

The changing patterns of disease in a country which still has a major proportion of the population in rural areas may be predictors of stories which may foretell a gloomy future. The explosive growth of diabetes from across the country from the 1980s till now is essentially multifactorial. The many reasons for the problem would be included:

- *Cable television*: Indeed television usage really increased markedly in the year 1989, with the introduction of television through the cable TV network in India by the business magnate, Rupert Murdoch was one of the important drivers of the diabetes epidemic
- Economic liberalization in India in 1991, with a direction towards a more free market economy compared to a more socialistic one prior to that
- More processed food and high calorie density fast food at a cheaper rate, compared to healthier low calorie food. Hence, the socioeconomically deprived, may in fact have a greater propensity to develop weight gain through the food which they eat, rather than those who are well off. In other words certainly cheaper oils are abundantly and are not expensive compare to fresh fruits and vegetables
- The focus on academics rather than physical activities from a very early age as driven by the India school curricular system
- Increased life expectancy: It is currently 67 years for males now as opposed to 56 years in 1980 and 64 years for females, at the present point of time.

Asian Indian Phenotype and its Characterization

Besides epidemiological factors and changes in the demography, there is a baseline difference with regards to the physical habitus of the Asian Indian. The overall physical frame differs with a lower body mass index (BMI). Besides being shorter overall, there is a centripetal distribution of fat which is present. A number of studies have compared the Asian Indian phenotype by studying immigrant populations of Asian Indians with the white Caucasian and other ethnic groups in those countries. For the same BMI, the percentage body fat (BF) may be more than 7% higher for Asian Indian men compared to Europeans in the same population when measured by dual energy absorptiometry (DXA).

The ratio of abdominal fat to thigh fat, when adjusted for height, weight, and %BF, is generally significantly higher for Asian Indian men when compared to white Caucasian men (Fig. 2.1).

The differences in phenotype extend much beyond BMI—including high total body fat, high truncal, subcutaneous and intra-abdominal fat, and low muscle mass. The biochemical parameters which differ include more profound hyperinsulinemia, hyperglycemia, dyslipidemia, hyperleptinemia, lower levels of adiponectin and high levels of C-reactive protein, all these factors are associated with a procoagulant state and endothelial dysfunction.

The World Health Organization (WHO) has standardized the cutoff for obesity using data from across Asia and has laid down the guidelines for a lower BMI in this regard, and

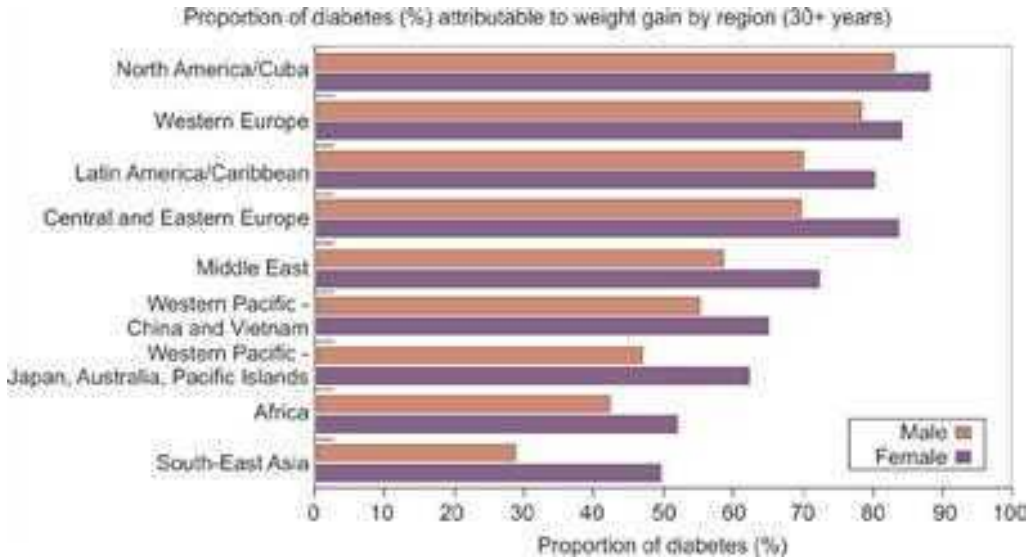


Fig. 2.1: Proportion of diabetes (%) attributable to weight gain (30+ years).

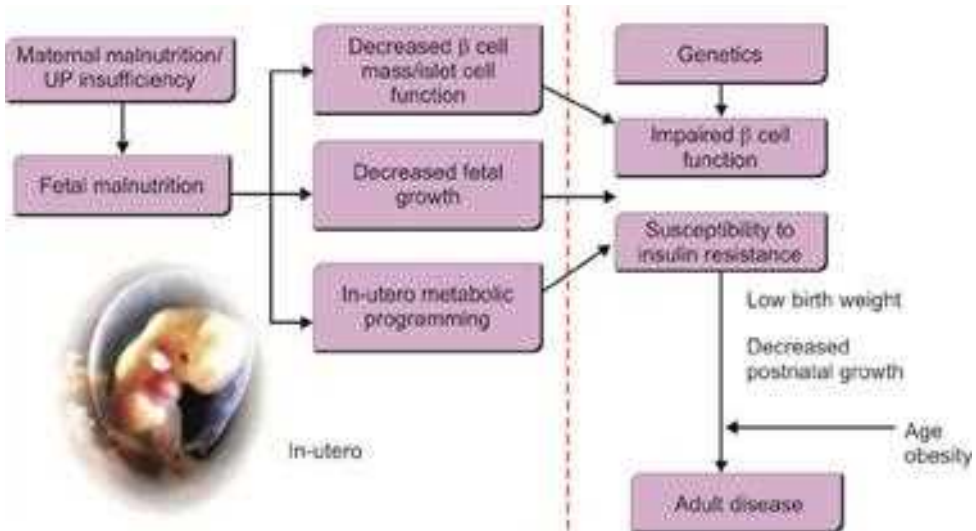
Source: International Diabetes Federation. Diabetes Atlas, 2nd edition, Executive Summary. Brussels: International Diabetes Federation; 2003.

there is clearly a shift to the left in terms of BMI in the Asian populations. The term “Asian” is sometimes used rather liberally, and applies in general to anyone from the Middle East to Japan. However, it is evident from the data that has been analyzed, that a significant shift to the left is present in terms of BMI as a risk for cardiovascular disease and diabetes in both the East Asian populations as well as in the South Asian populations (which comprise the Asian Indians as well). The difference in body composition is profound in terms of BF% leading to graphic illustrations as described in the Y-Y paradox case report, where in the relative quantity of total body fat may be double that seen in an Asian Indian versus a white Caucasian subject.

Beyond BMI (which in itself may not be the most suitable of criteria), the waist circumference (WC) may be a better index in itself as a more direct representation of intra-abdominal fat, and in general correlate with the cardiovascular endpoints. The WC has been convincingly established across the world from multicentric data analysis to be superior to BMI as a marker for cardiovascular risk and may therefore be used as a better correlate for identifying obesity in the Asian Indian phenotype than BMI. The increase in WC as a surrogate marker of intra-abdominal fat, indeed correlates well with a higher likelihood ratio of type 2 diabetes mellitus (T2DM) occurring in the Asian Indian population and this has been replicated well in a number of studies that have looked at the epidemiology of diabetes in India.

Thrifty Genotype versus Phenotype Hypotheses

In 1961, Neel et al. proposed that an individual’s adaptation to the environment was dependent on genes selected over a long period of time (thrifty genotype). In other words those genes

Flowchart 2.1: Sequence of maternal nutrition and its impact on the fetus.

that once favored survival in the presence of adverse environmental conditions, evolved to a status of being detrimental in circumstances of sustained energy surplus.

This theory was subsequently challenged by Hales and Barker who proposed that suboptimal fetal nutrition, at critical points of time in intrauterine development may cause permanent alterations in fetal structure, function, metabolism due to fetal programming (thrifty phenotype or fetal origins).

These theories are not mutually exclusive, but may complement one another, since the consequences of both theories are similar: adults are well adapted to an environment that is nutritionally limited, but are more likely to become unhealthy in a nutritionally rich environment.

The fetal insulin hypothesis (FIH) proposed by Hattersley states that genetic variants associated with insulin resistance may lead to impaired insulin-mediated growth prenatally, leading to low birth weight and adverse metabolic outcomes in adulthood. Thus, low birth weight is part of a syndrome that may be associated with in-utero insulin resistance which in turn may manifest with diabetes and hypertension at the time of adulthood (Flowchart 2.1).

PATHOGENESIS

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by the immune mediated destruction of the β -cells of the pancreas by T cells leading to absolute deficiency of Insulin. Multiple susceptibility genes that confer disease risk include the human leukocytic genes (HLA) at the major histocompatibility complex (MHC) loci and several non-HLA loci. Although, the exact etiology of T1DM remains unclear, evidences favor a

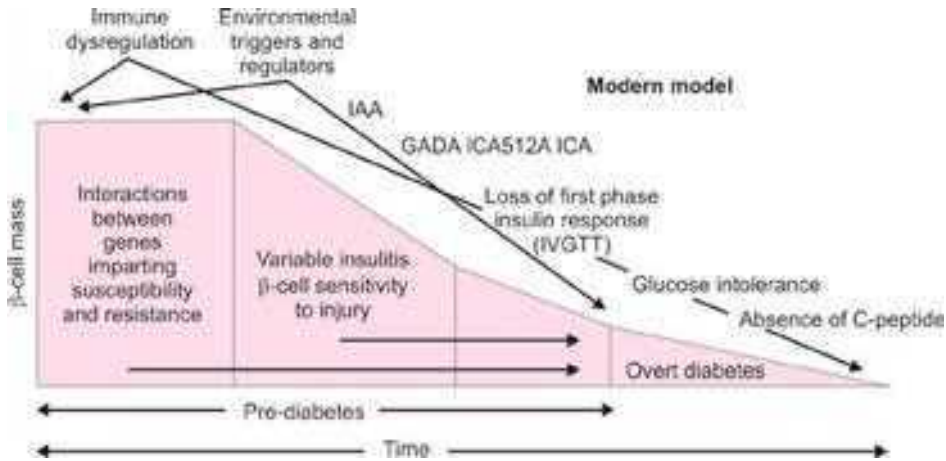


Fig. 2.2: Model of type 1 diabetes mellitus (T1DM) pathogenesis.

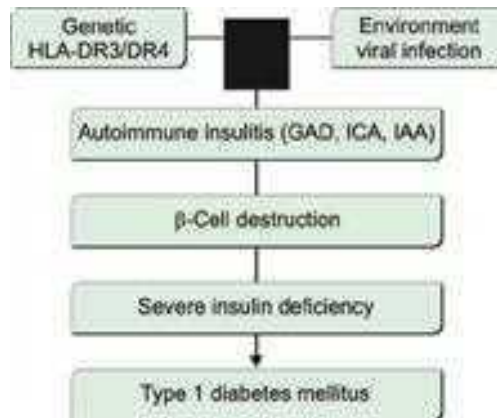
Source: Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. *BMJ*. 2004;328:750-4. (IAA: Insulin autoantibody; GADA: Glutamic acid decarboxylase antibodies; ICA: Islet cell antibodies; IVGTT: Intravenous glucose tolerance test).

complex interaction between genetic components and several environmental insults (virus, cow milk protein, etc.) in the disease causation (Fig. 2.2).

Genetically susceptible individuals when exposed to an environmental insult such as viruses (coxsackie, cytomegalovirus, rubella, and mumps) or dietary protein initiates a cascade of autoimmune events that eventually leads to selective destruction of pancreatic β -cells. Autoantibodies to glutamic acid decarboxylase-65 (GAD65), insulinoma antigen 2 (IA-2) and insulin autoantibody (IAA) appear in the serum of subjects as a response to underlying destructive process (and do not contribute to disease pathogenesis) even before the clinical onset of the disease. This is followed by cellular infiltration of the pancreas by monocytes, macrophages and T cells which initiate immune destruction. The hallmark of immune infiltration at this stage is referred to as “insulinitis”. Subsequent chronic destruction of the insulin producing cells brings about a stage of absolute insulin deficiency and at clinical presentation almost 60–70% of the pancreatic β -cells are destroyed (Flowchart. 2.2).

Genetic Factors

The genetic basis of T1DM is complex and more than 30 chromosomal loci have been linked to T1DM susceptibility, suggesting that T1DM is polygenic and implicated genes are risk modifiers. The HLA region has been proposed to account for about 40–50% of the genetic susceptibility and the HLA class II genes mediated susceptibility/protection is mediated through antigen presentation in the islets and by the development of central and peripheral tolerance. It is known that HLA-DQ association confers the strongest risk especially in individuals heterozygous for DQA1*501-DQB1*0201/DQA1*0301-DQB1*302 (encoding DQ2 and DQ8) haplotype, while protection from T1DM is conferred by DRB1*1501-DQA1*0102-DQB1*0602 haplotype. Besides, some of the non-DQ/DR genes have also shown

Flowchart. 2.2: Pathogenesis of type 1 diabetes.

(IAA: Insulin autoantibody; GAD: Glutamic acid decarboxylase; ICA: Islet cell antibodies; HLA: Human leukocytic genes).

Table 2.1: Candidate genes associated with type 1 diabetes mellitus (T1DM).

Gene	Position	Putative function
INS VNTR	11p15.5	Autoantigen/shaping of the T-cell repertoire in the thymus
CTLA4	2q33	Downregulation of the T-cell function and regulation of immune responses (IDDM 12)
PTPN22	1p13	Negative regulator of T-cell reactivity
CD4	12p12	Early phase of T-cell activation and clonal expansion
IRS-1	2q36	Part of insulin receptor
VDR	12q12-14	Vitamin D having immunoregulatory function

to be associated with T1DM risk. Candidate genes outside the HLA region reported to be associated with increased T1DM risk are given in Table 2.1.

Some genetic loci (CD3, TCR, IFNG, IL1B, IL1R1, IL10 and IL12B) have shown inconclusive risk modifying effect in T1DM susceptibility.

Autoimmunity

“Islet autoantibody” refers to antibodies that are directed against the islets of Langerhans in general and in some circumstances specifically against the autoantigens of the insulin producing β -cells. Islet autoantibodies appear prior to the onset of the disease and may persist for several years after the clinical presentation but with much lower titers. Therefore, autoantibodies appear to be good predictors of T1DM, although a minor proportion of individuals who are antibody positive do not develop diabetes. The list of islet antibodies and autoantigens till date has been many, but the most important include the GAD autoantibodies, IA2 associated protein, IAA and zinc transporter 8 (ZnT8) islet autoantibody. Other antibodies are difficult to measure and/or not sufficiently sensitive or specific markers in T1DM. Table 2.2 shows the salient features of the important antibodies in T1DM.

Table 2.2: Antibodies in type 1 diabetes mellitus (T1DM).

GAD	Exists in two isomeric forms GAD65 and GAD68, based on molecular weight Most persistent autoantibody and is also useful in the diagnosis of LADA Catalyzes the conversion of glutamic acid to the inhibitory neurotransmitter GABA (γ -amino butyric acid)
IA-2A	Member of the protein tyrosine phosphatase family and is a transmembrane protein Less common at T1DM onset Autoreactivity to the predominant c-terminal epitope of IA-2A is known as ICA512 autoantibodies
ICA	Detected in 70–80% individuals with T1DM First antibody to appear in T1DM Declines in few years after diagnosis and about less than 5% of individuals remain positive for longer periods Most difficult antibody to measure because ICA assays are subject to variations in pancreatic tissue, conjugate incubation time, etc. Reacts against sialoglyco conjugate, an insulinoma associated autoantigen
IAA	Is the only specific β -cell autoantibody Most common in the new onset young T1DM than adults IAA determinations in serum are no longer valid once insulin treatment is initiated in patients with T1DM Most difficult to accurately measure and reproduce
ZnT8A	Is a 369 AA, 6-transmembrane ZnT8 protein that concentrates Zn in insulin secretory granules The ZnT8 protein is encoded by SLC30A8 gene. Alleles of SLC30A8 have been shown to be also associated with T2DM

(IAA: Insulin autoantibody; GAD: Glutamic acid decarboxylase; ICA: Islet cell antibodies; T2DM: Type 2 diabetes mellitus; ZnT8: Zinc transporter 8; IA-2A: Insulinoma associated-2 autoantibodies; LADA: Latent autoimmune diabetes of adults).

Role of Islet Autoantibody Testing in Clinical Practice

Islet autoantibody testing in clinical practice may be important in the following situations:

- Diagnosis of autoimmune diabetes (T1DM and LADA)
 - Differentiating young onset T2DM from young T1DM
 - Acute onset ketotic or ketoacidotic diabetes in obese individual
 - Nonketotic diabetes in a lean individual
 - In conjunction with other antibody testing in polyglandular autoimmune disease
 - In conjunction with other coexisting conditions like celiac disease, Hashimoto's thyroiditis.
- It is important to note that differentiating autoimmune diabetes from other forms is critical in early initiation of insulin therapy to preserve β cell function and good glycemic control from early periods to delay the onset of microvascular complications.

Environmental Factors

Although there is little direct relationship between environmental factors and T1DM development, sufficient evidence have demonstrated the role of certain viruses and dietary factors in disease etiopathogenesis. Potential dietary triggers investigated include early exposure to cow's milk, gluten-containing diet, shorter duration of breast feeding and some food additives.

Viruses as an etiological trigger were suspected in view of coincidence between seasonally occurring T1DM and viral epidemics and presence of proinflammatory cytokine interferon alpha (IFN- α) only in T1DM subjects prior to viral infections. The strongest evidence was for rubella infection, where direct destruction of β -cells has been reported. Other viruses reported in T1DM trigger include coxsackie and certain enteroviruses.

Type 2 Diabetes Mellitus

It is one of the leading health problems of the world and its prevalence has risen dramatically over the years due to the increased calorie consumption and sedentary life-style. The imbalance between energy intake and expenditure is the most important underlying pathology and is regulated by complex interaction between multiple genes and environmental factors. The disease is most often suspected to be due to defects both at the level of insulin resistance and insulin secretion.

Genetic Factors

The heritability of T2DM is high (estimated to be >50%) and provides evidence to the genetic risk associated with T2DM. However, only 10% of the heritability can be attributed to the genetic loci discovered so far, because most of this loci display very low effect size. Approximately 30 loci have been identified to be associated with diabetes related traits. Of these, TCF7L2 is the strongest susceptibility locus associated with β -cell dysfunction. Other robustly associated loci include the non-synonymous variants in the PPARG and KCNJ11 genes. A concise list of important genetic variants and their putative function is listed in the Table 2.3. Studies on the risk variants of T2DM in healthy population have demonstrated that these variants act through perturbation of insulin secretion rather than insulin action.

Environmental Factors

Lifestyle: The major precipitating factor is environment and high calorie food intake with sedentary lifestyle has been indisputably linked to development of obesity and T2DM. Dietary culprits chiefly include processed, energy-dense foods characterized by high sugar and fat. Micronutrient imbalances that include intake of diet low in Vitamin D, Vitamin B12 and increased body iron stores have also been implicated in the pathogenesis of T2DM. The lack of physical activity due to increased preference to access motorized transport, escalators and elevators; professions which entail little physical activity and a sedentary posturing increase T2DM risk. Other environmental factors such as sleep deprivation, socioeconomic status has also shown to have a bearing on development of T2DM.

Fetal and Neonatal Programming/Epigenetic Effects

Fetal and neonatal programming has shown to have important implications in the development of adult disease. There are strong evidences that provide a link between intrauterine growth restriction and adult disease such as obesity, hypertension, T2DM and cardiovascular disease. An inverse relationship is found between birth weight and adult T2DM suggesting

Table 2.3: Candidate genes in type 2 diabetes mellitus (T2DM).

<i>Locus</i>	<i>Gene name</i>	<i>Association</i>	<i>Putative function</i>
PPARG	Peroxisome proliferator-activated receptor γ	T2DM	A
KCNJ11	Potassium inwardly reflecting channel, subfamily J, member 11	T2DM	A
TCF7L2	Transcription factor 7-like 2	T2DM, glucose and HbA1c levels	A
HNF1	HNF1 homeobox	T2DM	A
WFS1	Wolfram syndrome 1	T2DM	A
FTO	Fat mass and obesity associated	T2DM, BMI	IR
HHEX/ IDE/KIF11	Homeobox, hematopoietically expressed/ insulin degrading enzyme/kinesin-interacting factor 11	T2DM	A
CDKAL1	CDk5 regulatory subunit associated protein 1-like 1	T2DM	A
IGFBP2	Insulin-like growth factor binding protein-2	T2DM	A
KCNQ1	Potassium voltage gated channel, KQT-like subfamily, member 1	T2DM	A
IRS1	Insulin receptor substrate 1	T2DM	IR
MTNR1B	Melatonin receptor 1B	T2DM, glucose and HbA1c levels and HOMA- β	A, B
GCK	Glucokinase	T2DM, glucose, HOMA- β HbA1C	C
ADCY5	Adenylate cyclase 5	T2DM, glucose, HOMA- β HbA1c	B
IGF1	Insulin-like growth factor	Insulin, HOMA-IR	IR

A: Role in β -cell development, β -cell function and insulin secretion

B: Role in regulation of circadian rhythm

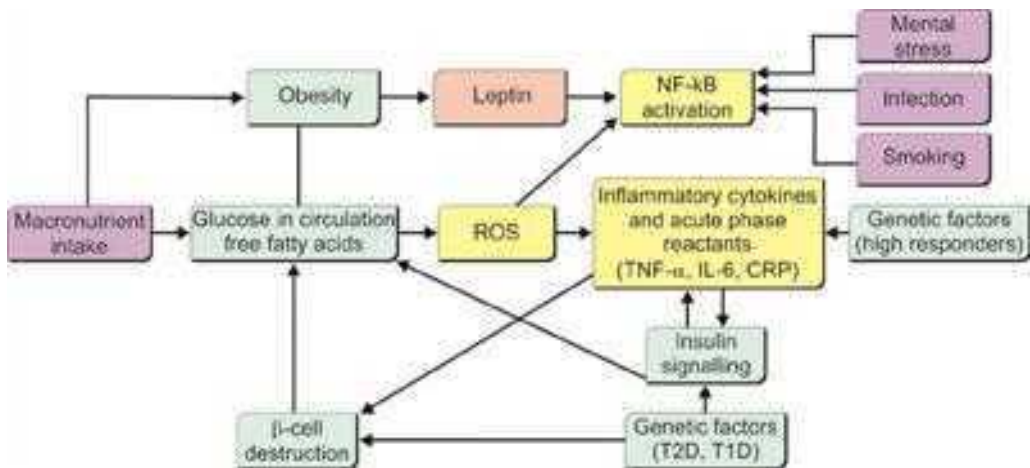
C: Role in glucose sensing

IR: Role in Insulin resistance

(BMI: Body mass index; HbA1c: Glycosylated hemoglobin; HOMA: Homeostatic model assessment).

that fetal undernutrition might be important in the etiology of T2DM. Thinness at birth and in adult life have opposing effects on insulin resistance, such that subjects who were underweight at birth and become overweight in middle age have a greater risk for T2DM. Low birth weight, by multiple mechanisms may lead to a greater propensity for T2DM, later in life which includes both insulin resistance as well as insulin secretory defects. This could be due to increased peripheral insulin resistance, especially in muscles and reduced hepatic insulin sensitivity. Additionally defects in glucose transporter type 4 (GLUT-4) and insulin secretion have been identified in those born low birth weight. A secretory defect in the β -cell may be present from a fairly early point of time in life.

Vitamin B12 deficiency during pregnancy, particularly in women replete for folic acid have been shown in some situations, to give birth to offspring who develop childhood adiposity and insulin resistance in adulthood.

Flowchart. 2.3: Role of genetic factors, obesity and inflammation in diabetes.

Source: Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol.* 2004;25:4-7.

(ROS: Reactive oxygen species; NF-κB: Nuclear factor-kappaB; CRP: C-reactive protein; TNF: Tumor necrosis factor; IL: Interleukin; T1D: Type 1 diabetes; T2D: Type 2 diabetes).

Higher birth weight (> 4.0 kg) in the presence of maternal diabetes, may also be associated with an increased risk of diabetes. Children born prematurely, irrespective of their birth weight, may be at increased risk for type 2 diabetes and other diseases of adulthood associated with insulin resistance.

Role of Obesity and Inflammation

Plasma concentrations of inflammatory mediators such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) are increased in insulin resistant states such as obesity and T2DM. Two mechanisms are possibly involved in this inflammatory state—(1) glucose and macronutrient intake causes oxidative stress and inflammatory changes. Chronic overnutrition in obesity may thus be a proinflammatory state with oxidative stress; (2) the increased inflammatory mediators might interfere with insulin action by suppressing insulin signal transduction, in turn inhibiting the anti-inflammatory effect of insulin. Other inflammatory markers that are increased in plasma include C-reactive protein (CRP) and PAI-1.

Macronutrient intake causes induction of reactive oxygen species (ROS) and inflammation. This occurs in obesity due to increased free fatty acids and leptin. Infection, smoking and stress can also induce inflammation in genetically susceptible individuals. The induction interferes with insulin signaling resulting in hyperglycemia and proinflammatory changes leading to release of TNF- α , IL-6 and inhibition of insulin signaling. Inflammation in the β -cells leads to β -cell dysfunction which in combination with insulin resistance causes T2DM (Flowchart 2.3).

Other forms of diabetes such as lipodystrophic diabetes are covered in greater detail in the Chapter on “Secondary Diabetes and Other forms of Diabetes”.

PART B: CLASSIFICATION AND APPROACH

Nihal Thomas, Senthil Vasan K

CLASSIFICATION

The vast majority of cases of diabetes fall into two broad etiopathogenetic categories:

1. Type 1 diabetes mellitus (T1DM): Absolute deficiency of insulin secretion
2. Type 2 diabetes mellitus (T2DM): Combination of insulin resistance and inadequate compensatory insulin secretory response (relative insulin deficiency).

Diabetes can also develop secondary to other causes like genetic defects in beta cell function, genetic defects in insulin action and diseases of the exocrine pancreas or intake of certain drugs (Table 2.4).

Table 2.4: Etiological classification of diabetes.

I. Type 1 diabetes mellitus	
A. Immune mediated	
B. Idiopathic	
II. Type 2 diabetes mellitus	
III. Other specific types	
A. Genetic defects in beta cell function -	MODY type 1 to type 6 Mitochondrial diabetes
B. Genetic defects in Insulin action -	Type A Insulin resistance
	- Lipotrophic diabetes
C. Pancreatic diseases -	Fibrocalcific pancreatitis
	Pancreatectomy
	Cystic fibrosis
D. Endocrinopathies -	Acromegaly
	Cushing's syndrome
	Pheochromocytoma
	Hyperthyroidism
E. Drug induced -	Glucocorticoids
	Thyroid hormone
	Diazoxide
	Thiazides
	Dilantin
	Vacor, Pentamidine, Olanzapine, Rifampicin
F. Infections -	Congenital Rubella
	Cytomegalovirus
	Mumps
G. Uncommon forms of immune mediated diabetes -	"Stiff-man" syndrome
	Anti-insulin receptor antibodies
H. Genetic syndrome association -	Down's syndrome
	Turner's syndrome
	Klinefelter's syndrome
	Myotonic dystrophy
	Prader-Willi syndrome
IV. Gestational Diabetes	

(MODY: Maturity onset diabetes of the young).

The degree of hyperglycemia may change over time, depending on the extent of the underlying disease process.

HISTORY TAKING IN DIABETES

Demographic Data

It is essential to capture demographic details of all diabetic patients not only to facilitate good doctor patient interactions but also to make meticulous therapeutic decisions. It is important to know the correct age of the patient to be able to define the type of diabetes that the patient might have and also to identify future high risk periods like pregnancy and puberty. The working schedule and occupation is important to know the feasible dietary patterns and flexibility required in suggesting optimal therapeutic options, which the patient can follow without major inconvenience. This enables long-term compliance to both lifestyle and medications. It is essential to know the monthly income of the patient, to make certain the compliance to medications, as diabetic therapies could range from very negligible cost to huge sum of money per day. Moreover most of these medicines need to be continued on a long-term basis and hence need to fit the patient's pocket.

Chief Complaints

To ensure best patient's satisfaction it is important to address the prime reason that brought the patient to the hospital. As in addition to managing all other aspects of diabetes to the possible extent, if these primary issues are not addressed the patient shall not be satisfied. Many a times these are problems arising from poor glycemic control.

Diabetic History

It is of prime importance to know the duration of diabetes in every patient since this would indirectly reflect the extent and severity of disease process. This may also predict the extent of underlying diabetic complications that a particular patient may need to be screened for.

The history of diabetes begins from its inception. Though many a times it may not be possible to know the exact time of onset of diabetes, however the time of its first clinical detection is often an important indicator. The initial presenting symptoms and the initial glucose values also predict the severity of disease at that point and predict long-term cardiovascular outcomes.

Other etiological history like weight at the onset of diabetes, past history of diabetic ketoacidosis, response to prior medications, associated abdominal pain and steatorrhea may further characterize the type of diabetes. It is also essential to have a high index of suspicion for any features to indicate secondary diabetes, most of which are often curable.

It is imperative to note the current list of diabetic and nondiabetic medications and their compliance from all patients, as that would suggest the dose-response relation of these drugs to the present glucose values. If the patient is on insulin it becomes critical to inquire about the site, storage and technique of administration as that many a time may be the main reason for glycemic excursions in these patients.

It is also vital to find out the frequency and method of glucose monitoring and the type of control achieved over the past few months, in all patients with diabetes. This apart from glycemic control also displays patients' attitude, knowledge and seriousness towards the disease. All patients should be explored for probable hypoglycemic episodes that they may have experienced in the past. If so, we should further probe on the timing, precipitating event and recovery measures taken, to avoid further such episodes.

A detailed dietary history is indispensable in patients with diabetes. A detailed dietary recall and calorie intake is necessary to analyze prior to prescribing any medication. It is also imperative to know the total number of meals and snacks taken in a day. An approximate dietary calcium intake is also important in patients with diabetes especially those who have additional risk factors for fractures.

The type and duration of exercise and its frequency per week is obligatory to be determined. The timings of medications and exercise schedule should be planned with the help of this information.

Symptoms related to microvascular complications as enumerated in specific chapters should be assessed historically. In addition, the effect of these complications on the quality of life is more vital as accordingly the priority of management should be outlined.

Past history of macrovascular complications like coronary artery disease and cerebrovascular disease should be asked. However, symptoms like angina and transient ischemic attacks are often pointers of more fatal complications in future, which may be preventable.

Peripheral vascular disease should be evaluated by symptoms of claudication. These should differentiate from symptoms of neuropathic pain as covered in the chapter of diabetic foot. A detailed history of autonomic symptoms is also important, as they often hinder day to day normal functioning and require appropriate management.

To know past history of infective complications in patients with diabetes is also of paramount importance, as urinary tract and lower respiratory tract infections are the leading cause of death in developing countries in these individuals. Also history of associated disorders like hypertension, dyslipidemia and obesity should be inquired in all patients due to the similar pathogenesis in most such disorders.

Past Medical and Surgical History

Any other significant past medical and surgical history always provides a comprehensive picture of all other problems in a patient as whole and would always require an appropriate management or referral to provide complete medical treatment.

Family and Personal History

To know a detailed family history, covered up to three generations is almost indispensable in all patients with diabetes. Not only to know the members affected with diabetes, but also the age of onset of diabetes in them may provide a clue to the etiological diagnosis. At last a brief personal and socioeconomic history should also be asked to all patients, as many a time the compliance of therapy may be dependent on several such issues. In women, menstrual and obstetric history also can be used as a marker of general health and may indirectly reflect the control of diabetes.

DIAGNOSIS OF DIABETES MELLITUS

Diagnosis of diabetes is based upon plasma glucose levels. Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day. The 75 g oral glucose tolerance test (OGTT) is more sensitive and modestly more specific than fasting plasma glucose (FPG) in the diagnosis of diabetes, but is poorly reproducible. Because of its ease, patient acceptability and lower cost, measurement of FPG is the preferred diagnostic test. The use of the hemoglobin A1c (glycosylated hemoglobin or HbA1c) for the diagnosis of diabetes was previously not recommended due to lack of global standardization and uncertainty about diagnostic thresholds. Presently, because of a worldwide move towards a standardized assay and with increasing evidence about the prognostic significance of HbA1c, it is included as a diagnostic test in the 2011 American Diabetes Association (ADA) guidelines (Box 2.1).

CONCEPT OF PREDIABETES

The evolution of T2DM follows through different stages as shown in the Figure 2.3. Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are the fore-runners of future T2DM (collectively termed as prediabetes). These states include a proportion of people who belong to the intermediate group of subjects whose glucose levels, although do not meet the criteria for diabetes are nevertheless too high to be considered normal. These patients may develop diabetes in future if their glycemic status is not maintained by modification of lifestyle (Fig. 2.3).

The significance of impaired fasting glycemia and IGT

- Increased risk for cardiovascular/cerebrovascular diseases
- Predictor of subsequent diabetes mellitus
- Diabetic range values may be unmasked with stress.

Box 2.1: Criteria for diagnosis of diabetes mellitus.

- HbA1c \geq 6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay
OR
- Fasting \geq 126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours
OR
- 2-hr plasma glucose \geq 200 mg/dL during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water*
OR
- Symptoms of hyperglycemia and a casual plasma glucose \geq 200 mg/dL. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss

(NGSP: National glycohemoglobin standardization program; DCCT: Diabetes control and complications trial; OGTT: Oral glucose tolerance test).

*In the absence of unequivocal hyperglycemia, the first three criteria should be confirmed by repeat testing on a different day.

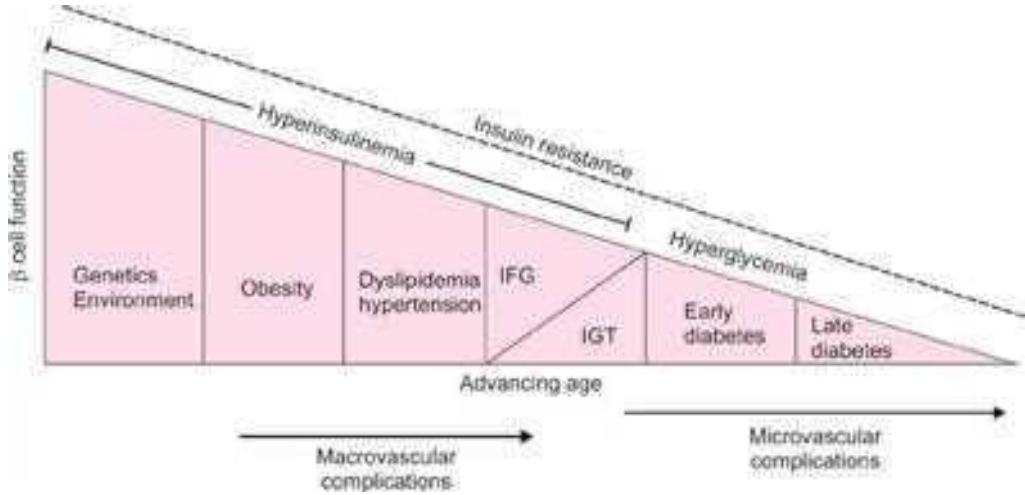


Fig. 2.3: Natural history of type 2 diabetes: Disease evolution.

Table 2.5: Diagnosis of IFG and IGT based on International Diabetes Federation criteria.

	Plasma (mg/dL)	Venous whole blood (mg/dL)	Capillary whole blood (mg/dL)
Impaired fasting glucose			
Fasting glucose	110–125	100–109	100–109
2 hour postglucose load	< 140	< 120	< 140
Impaired glucose tolerance			
Fasting glucose	<126	<110	<110
2 hour postglucose load	140–199	120–179	140–199

Diagnosis of Impaired Fasting Glycemia and Impaired Glucose Tolerance

The diagnosis of IFG and IGT based on International Diabetes Federation (IDF) criteria is given in Table 2.5.

CONCEPT OF “THE METABOLIC SYNDROME”

The metabolic syndrome also referred to as syndrome X or insulin resistance syndrome refers to a cluster of cardiovascular disease risk factors and metabolic alterations associated with excess body fat.

Even though there are different definitions the following are central to the diagnosis—abdominal obesity, dyslipidemia, hypertension and glucose intolerance or diabetes. Insulin resistance and accompanying hyperinsulinemia is said to play a central role in the pathogenesis of the syndrome with a casual relationship to hypertension. This may be due to the effects

of insulin in the periphery on vasculature as well as a central action leading to stimulation of sympathetic activity and in turn the renin-angiotensin-aldosterone system.

A new joint statement from a number of professional organizations on October 12, 2009 has identified specific criteria for the clinical diagnosis of the metabolic syndrome, tightening up the definition, which previously differed from one organization to the next. The statement, published online on October 5, 2009 in circulation, includes the participation of the International Diabetes Federation (IDF), the National Heart, Lung and Blood Institute (NHLBI), the World Heart Federation, the International Atherosclerosis Society and the American Heart Association (AHA) and is an attempt to eliminate some of the confusion regarding how to identify patients with the syndrome.

The problem that still exists is that regional differences around the world may be substantial in terms of what waist circumference (WC) confers additional risk for heart disease and diabetes. The new definition relies on different geographic regions, or different countries, to drill down into their own databases in terms of relating WC to risk. It is to be noted that the IDF previously considered elevations in WC mandatory when defining metabolic syndrome, although the ATP III did not. Now, WC is just one of five criteria that physicians can use when diagnosing the metabolic syndrome. Patients with three of the five criteria—including elevated waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL)-cholesterol levels, elevated blood pressure, and elevated fasting-glucose levels are considered to have the syndrome (Fig. 2.4 and Table 2.6).

Clinical Context

The metabolic syndrome has received significant attention because of its role in disease. In general, patients with this syndrome exhibit a proinflammatory state and in addition to high serum levels of triglycerides and low levels of HDL cholesterol, they tend to have high levels of apolipoprotein B and elevations in small low-density lipoprotein (LDL) particles. All of these factors contribute to doubling the risk for incident cardiovascular disease within 5–10 years as well as a five-fold increase in the risk for incident type 2 diabetes.

Despite the importance of the metabolic syndrome as a risk marker, there remains disagreement regarding the best way to define it. The current scientific statement attempts to clarify the definition of metabolic syndrome and identifies possible future refinements to this definition.

Study Highlights

- The primary factors used to define the metabolic syndrome have been atherogenic dyslipidemia, elevated blood pressure, and elevated blood glucose levels.
- Whereas some criteria for metabolic syndrome excluded patients with existing type 2 diabetes, current recommendations do not.
- The most significant controversy regarding the definition of the metabolic syndrome has been the inclusion of abdominal obesity. It has been required in some recommendations to diagnose the metabolic syndrome, whereas it has served as a nonintegral variable in the diagnosis in other algorithms.

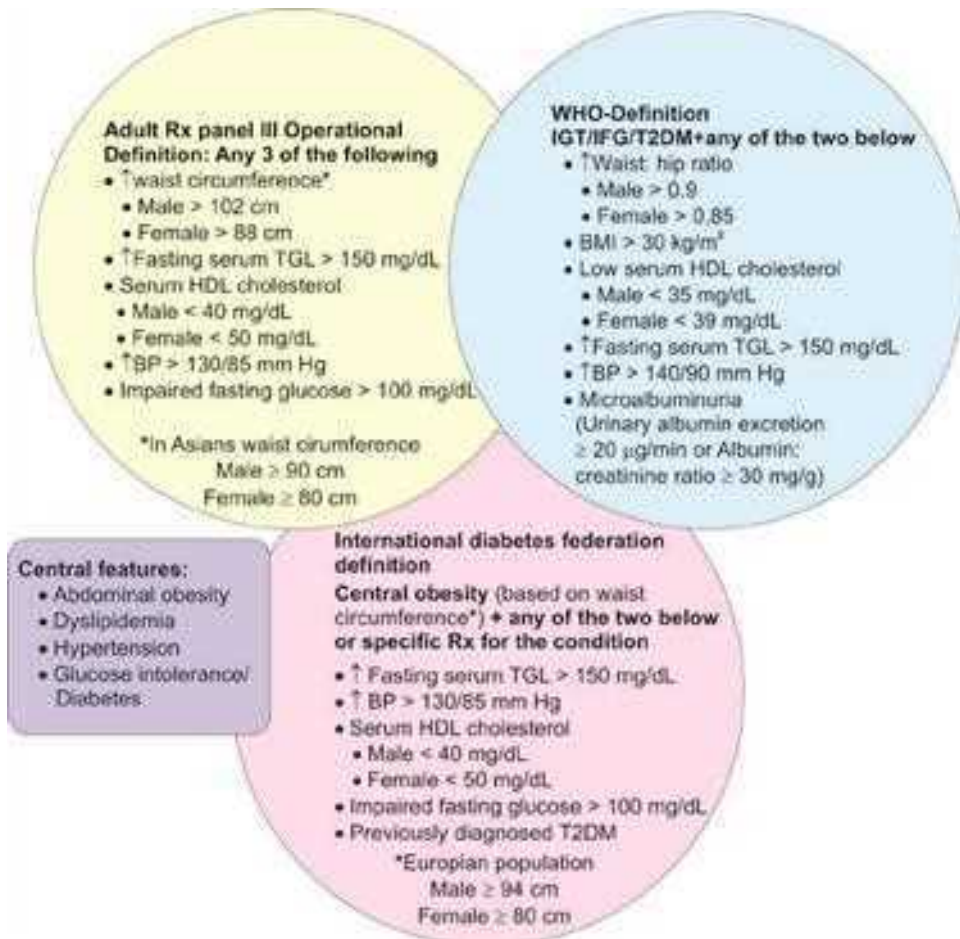


Fig. 2.4: Different definitions of metabolic syndrome.

(TGL: Triglycerides; HDL: High-density lipoprotein; BP: Blood pressure; IGT: Impaired glucose tolerance; IFG: Impaired fasting glucose; T2DM: Type 2 diabetes mellitus; BMI: Body mass index).

Table 2.6: Criteria for clinical diagnosis of the metabolic syndrome.

Measure	Categorical cut points
Elevated waist circumference	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	> 150 mg/dL
Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)	< 40 mg/dL for males and < 50 mg/dL for females
Elevated blood pressure (drug treatment for elevated blood pressure is an alternate indicator)	Systolic >130 mm Hg and/or diastolic >85 mm Hg
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	>100 mg/dL

(HDL: High-density lipoprotein).

- Moreover, the definition of abdominal obesity is challenging. Predictive values for various levels of abdominal obesity for cardiovascular disease and diabetes may differ. Different health systems may define abdominal obesity based on more strict or loose criteria to satisfy pragmatic public health or economic concerns.
- Most important, the WC threshold for abdominal obesity varies according to sex and ethnic group. For example, the World Health Organization cutoff values for abdominal obesity for Caucasians are 94 cm or more and 80 cm or more for men and women, respectively. Their respective cutoff values for Asian men and women are 90 cm and 80 cm, and the Japanese Obesity Society defines its respective cutoff values at 85 cm and 90 cm.
- The population-specific method of defining abdominal obesity is also limited by a lack of information from large regions, including the Middle East and Africa.
- At the same time, the use of common diagnostic thresholds across international borders and types of patients will make the diagnosis of metabolic syndrome easier to understand and treat.
- Using recommendations from the different organizations, the authors of the current scientific statement therefore recommend five specific criteria and categorical cutoff points to diagnose metabolic syndrome. Patients with at least three of these five criteria may be considered to have the diagnosis. The criteria are as follows:
 - Elevated triglyceride levels or drug treatment of these elevated levels [≥ 150 mg/dL (≥ 1.7 mmol/L)]
 - Reduced HDL cholesterol levels or drug treatment of these reduced levels [< 40 mg/dL (1.0 mmol/L) in men; < 50 mg/dL (1.3 mmol/L) in women]
 - Elevated blood pressure or treatment of hypertension (systolic 130 mm Hg and/or diastolic ≥ 85 mm Hg)
 - Elevated fasting glucose levels or treatment with antihyperglycemic medications (≥ 100 mg/dL)
 - Elevated WC (population and country-specific definitions)
 - New data should emerge, which may help to determine a standard definition for elevated WC and additional meetings between lead organizations will focus on the development of a single set of diagnostic criteria for metabolic syndrome.

Clinical Implications

The metabolic syndrome is associated with high levels of apolipoprotein B and increases in small LDL particles as well as a two-fold increase in the risk for incident cardiovascular disease and a five-fold increase in the risk for incident type 2 diabetes

The current international guidelines set cutoff points for four of the five criteria that contribute to the diagnosis of metabolic syndrome, but the variability of WC based on sex and race makes a uniform definition for abdominal obesity difficult.

SCREENING FOR DIABETES

The following are the ADA guidelines to select asymptomatic adult individuals who will need testing for prediabetes and diabetes.

1. Testing should be considered in all adults who are overweight [body mass index (BMI) $\geq 25 \text{ kg/m}^2$] and have additional risk factors:
 - A. Physical inactivity
 - B. First-degree relative with diabetes
 - C. Members of a high-risk ethnic population (e.g. African American, Latino, Native American, Asian American, Pacific Islander)
 - D. Women who delivered a baby weighing $>4 \text{ kg}$ or were diagnosed with gestational diabetes mellitus (GDM)
 - E. Hypertension ($\geq 140/90 \text{ mm Hg}$ or on therapy for hypertension)
 - F. HDL cholesterol level $<35 \text{ mg/dL}$ (0.90 mmol/L) and/or a triglyceride level $>250 \text{ mg/dL}$ (2.82 mmol/L)
 - G. Women with polycystic ovarian syndrome (PCOS)
 - H. IGT or IFG on previous testing
 - I. Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)
 - J. History of cardiovascular disease.
2. In the absence of the above criteria, testing for prediabetes and diabetes should begin at the age of 45 years.
3. If results are normal, testing should be repeated at least at 3 year intervals, with consideration of more frequent testing depending on initial results and risk status.

SUMMARY OF RECOMMENDATIONS FOR ADULTS WITH DIABETES

Glycemic Control Targets

- HbA1c: $<6.5\%$
- Fasting glucose: $70\text{--}130 \text{ mg/dL}$
- Postprandial glucose: $<180 \text{ mg/dL}$
- Blood pressure: $<130/80 \text{ mm Hg}$

Lipids

- LDL cholesterol: $<100 \text{ mg/dL}$ ($<70 \text{ mg/dL}$ in patients with overt cardiovascular disease)
- Triglycerides: $<150 \text{ mg/dL}$
- HDL cholesterol: $>40 \text{ mg/dL}$ (men), $>50 \text{ mg/dL}$ (women)

Key Concepts in Setting Glycemic Goals

- Goals should be individualized based on duration of diabetes, age, life expectancy, known heart disease, advanced microvascular complications and hypoglycemia unawareness
- HbA1c is a primary target for glycemic control
- Certain group of people like children, pregnant women and elderly require special considerations

- More stringent glycemic goals (i.e. HbA1c <6%) may further reduce complications at the cost of increased risk of hypoglycemia especially in T1DM
- Postprandial glucose may be targeted if HbA1c goals are not met despite reaching preprandial glucose goals
- More recently some studies suggest that the elderly may have a poorer cardiovascular outcome with tight glycemic control (Hb <7%). However this evidence has not been supported by all studies.

GLYCOSYLATED HEMOGLOBIN

Glycation refers to nonenzymatic addition of a sugar residue to an amino group of a protein. Hemoglobin, plasma proteins, membrane proteins, lens protein, etc. may undergo glycosylation. HbA1c forms the major fraction (80%). In HbA1C, the N-terminal valine residue of each beta chain gets glycated.

HbA1c gives a retrospective index of integrated plasma glucose values over a 6–8 weeks period and is not subject to wide fluctuations in plasma glucose levels (Table 2.7). HbA1c serves as a reliable indicator of diabetes control during the past 90 days, effectiveness of treatment and risk of development of acute or long-term complications. Hence HbA1c should be performed routinely in all patients with diabetes, to assess the degree of glycemic control at initial visit and then as a part of continuing visits every three months to assess metabolic control.

Normal HbA1c values and interpretation:

- Normal nondiabetic range: 4.5–5.8%
- Serious risk of hypoglycemia: < 4.5
- Diabetic range: > 6.5%
- Prediabetic range: 5.8–6.5%

There are some conditions which may lead to a false elevation or reduction in HbA1c levels. Hemoglobinopathies like thalassemia, hereditary persistence of fetal hemoglobin, a low hemoglobin level per se (<7.0 g/dL) and uremia are known to cause altered levels of HbA1c. More recently there are consensus guidelines being developed to predict the risk of

Table 2.7: Approximate correlation between glycosylated hemoglobin (HbA1c) and mean plasma glucose levels.

<i>HbA1c%</i>	<i>Mean plasma glucose (mg/dL)</i>
5	97
6	126
7	154
8	183
9	212
10	240
11	269
12	298

Table 2.8: Follow-up of patients and frequency of testing.

<i>Tests</i>	<i>Time to visit</i>
Blood glucose	- Controlled (HbA1c < 7%)—every 3 months - Uncontrolled—every 2 weeks until target sugars achieved
HbA1c	- Controlled (HbA1c < 7%)—6 months to 1 year - Uncontrolled—every 3 months
Tests for neuropathy	
Monofilament	- Annual
Biothesiometer	- Annual
Foot examination	- Once in 3 months
Test for retinopathy	
Fundus examination	- Annually. If evidence of retinopathy detected at first visit, follow-up every 3–6 months
Tests for nephropathy	
Urinary microalbumin (or 24 hours urinary protein)	- Annual
Serum creatinine	- Annual
Miscellaneous tests	
ECG	- Annual
Treadmill test	- By 5 years after onset of diabetes mellitus, then once in 2 years
Lipid profile	- annual. If abnormal every 6 months
Plain X-ray abdomen	- If BMI < 20 kg/m ² Or USG abdomen

(BMI: Body mass index; USG: Ultrasonography; ECG: Electrocardiography; HbA1c: Glycosylated hemoglobin).

diabetes with HbA1c. HbA1c criteria for identifying patients with impaired glucose regulation were derived using data from the National Health and Nutrition Survey, 2005–2006. Compared with other cut points, a HbA1c cut point of 5.7% had the best sensitivity (39%) and specificity (91%) for identifying cases of IFG (FPG \geq 100 mg/dL). The expert committee has also suggested that patients with HbA1c levels between 5.7% and 6.4% are at high risk and should receive proven preventive interventions (Table 2.8).

Individuals with diabetes mellitus would have periodic assessment of this glycemic status, and also screening for the micro- and macrovascular complications of diabetes. A model diabetes case record is shown in Appendix 2.1.

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SELF-ASSESSMENT

1. **Regarding anthropometric measurements in relation to obesity, which of the following are least likely to be true:**
 - (a) Body mass index less than 23 kg/m² indicates malnutrition
 - (b) Body mass index more than 40 kg/m² indicates morbid obesity
 - (c) Body mass index more than 27 kg/m² in males indicates overweight
 - (d) Waist-hip ratio in males more than 0.9 is abnormal
 - (e) Waist-hip ratio more than 0.85 in females is abnormal
2. **A 39 year-old man presents with the following profile: BMI: 26 kg/m², AC: 120 mg/dL, PC 160 mg/dL, Total Cholesterol: 240 mg/dL, LDL Cholesterol: 140 mg/dL, HDL Cholesterol: 50 mg/dL. Which of the following is not true?**
 - (a) He has impaired glucose tolerance
 - (b) He has an increased coronary vascular risk
 - (c) He does not have an increased cerebrovascular risk
 - (d) There is a component of impaired fasting glycemia
 - (e) Smoking would enhance coronary vascular risk whether it was present or not in this patient
3. **From the earlier case which of the following is false?**
 - (a) Impaired fasting glycemia could include plasma glucose of 116 mg/dL
 - (b) Impaired glucose tolerance could include postprandial plasma glucose of 180 mg/dL
 - (c) Type 2 diabetes could be present with FPG of 200 mg/dL without ketosis
 - (d) Type 1 diabetes could be present with FPG of 220 mg/dL with ketosis
 - (e) A systolic BP of 142 mm Hg is acceptable in a patient with diabetes mellitus
4. **36-years-old Mr R who had his blood glucose levels checked since he had a family history of diabetes. BMI: 31 kg/m², FPG: 118 mg%, 2-hr PPPG: 155 mg. What is the diagnosis?**

(a) IGT	(b) LADA
(c) T1DM	(d) T2DM
5. **A 20-years-old gentleman was diagnosed to have diabetes on pre-employment check-up. He was born of nonconsanguineous marriage. His mother and maternal grandfather were having diabetes. His BMI was 21 kg/m², BP is 120/80 mm Hg. What is the diagnosis?**

- (a) MODY (b) LADA
(c) T1DM (d) Secondary diabetes

6. 39-years-old Mr Al was diagnosed to have diabetes. Polyuria and weight loss in previous 4 months. No recurrent abdominal pain/steatorrhea. Urine ketones: negative glycemic control for first 1 year achieved with OHAs. She required insulin thereafter. GAD antibodies were positive BMI: 20 kg/m². What is the type of diabetes?

- (a) MODY (b) LADA
(c) T1DM (d) Secondary diabetes

7. Which of the following is not a component of metabolic syndrome:

- (a) High LDL (b) High triglycerides
(c) Impaired glucose tolerance (d) Microalbuminuria

8. The typical dyslipidemia in metabolic syndrome is:

- (a) Increased HDL, Decreased TG, Normal LDL
(b) Increased TG, Decreased HDL, Normal LDL
(c) Increased LDL, Decreased HDL, Normal TG
(d) Increased TG, Increased LDL, Normal HDL

9. The type of diabetes with autosomal dominant transmission is:

- (a) MODY (b) Glucocorticoid induced diabetes
(c) Type 2 diabetes mellitus (d) Type 1 diabetes mellitus

10. The current cutoff of blood sugar for diagnosis of diabetes mellitus is based on:

- (a) Mean \pm 2SD of normal population
(b) Blood sugar levels above which prevalence of retinopathy increases
(c) Blood sugar levels above which prevalence of microvascular diseases increases
(d) Blood sugars associated with poor prognosis in fetuses of pregnant mothers.

CHAPTER

3

Practical Medical Nutritional Therapy

Leepica Kapoor, G Sai Mala

*“Food! Glorious food! Eat too much and suffer
Carbs to be counted, take a bit of fiber
Balance your diet with greens from the racks
Avoid oil; ensure—three meals and three snacks”*

The most challenging part of medical nutrition therapy in diabetes is that it does not go in line with the “one-size-fits-all” eating pattern for individuals with diabetes. The diet has to be individualized as per the patient’s specific nutritional needs engaging them in self-management of a healthy eating pattern and physical activity. Nutrition therapy is recommended for all individuals with diabetes as a necessary component of the overall treatment plan.

GOALS OF NUTRITION THERAPY

- To promote the nutritional status through consumption of nutrient dense foods in appropriate portion sizes specifically to attain individualized glycemic goals based on age, history of diabetes, health and other present health conditions.
- To achieve and maintain body weight as metabolic control has proved to be a landmark in diabetes management.
- To delay and prevent complications of diabetes.
- To formulate an individualized diet plan keeping in mind the following factors that may influence patients’ personal preferences. They are food habits (vegetarian/nonvegetarian), region, religion, climate, profession, likes and dislikes, availability of food items, socio-economic status, customs and beliefs as well as barriers to change.
- To provide ample variety of food choices.
- To have a pragmatic outlook toward meal planning so that it can be practiced in day-to-day living by doing simple meal modifications rather than focusing on individual macronutrients.

MAINTENANCE OF BODY WEIGHT

More than three out of four people with diabetes are overweight, and obesity is prevalent in nearly half the population with diabetes. As excess body weight is directly linked with insulin

resistance weight loss is highly recommended. A weight loss of more than 6 kg (approximately a 7–8.5% loss of initial body weight) with regular physical activity is considered to be beneficial.

Various studies have been designed to reduce excess body weight by using a variety of eating patterns, which focus on energy restriction with various macronutrient intakes along with a follow-up support. An eating pattern can be defined as different permutations and combinations of food groups designed to promote health and prevent disease. Well, there is no “ideal” eating pattern that will benefit all (Table 3.1).

However, amongst the various studies conducted to study the effectiveness of eating patterns, the Mediterranean style eating pattern reported the largest improvement in biochemical parameters at the end of 1 year.¹ The Look AHEAD study showed the benefit of intensive life style intervention and its impact on cardiovascular mortality and morbidity.² Whichever eating pattern is chosen by the individual, the main consideration should be on portion sizes and thus the energy intake.

MACRONUTRIENTS

The components of a balanced diet are summarized in Figure 3.1.

Recommended nutrient intake as percent of total calories:

- *Carbohydrate*: 50–60% of total calories
- *Protein*: Approximately 15–20%
- *Total fat*: 25–35%
- *Saturated fat*: Less than 7%

Table 3.1: Various eating patterns.

<i>Eating pattern</i>	<i>Foods in liberal quality</i>	<i>Foods to be avoided</i>
Mediterranean style	Seasonal fruits, vegetables, cereals, nuts and olive oil as principal source of fat	Dairy products (cheese and yogurt), red meats and wine, less than 4 eggs/week
Vegetarian and vegan <i>Vegan</i> : Diets with no flesh foods or animal products. <i>Vegetarian</i> : Diets with no flesh foods but inclusive of eggs and milk products.	Fruits, vegetables, whole grains, nuts, soya products and phytochemicals	Flesh foods and saturated fat
Low fat	Starchy vegetables, fruits, breads, pasta, whole grains, lean protein and low-fat dairy products	Fat
Low carbohydrate	Foods rich in protein (fish, meat, poultry, cheese), fats (olives, avocado) and vegetables low in carbohydrate (greens salad, cucumbers, broccoli)	Sweet foods and cereal products like pasta, rice and bread
DASH	Fruits, vegetables, low-fat dairy products, whole grains, poultry, fish and nuts	Saturated fat, red meat, sweets and sodium

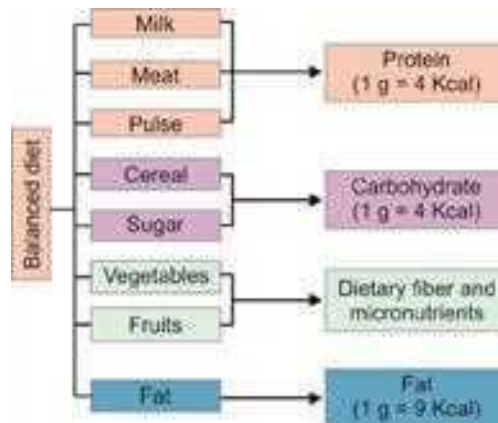


Fig. 3.1: Components of a balanced diet.

- *Polyunsaturated fat:* Up to 10%
- *Monounsaturated fat:* Up to 20%
- *Cholesterol:* Less than 200 mg/day.

CARBOHYDRATE

Recommended Intake

The percent of energy from carbohydrate indicated for people with diabetes depends on individual preference, diabetes medication and weight management goals. The recommended dietary allowance for carbohydrate is set at a minimum of 130 g/day for adults and children, based on the average minimum amount of glucose used by the brain. Both the type and amount of carbohydrate found in foods influence postprandial glucose levels and can also affect overall glycemic control in individuals with diabetes. The types of carbohydrates are simple carbohydrate and complex carbohydrate.

Simple Carbohydrate

Simple carbohydrates are various forms of sugar, completely metabolized and are the quickest source of energy. They include monosaccharides (glucose, fructose and galactose) and disaccharides (sucrose, maltose and lactose).

Complex Carbohydrate

Complex carbohydrate includes starch and dietary fiber. Starch is completely metabolized to glucose. For example, rice, potato, refined wheat flour (maida). Dietary fiber is nonstarchy polysaccharides and lignin that are not digested by enzymes in the small intestine and typically refers to the nondigestible carbohydrates from plant foods. Because dietary fiber is not digested in the human small intestine, it is not considered a part of the immediate glucose supply. Evidence shows lowering of preprandial glucose with intakes of more than 50 g

of fiber/day.³ The recommendations for dietary fiber are about 25 g/day for adult women and 38 g/day for adult men with diabetes.⁴

Benefits of Increasing Dietary Fiber

- Insoluble fiber forms the bulk of the feces. Promotes regularity and prevents constipation by absorbing water.
- Removes toxic waste through colon in less time.
- It Increases satiety, People feel full after a meal, eat less and do not feel hungry soon, thereby reducing total calorie intake.
- Prolongs gastric emptying time, and sugar is released and absorbed slowly. Improves glucose tolerance and insulin response.
- Reduces total cholesterol by increased binding and thereby excretion of bile acids. This reduces the total pool of cholesterol as more cholesterol is transformed to bile acids.

There are two types of dietary fiber namely soluble fiber and insoluble fiber based on solubility in water.

Soluble fiber: It dissolves in water to form a gel-like substance. It is highly viscous. It is the edible portion of plant foods, resistant to digestion and absorption in small intestine. For example, oats, pulp of fruits, legumes.

Sources of insoluble fiber: It is made up of the structural material of the cell wall of plant foods. It does not dissolve in water but soaks up water adding bulk and softening the stool and increases the transit time through the intestinal tract. For example, wheat bran, vegetables and skin of various fruits.

Fructans an indigestible form of fiber has been found to lower glucose levels in the body. Inulin is a common fructan is added to many ready to eat and processed foods. Also, foods with high content of amylose as in some legumes or specially formulated corn starch may prevent hypoglycemia and improve glycemic response.

Glycemic Index of Foods

Glycemic index (GI) is the ability of carbohydrates to raise the blood glucose. The GI assesses the blood glucose response of a fixed amount of available carbohydrate (generally 50 g) from a test food to the same amount of available carbohydrate from a standard food (glucose or white bread). The test food's blood glucose response area is then expressed as a percentage of the standards. Foods with protein and/or fiber have low GI.

Low GI Foods (< 55)

- *Cereals and pulses:* Parboiled rice, barley, green peas, lentils, kidney beans, Soybeans, all dals and whole legumes.
- *Milk and milk products:* Milk, Curd, Cheese etc.
- *Vegetables:* All vegetables grown above the ground, and underground vegetables like carrot and turnip.
- *Fruits:* Apple, plum, orange, papaya and guava.

Medium GI Foods (55–69)

- *Cereals*: Whole wheat, basmati rice, semolina roasted, brown rice and oatmeal.
- *Vegetables and fruits*: Mango, pomegranate, custard apple, banana, pineapple, black grapes, raisins and beetroot.

High GI Foods (> 70)

Rice, potato, cornflakes, sugar, rice products and white bread.

Methods to Lower GI of the Meal

- To choose at least one low GI food at each meal.
- Combine a high GI food with a low GI food. For example, rice with dal and vegetables.
- Whole grain bread to be chosen more often than white bread.
- Inclusion of fresh fruit and vegetables as they have a low GI.

Glycemic Load

The glycemic load (GL) is a ranking system for carbohydrate content in food portions based on their GI and a standardized portion size of 100 g. As the standard for calculation of GI is 50 g of carbohydrate, the quantity of food tested is variable. For example, while testing for GI 65 g of rice and 300 g of mango which give 50 g of carbohydrate will be tested. But, the usual portion of size of one small mango may be around 100 g and GI does not take into consideration the portion size. GL of a particular food is the product of the GI of the food and the amount of carbohydrate in a serving.

$GL = (GI \times \text{the amount of carbohydrate in the portion consumed in the meal}) \text{ divided by } 100.$

For example, apple has a GI of 40 and a medium size apple (100 g) contains 15 g of carbohydrate.

$$GL = 40 \times 15/100 = 6$$

Potato has GI is 80 and if a person is consuming 100 g as a serving, it will contain 23 g of carbohydrate. $GL = 80 \times 23/100 = 18.$

Therefore, although equal quantities of apple and potato are consumed, potato will have thrice the rise in blood sugar than an apple. Watermelon has a GI of 73 and is considered high. But, even when 120 g of watermelon is consumed, the GL is only four and can be recommended to a diabetic.

A GL greater than 20 is considered high, a GL of 11–19 is considered medium, and a GL of 10 or less is considered low. Overall GL of a meal has to be considered rather than individual food item.

PROTEIN

Role of Protein in Diabetic Diet

- Protein flattens the glycemic response of the food, i.e. reduces GI of food.
- It has the highest satiety index. Protein foods slow the stomach emptying time and the individual feels full for a longer time.

- The thermic effect of protein is higher. The body uses more energy to digest protein than it does to digest fat or carbohydrate and thereby increases the basal metabolic rate.
- Moderate hyperglycemia increases the protein turnover in type 2 diabetes.

Recommended Daily Allowance for Protein

- 15–20% of total calories
- 1 g/kg present body weight
- 1 g/kg ideal body weight if obese
- 0.8 g/kg in nephropathy
- 50% of daily protein has to be from Class 1 sources
- Protein needs differ for children and women during pregnancy and lactation.

Sources

Complete or Class 1 sources: Class 1 protein sources refer to those foods which contain all the essential amino acids. They include meat, poultry, fish, eggs, milk, cheese and soy.

Incomplete or Class 2 sources: These foods do not contain one or more essential amino acids. For example, legumes, pulses and cereals. Deficiency of an amino acid in one food item can be compensated for by combining it with another food item that has it in adequate amounts. This is known as mutual supplementation. To improvise protein quality from vegetarian sources, cereal protein can be combined with pulse protein or animal protein. For example, idli, dosa, rice/roti with dal/paneer, dahi vada, etc.

Soybean has a powerful trypsin inhibitor that is destroyed by dry roasting for 15–20 min. Therefore, cooking and heat treatment is essential while using soy.

FAT

The primary goal with respect to dietary fat in individuals with diabetes is to limit saturated fatty acids (SFAs), trans fatty acids and cholesterol intake so as to reduce risk for cardiovascular disease. Saturated and trans fatty acids are the principal dietary determinants of plasma LDL cholesterol. Diets high in monounsaturated fatty acids (MUFAs) result in improvements in glucose tolerance and lipids compared with diets high in saturated fat. A greater SFA content of membrane phospholipids increases insulin resistance. Diets enriched with monounsaturated fat may also reduce insulin resistance.

Recommendations for Fat Intake

Based on recommendations of the National Cholesterol Education Program Adult Treatment Panel III and the American Diabetes Association.

- Total calories from fat up to 25–35% of total calories
- Limit saturated fat to less than 7% of total calories
- Polyunsaturated fat—up to 10%
- Monounsaturated fat—up to 20%

- Intake of trans fat should be minimized
- Limit dietary cholesterol to less than 200 mg/day
- Foods containing omega-3 fatty acids confer cardioprotective effects. Two or more servings of fish per week are recommended.

Visible Sources of Fat

They are visible to the naked eye. It includes all the fats and oils that are used for cooking like vegetable oils, butter, ghee, hydrogenated fat (e.g. dalda, vanaspati, etc.).

Invisible Sources of Fat

They are not visible to the naked eye but add to the total fat in the food. All foods contain invisible fats in varying amounts.

For example, dairy products, nuts, oilseeds, eggs, meats, cereals and pulses.

Hence, while estimating the calories provided by fat in the diet, both visible and invisible sources have to be taken into consideration.

Composition of Commonly used Oils

Fatty acid composition of edible oils (Fig. 3.2).

- *Oils with SFA as the predominant fatty acid:* Ghee, butter, palm oil, palm olein oil and coconut oil.
- *Oils with PUFA as the predominant fatty acid:* Sunflower oil, safflower oil and cottonseed oil.

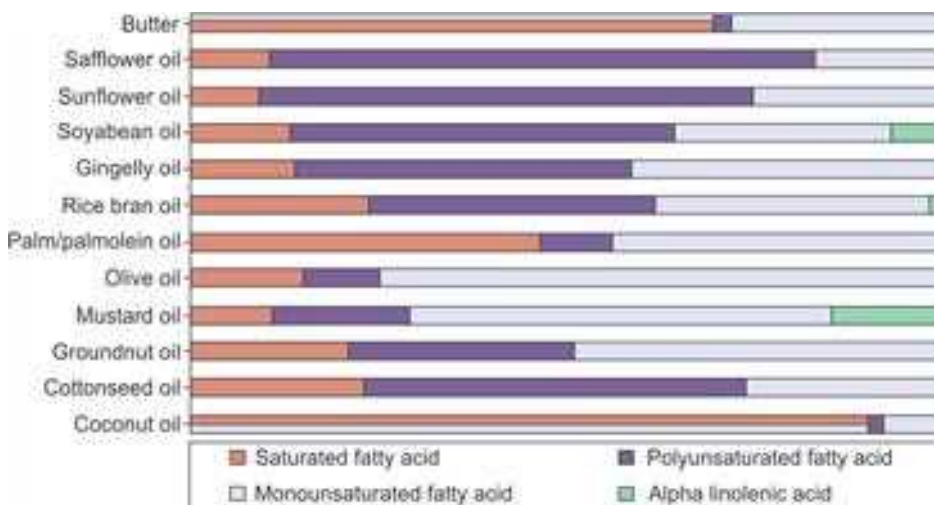


Fig. 3.2: Composition of commonly used oils.

Note: Based on data provided in Nutritive Value of Indian Foods of the National Institute of Nutrition, Indian Council of Medical Research.

- *Oils with MUFA as the predominant fatty acid:* Olive oil, mustard oil, groundnut oil, gingelly (til) oil and rice bran oil.
- *Oils with alpha linoleic acid:* Alpha linoleic acid present in oils is converted in the body to omega-3 fatty acids and hence is recommended. The oils are flax seed oil, mustard oil, soybean oil and rice bran oil.

Recommended Oils

Based on research and recommendations of the National Cholesterol Education Program Adult Treatment Panel III and the American Diabetes Association, a source of fat/oil high in MUFA has better outcome measures over polyunsaturated fatty acid (PUFA) and SFA. To attain the recommended levels in diet, oil high in MUFA and linoleic acid are preferable. Mustard oil, groundnut oil, gingelly (til) oil, rice bran oil and soybean oil can be used on a rotational basis each month. Use of ghee, butter, hydrogenated oil is to be minimized.

Recommended Quantity of Oil

As the diet contains fat from both visible and invisible sources, it is best to keep the visible oil content at a minimum level. The practical recommended quantity per person is 3 teaspoons per day or half a kilogram of oil for a month.

Foods that contain invisible fat have to be minimized. Whole milk or buffalo milk can be replaced with skimmed milk. Oilseeds like groundnut, coconut and gingelly seeds are commonly used during preparation of Indian dishes which can be replaced with Bengal gram seeds or flour. Skinless chicken has less fat when compared to chicken with skin and mutton.

Sources of Trans Fat in Diet

The process of hydrogenation is commonly employed to convert liquid vegetable oils to solid or semi-solid fats. Hydrogenated fats are used as substitutes for butter and ghee and are preferred for baking and making of sweets and snacks. Hydrogenated vegetable fat is cheaper than animal source fat and has other characteristics like taste and shelf life that makes its use desirable in food industry. During the process of hydrogenation, some naturally occurring cis isomers are converted to trans isomers and are called as trans fats. The consumption of trans fats increases the risk of coronary heart disease by raising levels of LDL cholesterol and lowering levels of “good” HDL cholesterol.

All products made with hydrogenated fat are sources of trans fat as. For example, bakery products like biscuits, puff, cakes, sweets, snacks like French fries, chips, pizza, samosa, etc. Some restaurants use hydrogenated fat for making biryani and other vegetable preparations.

Omega-3 Fatty Acids

N-3 fatty acid supplements have been shown to reduce plasma triglyceride levels, especially in hypertriglyceridemic individuals, have beneficial effects on platelet aggregation and

thrombogenicity and reduce blood pressure in hypertensives. Increasing the intake of N-3 polyunsaturated fatty acids has been shown to be beneficial in subjects with diabetes.

There are three important omega-3 fatty acids for human nutrition:

- *Eicosapentaenoic acid*
- *Docosahexaenoic acid*
- *Alpha-linolenic acid*: Available in plant sources and converted to omega-3 fatty acids in the body.

Humans cannot synthesize omega-3 fatty acids and must be obtained from the diet.

Good dietary sources include:

- Fish such as salmon, herring, mackerel, anchovies, sardines and fish oils.
- Flaxseed oil (about 55% ALA) and flax seeds, canola oil, walnuts and walnut oil, soybeans and soybean oil, pumpkin seeds, mustard oil. Plant stanols and sterols.

Certain food items like yogurts, dairy products, breads are enriched with plant stanols and sterols.

These esters inhibit the absorption of dietary and biliary cholesterol and thereby reduce the total cholesterol. They are recommended as 1.6–3 g/day.

MICRONUTRIENTS

Adequate intake of micronutrients prevents deficiency diseases and is important in maintaining the health and well-being of patients with diabetes. Nutrient recommendations for adults, adolescents, and children with type 1 or type 2 diabetes and for women with diabetes during pregnancy and lactation are similar for people with or without diabetes. However, uncontrolled diabetes is often associated with micronutrient deficiencies. Since diabetes may be a state of increased oxidative stress, there has been interest in antioxidant therapy. No specific recommendations are provided by the American Diabetes Association. However, a diet that is balanced with adequate intake of fruits and vegetables will supply adequate micronutrients.

Sodium: As per the recommendations, the consumption of sodium should be less than 2,300 mg/day, which is also beneficial for the general population.

NON-NUTRITIVE SWEETENERS

The recommended dose of non-nutritive sweeteners is given in Table 3.2.

Some artificial sweeteners may leave an aftertaste. The patient has to experiment with artificial sweeteners to find one or a combination that is acceptable. The thumb rule for quantity of sweeteners can be about four sachets per day.

ALCOHOL AND DIABETES

If adults with diabetes choose to use alcohol, daily intake should be limited to one drink per day or less for women and two drinks per day or less for men. Preference can be given to red wine. To reduce risk of nocturnal hypoglycemia in individuals using insulin or insulin secretagogues, alcohol should be consumed with food as liver preferentially metabolizes alcohol and stops release of glucose into the blood stream. Care should be taken to avoid fried snacks with alcohol. Grilled, dry roasted foods are to be preferred over deep fried snacks.

Table 3.2: Recommended dose of non-nutritive sweeteners.

Sweeteners	Accepted daily intake (mg/kg body weight)
Sucralose Sucralose is heat stable and hence can be used while cooking and for baking. It is deemed safe for use with all populations, including pregnant and lactating women as well as children	15 mg/kg body weight/day
Aspartame Aspartame is advised to be used after removing the food from heat	50 mg/kg body weight/day
Acesulfame K Acesulfame K is heat stable and can be used in cooking	15 mg/kg body weight/day
Saccharin	5 mg/kg body weight/day

One standard drink is equal to 2 oz (60 mL) beer/5 oz (150 mL) of wine/1.5 oz (45 mL) of distilled spirits (whiskey, rum, etc.). It gives 15 g alcohol and 100 Kcal.

FENUGREEK

Fenugreek is an herb and a spice. It contains polysaccharide galactomannan, saponins, mucilage/soluble fiber, alkaloids and 4-hydroxyisoleucine, an active ingredient for blood glucose control. It helps lower elevated cholesterol and triglyceride levels in the blood, including in those with diabetes, according to several controlled studies. The typical range of intake for diabetes or cholesterol lowering is 5–30 g with each meal or 15–90 g all at once with one meal. Alternatively, 5 g of fenugreek (1 teaspoon) can be soaked and had with each meal. Fenugreek can also be added to idli/dosa batter or chapatti atta or with curries. Fenugreek leaves have not shown to have the effects that the seeds have.

FOOD EXCHANGES

In this exchange system, food are divided into six groups or categories, which are cereal, pulse, fruit, vegetable, milk, nonvegetarian foods and nuts and oil seeds. Patients can replace certain food for other foods in the same category. The list is provided Appendix 2.

MEAL PLANNING

Making a diet plan:

Step 1: Assess the patient's medical history, BMI, physical activity and diet history.

Step 2: Identify the areas for dietary intervention.

Step 3: Formulation of meal plan.

Step 4: Monitor progress.

Step 1: Assessment has Four Components

- *Medical history* includes a patient's previous illnesses, present conditions, symptoms, medicines used, biochemical parameters and health risk factors.

Table 3.3: Classification of weight status according to BMI in Asians.

Grade	BMI (kg/m ²)
Underweight	< 18.5
Normal range	18.5–22.9
Overweight: at risk	23–24.9
Obese Class I	25–29.9
Obese Class II	30–34.9
Obese Class III	> 35

Source: Adapted from WHO Asia Pacific guidelines.

- **Body mass index:** The grading of BMI for Asians is given in Table 3.3. In overweight and obese insulin-resistant individuals, modest weight loss has been shown to improve insulin resistance. Thus, weight loss is recommended for all such individuals who have or are at risk for diabetes. For weight loss, low-carbohydrate and low-fat calorie-restricted diets can be effective along with regular physical activity.
- **Physical activity** pattern can be classified in various forms as sedentary, moderate, active or bed ridden. Depending on activity level, nutrient requirements change.
- **Dietary assessment:**
 - **Diet habits/pattern:** Vegetarian/nonvegetarian/egg. Pattern of meal includes meal timings, packed meals from home/restaurant/canteen, traveling habits, frequency of nonvegetarian intake, snacking habit, type of oil and milk used, mode of preparation to estimate the intake especially of nuts and oilseeds, alcohol intake, snacks accompanying alcohol, etc.
 - **Likes and dislikes:** For example, sweet tooth, loves rice, hates salads, avoids fried foods, prefers nonvegetarian, etc.
 - **Diet history:** Diet history is a method of dietary assessment in which subjects are asked to recall their food consumption over a specific period of time usually one day right from morning to night. A patient can also be asked to record intake in the form of food diary usually for a period of three days. It is preferable to include spouse or person cooking at home while taking the diet history.

Step 2: Identify the Areas for Dietary Intervention

For example, oversized portion sizes, low fruit intake; high fat intake; high junk food intake, skipping/late breakfast, long gap between lunch and dinner, traveling a lot and needs to depend on restaurant food, substituting honey for sugar, unable to cut down rice, having only fruits for breakfast, skipping meals as meal intake may increase sugar, etc.

Strategies may be aimed at improving food selection, e.g. reducing fats and saturated fats, spreading meals throughout the day, advise regular exercise, education and motivation.

Step 3: Formulation of Meal Plan

Nutrition assessment is used to determine what the individual with diabetes is able and willing to do. Plan a meal by distributing carbohydrate, protein and fat through small frequent meals. Help patient set short-term and long-term goals.

Determine the Calorie Requirement

The nutritional requirements of all individuals vary from one another depending upon age, gender, physical activity, physiological stress or condition (e.g. pregnancy or lactation) as specified by the Indian Council of Medical Research (Table 3.4). The requirements for diabetic are not different from an individual who is not diabetic.

Quick assessment of approximate calorie requirement for adult individuals of type 2 diabetes:

Obese inactive, sedentary men/women	20 Kcal/kg of present weight
Normal BMI, sedentary men/women	22–25 Kcal/kg
Normal BMI, active men/women	30 Kcal/kg
Thin/Very active	40 Kcal/kg

One-third of the total calories can be distributed for early morning and breakfast. Another one-third for midmorning snack and lunch, and the remaining one-third for evening snack and dinner.

However, the nutrition prescription is determined considering treatment goals and lifestyle changes the diabetic patient is willing and able to make rather than predetermined energy levels and percentages of carbohydrate, protein and fat. A patient finds it difficult to comprehend and calculate calorie content of foods as well as calorie distribution and hence is not a practical approach.

Practical meal planning approach: Table 3.5 shows the recommended intake of different food groups for adults.

Distribution of Carbohydrate Load through Small Frequent Meals

Carbohydrate is the main nutrient affecting postprandial glycemic response. Hence, care has to be taken to ensure that carbohydrate is distributed evenly throughout the day and the carbohydrate load in any meal would not cause a steep increase in blood sugar.

The advantages of small frequent meals over three major meals are:

- Provides satiety, hence total daily caloric intake is low as compared to three meals pattern
- Increases total day's energy expenditure (by increasing basal metabolic rate)
- Reduces the incidence of hypoglycemia and hyperglycemia; hence protective for heart and brain.
- The summary of macronutrient management in patient with type 2 diabetes is summarized in Flowchart 3.1.

Healthy Snack Options (Midmorning and Evening)

- Fruit
- Sprouts/boiled legumes (with grated carrot/radish and lime juice)
- Murmura with roasted Bengal gram, peas, onions, tomatoes, etc.
- Roasted chana/peas: 1 cup
- Badam and walnuts: fistful
- Coffee/tea/low fat milk: 1 cup
- Avoid biscuits of any type as the ingredients will include refined wheat flour and hydrogenated fat.

Table 3.4: Recommended dietary allowance, the Indian Council of Medical Research, 2010.

Group	Category	Body (Kg)	Energy	Protein
		Weight	(Kcal/Day)	(G/Day)
Man	Sedentary	60	2320	60
	Moderate		2730	
	Heavy		3490	
Woman	Sedentary	55	1900	55
	Moderate		2230	
	Heavy		2850	
	Pregnant		+ 350	78
	Lact. < 6 months		+ 600	74
	Lact. 6-12 months		+ 520	68
Children	1-3 years	12.9	1060	16.7
	4-6 years	18.0	1350	20.1
	7-9 years	25.1	1690	29.5
Boys	10-12 years	34.3	2190	39.9
Girls	10-12 years	35.0	2010	40.4
Boys	13-15 years	47.6	2750	54.3
Girls	13-15 years	46.6	2330	51.9
Girls	16-17 years	55.4	3020	61.5
Boys	16-17 years	52.1	2440	55.5

Table 3.5: Meal planning in adults with diabetes.

Food group	Quantity
Cereals	6 exchanges/day or 2 exchanges/major meal. Gradually decrease the current intake based on patient's acceptance to 6 exchanges/day
Pulses	2-3 exchanges/day
Vegetables (exclusive of restricted root vegetables)	500 g/day
Fruits (2 hours after a major meal and avoiding fruit juices)	1-2 exchanges/day
Milk and milk products	Half liter of low fat milk/day
Nonvegetarian foods	Approximately 100 g/serving (size of fist) preferably fish or skin less chicken as second choice
Fats and oils (Preferred oils are those with high monounsaturated fatty acid content)	About 3 teaspoons of oil/day or 500 g/month

Note: Different set of recommendations are applicable to individuals who are physically active or during pregnancy, lactation and growth years.

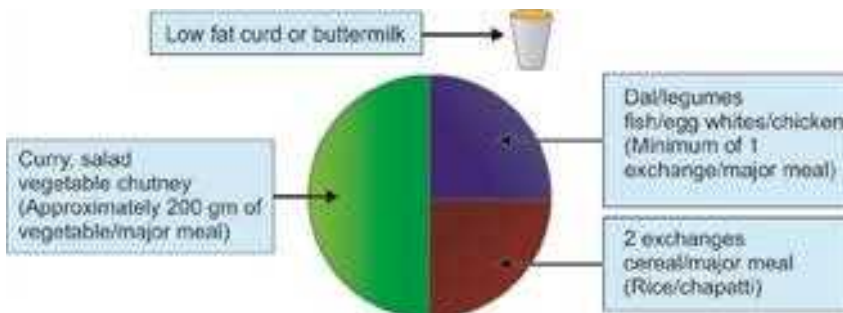
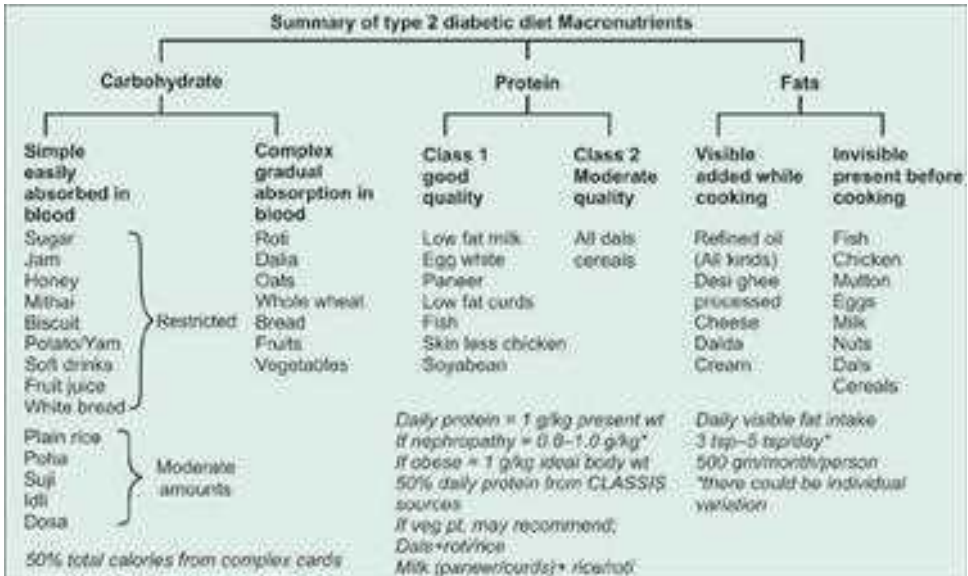
Flowchart 3.1: Summary of type 2 diabetic diet macronutrients.**Fig. 3.3:** Plate method for lunch/dinner.

Plate Method

Plate method is an easy way to plan meals especially for lunch and dinner. It helps to get clarity on portion size. Draw an imaginary line on the plate as shown in Figure 3.3.

- The Indian meal is predominantly cereal based with rice or roti (chapatti) which takes up half the plate. This proportion has to shift from half to quarter. The number of cereal exchanges per meal has to be gradually reduced from the current intake to a minimum of two cereal exchanges per meal.

The common perception of diabetic diet is just reduction in cereal portion (rice or roti).

There has to be concomitant increase in the amount of protein and fiber.

- Half the plate should contain vegetables, avoiding root vegetables. Double the amount of vegetable normally consumed. The vegetable consumption can be in the form of salad,

curry, vegetable chutneys or by addition of more vegetables to dal, sambar or curd. This will ensure satiety as well as provide ample micronutrients.

- Every meal should contain one protein exchange that can either be from vegetarian or nonvegetarian foods chosen from the food exchange list.
- A cup of curd or buttermilk made from low fat milk will complete the meal. Vegetables like grated cucumber or carrot can be added to the curd.

Nutritional Management of Nephropathy

Reduction of protein intake to 0.8–1.0 g/kg body weight/day in individuals with diabetes and the earlier stages of chronic kidney disease and to 0.8 g/kg body weight/day in the later stages of chronic kidney disease may improve measures of renal function. The usual intake of protein in Indian vegetarian diets is about 0.6–0.8 g/kg body weight even when pulses and legumes are used in every meal. Hence, there is no need to restrict protein from vegetarian sources. Egg whites and fish can be used in one meal as long as the protein is within the recommended intake of 0.8 g/kg body weight. Complete restriction of vegetarian protein will lead to malnutrition.

Nutritional Management of Cardiovascular Disease

For patients with diabetes at risk for cardiovascular disease, diets high in fruits, vegetables, whole grains and nuts may reduce the risk. These foods supply fiber, antioxidants and sufficient micronutrients, which can attenuate hypertension. Care should be taken to ensure that there is no significant hypoglycemia. For patients with diabetes and symptomatic heart failure, dietary sodium intake of about 2,000 mg/day or 5 g of salt (1 teaspoon) may reduce symptoms. Foods containing high salt content like pickles, papad, canned foods, preserved foods, namkeen/mixture, etc. are to be avoided. Also salt can be restricted in wheat flour dough, curd and buttermilk. Salt can be used for regular cooking, and it is not necessary to cook a salt free diet. A salt free diet will minimize intake of food and may lead to malnutrition. In most individuals, a modest amount of weight loss beneficially affects blood pressure. Cholesterol that comes from diet is about 25% and should be minimized. Sources include meat, poultry, fish, egg yolk, butter, cheese and full cream milk and its products. Cholesterol is present only in animal foods. All vegetable oils are free of cholesterol. Foods rich in omega-3 can be included in the diet like fish and flax seeds.

Nutritional Management of Type 1 Diabetes Mellitus

Children and adolescents with type 1 diabetes mellitus do not need a special diet as far as they are not having further complications of obesity, hypertension, hyperlipidemia and nephropathy. Normal growth of the child is considered as the best indicator of optimum health.

The goals of meal planning will be to:

- Balance insulin, exercise and diet
- Monitor the intake of those food items in the diet that can increase the risk of complications.

- Prevent the occurrence of hypoglycemia during play or exercise and during night sleeping hours.
- Manage and prevent episodes of hypoglycemia and ketoacidosis during illness.

There are unique challenges in caring for children and adolescents. These include developmental issues, unpredictability of a child's dietary intake and activity level, busy schedule, excessive consciousness on weight and skipping or delaying of insulin doses. Educating the family on management plays a very crucial role. The recommended daily intake will vary with sex, activity and age of the child and is provided by the Indian Council of Medical Research. Weight and growth patterns can help determine if a child with type 1 diabetes is getting enough nutrition.

When the child/adolescent is on split-mix insulin regimen, the meal timing and carbohydrate content should be constant for a certain meal on a day-to-day basis. Ideally, there meal plan comprises of three main meals and two snacks in between meals to cover for peak insulin action time along with a bed time snack to prevent hypoglycemia.

Those on basal-bolus regimen have more flexibility around meal timing. With these regimens, skipping or delaying a meal does not usually increase the risk of hypoglycemia and the carbohydrate intake can be varied from day to day. To make it practical for patients use, they are taught the concept of carbohydrate counting.

Step 4: Monitoring Progress

Successful medical nutrition therapy requires ongoing evaluation and adjustment. Food intake and blood glucose records should be correlated and evaluated together to ensure that goals are met. If initial goals are not met then there may be a need to change or re-negotiate goals that are more realistic and attainable. Barrier to change have to be identified and worked upon by the diabetes educator and the patient. If the initial goals are met, the next set of targets is to be set. The patient should have a clear idea of the plan and the goal.

CARBOHYDRATE COUNTING

It refers to the carbohydrate content of various food items, which can be counted for every meal and estimate the insulin dose that would be needed. Individualized insulin to carbohydrate ratio is worked out for different meals of the day. This ratio can be roughly calculated by using the formula of 500 divided by total daily dose. It gives the grams of carbohydrate for which 1 unit of rapid acting insulin is required. Using this insulin to carbohydrate ratio, the patient takes a bolus insulin dose before meals after estimation of carbohydrate in that meal.⁵

Importance of Diet during Sickness

As the child is unwell, his intake will be low which may lead to hypoglycemia; on the other hand, the raised levels of counter regulatory hormones can lead to hyperglycemia and ketoacidosis. If there is appearance of ketones and an elevated blood glucose levels above 180 mg/dL, the child is advised to have plenty of salty fluids to manage for the polyuria, and thereby prevent dehydration. On the contrary, if the blood glucose level is below 180 mg/dL with presence of

ketones, the patient is advised to have sweet fluids along with insulin administration to prevent the occurrence of hypoglycemia and correct ketosis.

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SELF-ASSESSMENT

1. **Oils do not contain cholesterol and hence can be consumed as desired. *True/False***
2. **Fruits are good for diabetics. *True/False***
3. **Gulab jamun made with artificial sweetener has no sugar and hence can be taken frequently. *True/False***
4. **Legumes, oats, fruits can help to control cholesterol and blood pressure. *True/False***
5. **Low fat butter has less fat and hence can be consumed regularly. *True/False***
6. **Vegetarian foods do not contain cholesterol. *True/False***
7. **Fruit can be added along with breakfast/lunch. *True/False***
8. **Sunflower oil is heart friendly oil and preferred over groundnut oil. *True/False***
9. **Having rice, a high glycemic index food, with a legume/soybean curry will reduce the glycemic response. *True/False***
10. **Soybean has to be roasted/cooked for 15–20 min before consumption. *True/False***

CHAPTER

4

Exercise

Jubbin Jagan Jacob, Samuel Vinod Kumar

*“Activity keeps you going, reduce insulin resistance,
With GLUT-4 glucose moves with persistence,
It’s not just the sugar that drops when you bend,
But the heart beats better so you’re fit till the end.”*

The adoption of a sedentary lifestyle is a clear risk factor for the development of type 2 diabetes mellitus. The accumulation of excess energy stores into the muscle cells and liver as free fatty acids and glycogen results in insulin resistance. The clinician can increase the chances of the patient “buying into” the exercise regimen by asking the patient to set his own exercise goals. Although it would be ideal to have the individual with diabetes to exercise daily, it is important to remember that even some exercise is better than none. In those subjects with physical limitations, comorbidities and complications of diabetes, exercise has to be modified and tailor made for the appropriate situation.

INTRODUCTION

Exercise is being increasingly recognized as a part of the treatment for diabetes mellitus. The beneficial effect of exercise on glycemic control largely results from increased tissue sensitivity to insulin. To understand the effects of exercise on diabetic patients, it is essential to understand the physiology of exercise on normal subjects. The physiological effects will depend on the type and duration of exercise.

PHYSIOLOGICAL CHANGES OCCURRING DURING EXERCISE

- *During the first few minutes of exercise:* Glycogen in the muscles is broken down anaerobically and used to fuel the muscles. As the physical activity continues, oxygen becomes available for the aerobic break down of carbohydrates, fats and proteins. In addition to the glycogenolysis, muscle takes up the glucose in the circulation.
- *After 5–10 minutes of activity:* Muscle glycogen break down decreases. The decrease in the blood glucose suppresses insulin and stimulates glucagon which in turn causes hepatic glycogenolysis. Glycogen is broken down in the liver to glucose and is released into the blood stream and is taken up by the muscles as fuel. This glucose becomes the major source of fuel (hepatic glycogenolysis).

- *At 20 minutes or more:* The muscle glycogen stores are now depleted. The counter-regulatory hormones other than glucagon (cortisol, epinephrine, norepinephrine and growth hormone) play an increasing role. Epinephrine and norepinephrine stimulate lipolysis and the resulting triglycerides break down into free fatty acids (FFA) and glycerol. FFA is used as a source of fuel for the muscles and glycerol can be converted into glucose through the process of hepatic gluconeogenesis.
- *Longer duration of exercise:* Should low-to-moderately intensive exercise continue for a long period of time, the muscles will continue to use the glucose derived from hepatic gluconeogenesis and FFA, as the fuel. FFA cannot completely replace the use of glucose and if carbohydrates are limited, then ketone bodies may form. This is not a risk in a person who has enough insulin, but may increase the risk of diabetic ketoacidosis in a person who is insulin deficient such as type 1 diabetic with poor glycemic control. If a carbohydrate snack is consumed during exercise, the decrease in blood glucose can be delayed and the exercise can be sustained for a longer period. This is often done by people with diabetes who are marathon runners or those who engage in moderate to intensive exercise for long periods of time.
- *Long-term training:* On a regular, long-term basis, moderate aerobic exercise increases the quantity of mitochondrial enzymes, the number of “slow twitch” muscle fibers and the development of new muscle capillaries. There is also an increased translocation of insulin-responsive glucose transporters to the muscle membrane.

CLINICAL IMPLICATIONS OF THE EFFECTS OF EXERCISE IN DIABETES

- Even short-term (2-week), regular aerobic exercise in type 2 diabetic patients results in significant improvement in both aerobic capacity and whole body insulin sensitivity
- Long-term endurance training in diabetic patients markedly improves whole body insulin sensitivity and increases the expression of key muscle enzymes regulated by insulin. However, the maintenance of this effect seems to require dedication to a regular and uninterrupted exercise regimen
- Intramyocellular lipid accumulation, which is associated with insulin resistance in muscle, can be acutely decreased by even a single bout of sustained endurance exercise, in a manner that depends on both the duration of exercise and the workload
- Exercise is beneficial for both the glucose uptake mechanisms and the anti-lipolytic effects of insulin (Fig. 4.1).

BENEFITS OF EXERCISE IN PATIENTS WITH DIABETES

- Improvement in glycemic control
- Improvement in insulin sensitivity and lowered insulin requirements often leading to a reduced dosage of insulin and/or oral hypoglycemic agents especially in people with type 2 diabetes
- Reduction in blood pressure
- Increased fibrinolysis

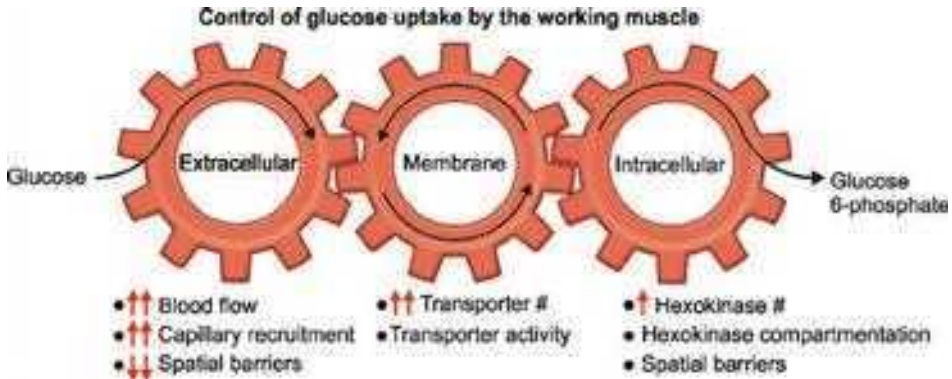


Fig. 4.1: Schematic representation of the control of muscle glucose uptake during exercise. Control of glucose is distributed between three serial steps. These are (1) extracellular glucose delivery from blood to muscle membrane (2) muscle membrane glucose transport and (3) intracellular glucose phosphorylation. Below each gear are known mechanisms of regulation. Arrows associated with those mechanisms reflect exercise adaptations. Note that acute exercise increases hexokinase II protein; however, this adaptation is slow in onset (Modified from Wasserman and Halseth).

- Improvement in dyslipidemia
- Increased vascular reactivity
- Reduction in risk for osteoporosis
- Reduction of coronary risk factors
- Favorable changes in body composition (decreased body fat and weight, increase in muscle mass)
- Maintenance and improvement in body weight
- Improvement of psychological well-being.

Randomized clinical trials have found that lifestyle interventions that included approximately 150 minutes of exercise per week and weight loss of 5–7% reduced the risk of people with prediabetes from progressing to type 2 diabetes by 58%.

POTENTIAL ADVERSE EFFECT OF EXERCISE IN PATIENTS WITH DIABETES

Cardiovascular

- Cardiac dysfunction and arrhythmia due to silent ischemia
- Excessive increments in blood pressure
- Exercise induced orthostatic hypotension.

Microvascular

- Retinal hemorrhage
- Increased proteinuria
- Acceleration of other microvascular lesions.

Metabolic

- Worsening of hyperglycemia and ketosis
- Hypoglycemia.

Musculoskeletal

- Foot ulcers
- Accelerated degeneration of joints.

Recommendations

- Indications for stress test (Treadmill testing)
- Age less than 40 years, with or without cardiovascular disease risk factors other than diabetes
- Age less than 30 years
- Type 1 or type 2 diabetes of less than 10 years duration
- Hypertension
- Cigarette smoking
- Dyslipidemia
- Proliferative or preproliferative retinopathy
- Nephropathy, including microalbuminuria
- Any of the following, regardless of age:
 - Known or suspected coronary artery disease, cerebrovascular disease
 - Autonomic neuropathy
 - Advanced nephropathy with renal failure.

EXERCISE PRESCRIPTION

The physiotherapist should develop an exercise prescription around the person's goals for activity, exercise history, diabetes history including control and complications, medical history, orthopedic conditions, cardiovascular status and motivation/psychosocial issues. Household chores, yard work, recreational activities and activities in work should be included and worked into the plan (Fig. 4.2). The first step in developing the prescription is to conduct an exercise assessment that addresses personal goals for exercise like:

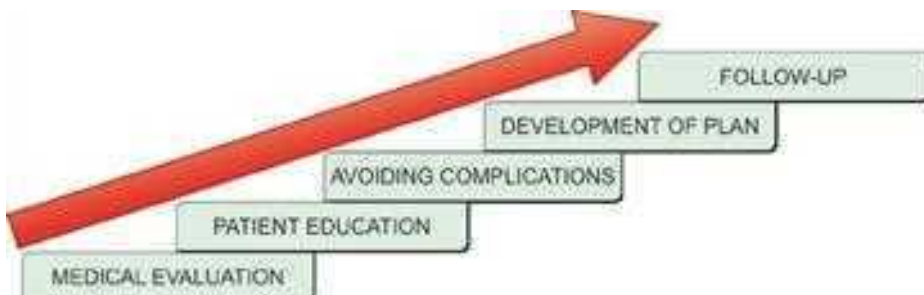


Fig. 4.2: Steps involved in exercise prescription.

- Improved blood glucose control
- Weight loss
- Increased strength and endurance
- Begin competitive athletics
- Reduce cardiovascular risk.

Medical Evaluation

Before beginning an exercise program, the individual with diabetes mellitus should undergo a detailed medical evaluation with appropriate diagnostic studies. This examination should carefully screen for the presence of macro and microvascular complications that may be worsened by the exercise program. A careful medical history and physical examination should focus on the symptoms and signs of disease affecting the heart and blood vessels, eyes, kidneys, and nervous system.

Medical history must include:

- Type and duration of diabetes
- Current level of blood glucose control (HbA1c)
- Presence of complications
- Current diabetes treatment regimen:
 - May range from meal planning and oral agents to intensive insulin therapy or some combination of each
 - Adjustments may need to be made to meal plan or medication to accommodate exercise and prevent hypoglycemia
- Frequency of self-monitoring blood glucose
 - Self-monitoring blood glucose may need to be frequent to determine effect of exercise and prevent hypoglycemia

Frequency and severity of hypoglycemia especially in relation to exercise will indicate the adjustments that need to be made so that the risk is minimized in the future

Comorbid conditions should also be assessed in order to develop a safe plan that will minimize risks.

Along with medical evaluation, other aspects like an exercise history and motivation/psychosocial issues need to be evaluated.

Exercise History

- Type of exercise that is currently performed or has been performed in the past
- Effect of exercise on health and diabetes control
- Enjoyment of activity.

Motivation/Psychosocial Issues

- Social support: Exercise partners and emotional support from family members and friends
- Interests, past successes and challenges with exercise
- Selection of a time and frequency of exercise that can be consistent, for the lifestyle of the individual.

Patient Education

- Patient hand-outs in different languages can be used
- Training should be given to the team to talk to individual patients
- Video programs on the subject can be shown in the patient waiting room
- Interview with patients who have benefited from exercise to share how they overcame barriers and how exercise has made a difference in their life and in the control of diabetes can be also be screened
- Once this is done, only the technical aspects can be addressed.

Avoiding Complications

In most patients, exercise lowers blood glucose levels and hypoglycemia and related complications are to be anticipated and avoided. Patient should be advised to:

- Stop exercise if symptoms of hypoglycemia occur during exercise
- Check blood glucose before and after exercise
- Eat a snack with 15–30 gm of quickly absorbed carbohydrate like hard candies, juices etc. prior to exercise depending on pre-exercise blood glucose
- Always have water and snacks handy during activity
- Wear a medical identification tag to protect in case of emergency
- Exercise with a friend whenever possible
- Avoid exercise when the patient is feeling ill.

Timing of Exercise

To prevent hypoglycemia, workouts should be timed in relation to meals and medication:

- Exercise should always be 1–3 hours after eating something
- Diabetics who are on insulin should not exercise when their insulin is at its peak
- Since exercise can lower blood glucose hours later, exercising just before bedtime should be avoided to prevent hypoglycemia in the middle of the night.
- Medications may also have to be adjusted.
- In untreated or recently treated patients with proliferative retinopathy, avoid exercises associated with:
 - Increased intra-abdominal pressure
 - Valsalva like maneuvers
 - Eye trauma
 - Rapid head movements

People with peripheral neuropathy, need to avoid repetitive, weight bearing exercises such as jogging, prolonged walking and step aerobics. Repetitive stress on feet affected by neuropathy can lead to ulcers, fractures and joint deformities.

They should be advised to do exercises that do not put stress on their feet such as swimming, bicycling, rowing, seated exercises, arm and upper-body exercises and other nonweight bearing exercises.

In people with diabetes with a severe degree of diabetic autonomic neuropathy, vigorous exercises may divert so much blood to the periphery, that the internal organs may not get sufficient blood. In some cases, blood flow to the brain may decrease such that the person may faint.

Also, autonomic neuropathy may reduce the body's ability to regulate its own temperature and so people with this problem should not exercise in very hot or cold environments because their bodies cannot safely adapt to these temperatures.

They should wear polyester or cotton blend socks to keep their feet dry during exercise. It is also important to drink plenty of water before, during and after exercise.

Realistic Plan for the Individual

A realistic short-term plan should be developed to ensure success. The plan can be adjusted after the person achieves success, to reach more long-term goals.

- The plan fits into the daily routine of the individual in terms of the frequency (the number of times a week), time of each day that is spent on exercise
- The type and intensity of the exercise is not too difficult for the person to master
- The activity or activities chosen are enjoyable for the person to perform
- Include whenever possible the daily activities that are done such as housework, walking to and from the bus stop, etc. and expand upon them so that they meet the recommendation of 30 minutes of exercise per day.

The exercise prescription should include:

1. *Warm-up period*: 5–10 minutes of aerobic activity such as walking or bicycling at low intensity. The warm-up is to prepare the muscles, heart and lungs for the forthcoming intensive activity
2. Period of intense exercise
3. *Cool down period*: Occurs following the period of intense exercise. It should last for 5–10 minutes and consists of the same activities as the warm-up. The purpose is to gradually bring the heart rate down to the pre-exercise level (Fig. 4.3).



Fig. 4.3: Warm-up and cool-down exercises.

4. Plan to increase intensity or duration of activity over time
5. Specify number of times a week and minutes of activity each day.

The following walking program is an example of an exercise prescription for a person who is interested in walking and has not been active. It has both a warm-up and cool-down period built into it and over time, works to make the person build up the amount of time they are spending doing more intense exercise.

Tips to Start a Walking Program

Before starting a walking program, consider the following points:

- Wear shoes with proper arch support, a firm heel and thick flexible soles that will cushion your feet and absorb shock
- Wear clothes that will keep you dry and comfortable
- Start gradually to avoid stiff or sore muscles and joints. Begin walking faster, further and walking for longer periods of time over several weeks
- Set goals and rewards
- Keep track of your progress with a walking journal or log
- A sample walking program is provided in Table 4.1.

The more you walk, the better you may feel and more the calories you may burn.

Exercise in Children

Children with well controlled diabetes who are on insulin usually have a fall in blood glucose during exercise. Paradoxically, children with poor glycemic control especially with blood glucose less than 250 mg/dL can have worsening of blood glucose control and ketonuria. This is because of the excess counter regulatory hormones leading to inward lipolysis and enhanced conversion of FFA to ketones. The details of exercise prescription and precaution in children are described in detail in the chapter on “childhood diabetes”. Children more than 6 years of age with HbA1c more than 8% are at a greater risk for exercise induced hypoglycemia.

TYPES OF PHYSICAL ACTIVITY

The Mnemonic: “SAFE” exercises are recommended:

- Strengthening exercises
- Aerobic exercises
- Flexibility exercises
- Endurance exercises.

Strengthening Exercises

These are activities that use muscular strength to move a weight or work against a resistive load. Examples include weight lifting and exercises using weight machines. When performed with regularity and moderate to high intensity, resistance exercise increases muscular fitness (Fig. 4.4). Intensity of resistance exercise will be described as “high” if the resistance is less than 75% of the maximum that can be lifted a single time and “moderate” if the resistance is 50–74% of maximum.

Table 4.1: A sample walking program.

	Warm up	Target zone exercising *	Cool down time	Total
<i>Week 1</i>				
Session A	Walk normally 5 minutes	Then walk briskly 5 minutes	Then walk normally 5 minutes	15 minutes
Session B	—Repeat above pattern—			
Session C	—Repeat above pattern—			
Continue with at least three exercise sessions during each week of the program. If you find a particular week's pattern tiring, repeat it before going on to the next pattern. You do not have to complete the walking program in 12 weeks				
Week 2	Walk 5 minutes	Walk briskly 7 minutes	Walk 5 minutes	17 minutes
Week 3	Walk 5 minutes	Walk briskly 9 minutes	Walk 5 minutes	19 minutes
Week 4	Walk 5 minutes	Walk briskly 11 minutes	Walk 5 minutes	21 minutes
Week 5	Walk 5 minutes	Walk briskly 13 minutes	Walk 5 minutes	23 minutes
Week 6	Walk 5 minutes	Walk briskly 15 minutes	Walk 5 minutes	25 minutes
Week 7	Walk 5 minutes	Walk briskly 18 minutes	Walk 5 minutes	28 minutes
Week 8	Walk 5 minutes	Walk briskly 20 minutes	Walk 5 minutes	30 minutes
Week 9	Walk 5 minutes	Walk briskly 23 minutes	Walk 5 minutes	33 minutes
Week 10	Walk 5 minutes	Walk briskly 26 minutes	Walk 5 minutes	36 minutes
Week 11	Walk 5 minutes	Walk briskly 28 minutes	Walk 5 minutes	38 minutes
Week 12	Walk 5 minutes	Walk briskly 30 minutes	Walk 5 minutes	40 minutes
Week 13 and thereafter: Check your pulse periodically to see if you are exercising within your target zone. As you get more in shape, try exercising within the upper range of your target zone. Gradually increase your brisk walking time to 30–60 minutes, three or four times a week. Remember that your goal is to get the benefits you are seeking and enjoy your activity				
*Here is how to check if you are within your target heart rate zone:				
1. Right after you stop exercising, take your pulse: Place the tips of your first two fingers lightly over one of the blood vessels on your neck, just to the left or right of your Adam's apple. Or try the pulse spot inside your wrist just below the base of your thumb				
2. Count your pulse for 10 seconds and multiply the number by 6				
3. Compare the number to the right grouping below: look for the age grouping that is closest to your age and read the line across. For example, if you are 43, the closest age on the chart is 45; the target zone is 88–131 beats per minute.				
<i>Age</i>	<i>Target heart rate zone</i>			
20 Years	100–150 beats per minute			
25 Years	98–146 beats per minute			
30 Years	95–142 beats per minute			
35 Years	93–138 beats per minute			
40 Years	90–135 beats per minute			
45 Years	88–131 beats per minute			
50 Years	85–127 beats per minute			
55 Years	83–123 beats per minute			
60 Years	80–120 beats per minute			
65 Years	78–116 beats per minute			
70 Years	75–113 beats per minute			

Source: The above sample walking program is adapted from National Institute of Health, August 1993 publication no 93-1667.

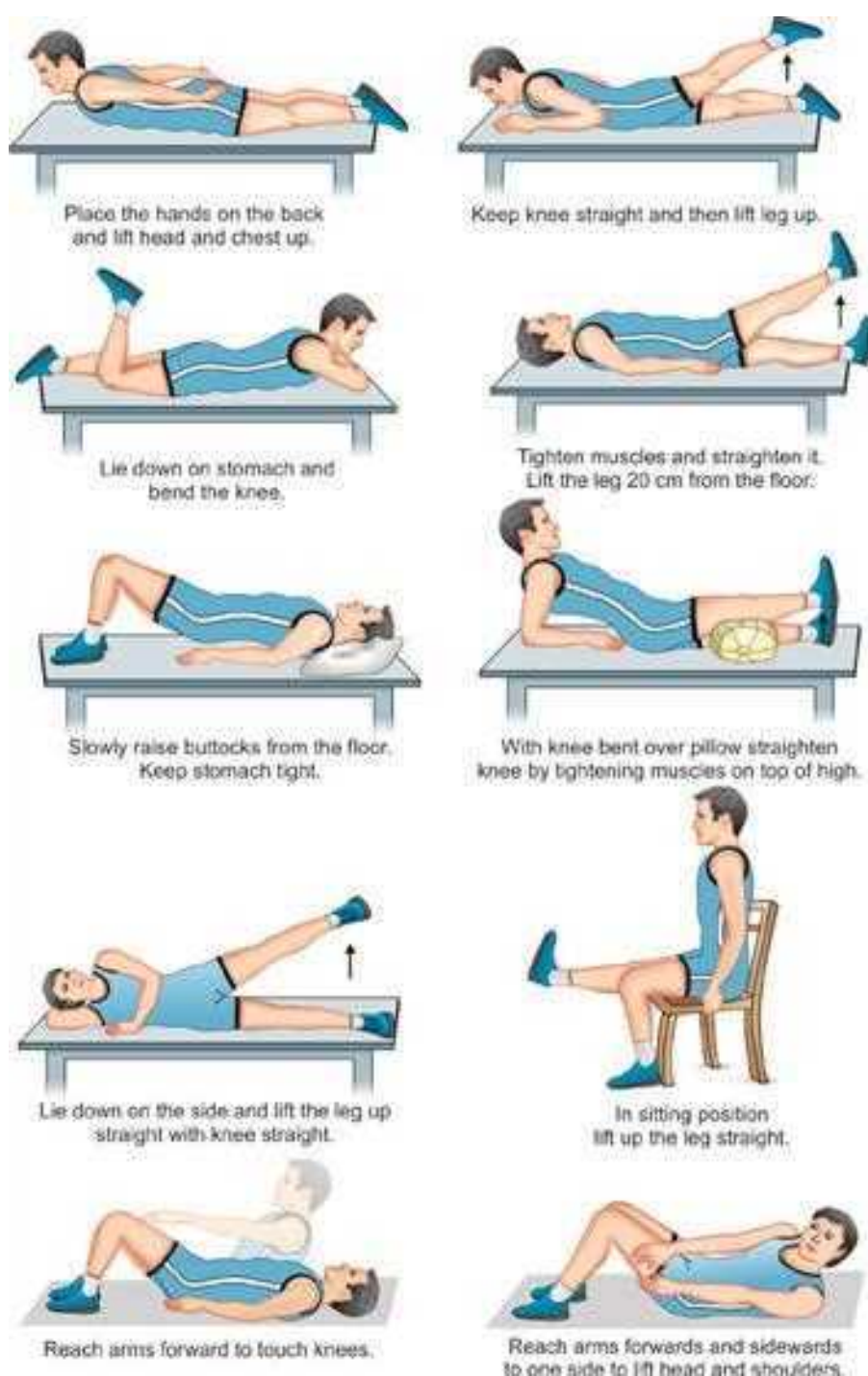


Fig. 4.4: Strengthening exercises.

Aerobic Exercises

Aerobic exercise uses large muscle groups and requires oxygen for sustained periods. This consists of rhythmic, repeated, and continuous movements of the large muscle groups. A total time of about 30–45 minutes a day, at least 5 days a week is recommended for most people. Thirty minutes does not have to be done at the same time. Walking 10 minutes in the morning, 10 minutes at lunch and 10 minutes in the evening can have the same benefit. It is important to get a total of 30 minutes of activity per day, however it is done. Examples include walking, bicycling, jogging, continuous swimming, water aerobics, and many of the sports activities. When performed at sufficient intensity and frequency, this type of exercise increases cardiorespiratory fitness. Intensity of aerobic exercise will be described as “moderate” when it is at 50–70% of maximum heart rate and “vigorous” when it is at less than 70% of maximum heart rate.

Flexibility (stretching) Exercises

Flexibility exercises are aimed at increasing or maintaining range of motion at joints, also improve tone in muscles and keep it supple. They help in developing better muscular and body control. There are various types of flexibility and stretching exercises (Figs. 4.5 to 4.7).

Duration: One should start by holding a stretch for 10 seconds. With practice, one can comfortably hold a stretch for up to 60 seconds.

Frequency: A person can plan to do these exercises at least five times a week.

Endurance Exercises

Endurance refers to ability to perform low intensity, repetitive, or sustained activities over a prolonged period of time. Cardiorespiratory endurance is associated with repetitive, dynamic motor activities such as walking, cycling swimming, or upper extremity ergometry that involve the use of the large muscle of the body.

Non-weight Bearing Exercises

Weight bearing exercises may be difficult for some individuals with significant obesity (body mass index $> 35 \text{ kg/m}^2$), especially those with associated joint degeneration. For these individuals gradually increasing non-weight bearing moderate-intensity physical activity should be encouraged. Non-weight bearing exercise options include stationary cycling, recumbent cycling, seated stepping, upper body ergometry and seated aerobics. In patients with access to a swimming pool regular swimming and water aerobics are other excellent choices.

PRACTICAL CONSIDERATIONS (FIG. 4.8)

How Much Exercise?

- Exercises should be done according to FITT principle:
 - *FREQUENCY:* Exercising 4–6 times a week



Fig. 4.5: Stretching exercises.



Fig. 4.6: Neck range of motion exercises.

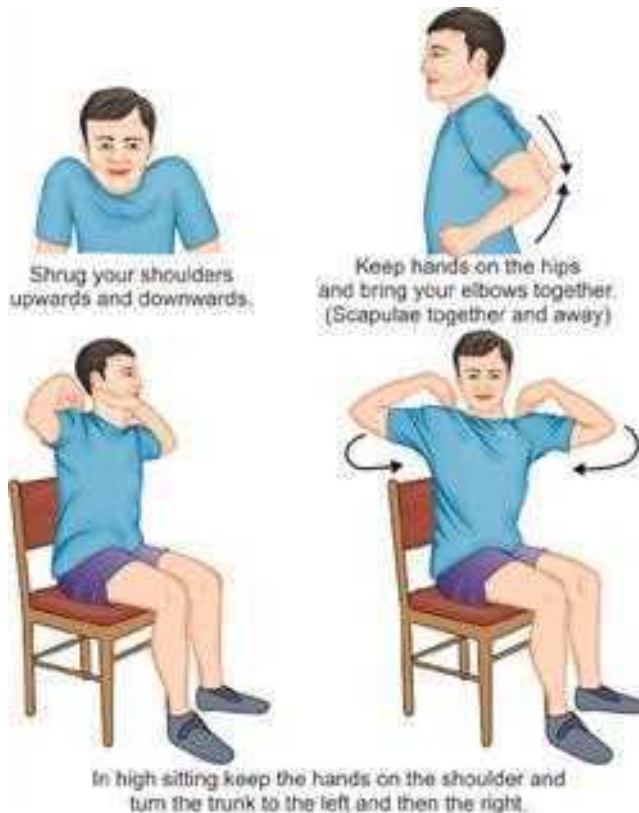


Fig. 4.7: Shoulder range of motion exercises.

- **INTENSITY:** 30–40 minutes of exercise at 50–80% of target heart rate
- **TYPE:** SAFE exercises are recommended
- **TIME:** Morning is ideal.



Fig. 4.8: Steps in prescribing exercise.
(CVD: Cardiovascular disease, BP: Blood pressure).

Table 4.2: Calories utilized in common activities.

Exercise/Activity undertaken	Calories utilized per hour of activity	
	60 kilograms individual	80 kilograms individual
Aerobics general	384	531
Badminton	266	368
Basketball, playing, non-game	354	490
Calisthenics, light, push-ups, sit-ups	207	286
Cycling, more than 10 mph	236	327
Housework, moderate	207	286
Jumping rope, moderate	590	817
Stationary cycling, moderate	413	572
Swimming laps, freestyle, slow	413	572
Tennis- Singles	413	572
Walking 3.5 mph, brisk pace	224	311

Which is the Best Exercise?

The best exercise is the one that your patient will stick to. Walking is considered one of the best choices because it is easy, safe and cheap. Brisk walking can burn as many calories as running, but is less likely than running or jogging to cause injuries. And it does not require any training or special equipment, except for good shoes. Walking is an aerobic and weight-bearing exercise, so it is good for the heart and helps prevent osteoporosis.

How Much Calories Do I Burn with Various Exercise?

The calories burnt in various different activities, depend on a variety of factors including the weight and height of the individual undertaking the exercise and the intensity of the activity. An approximation of the calories utilized in common activities for a 60 kg and 80 kg individual is given in the Table 4.2.

SUGGESTED READING

1. Bally L, Laimer M, Stettler C. Exercise-associated glucose metabolism in individuals with type 1 diabetes mellitus. *Curr Opin Clin Nutr Metab Care*. 2015 May 21. [Epub ahead of print].
2. Roden M. Future of muscle research in diabetes: a look into the crystal ball. *Diabetologia*. 2015 May 24. [Epub ahead of print].

SELF-ASSESSMENT

1. **A 70-year-old lady with diabetes of 10 years duration, evidence of diabetic neuropathy, moderate nonproliferative retinopathy and microalbuminuria, presents to the outpatient seeking advice on exercises. She has no history suggestive of IHD and her recent ECG shows normal tracing. She also has symptoms of degenerative arthritis of the knees. Which of the following statement is not true?**
 - (a) She needs MCR footwear while at home and outside
 - (b) Microvascular complications will interfere with her ability to exercise
 - (c) Her degenerative joint disease limits the weight bearing
 - (d) A Treadmill test is strongly recommended before any exercise prescription
2. **A 22-year-old college going male with grade 3 obesity and recently diagnosed type 2 diabetes, with no evidence of micro- or macrovascular complications has been advised weight loss. All of the following are true except:**
 - (a) Generalized physical deconditioning would limit his effort tolerance to exercise
 - (b) Weight bearing would unduly stress his joints
 - (c) Combination of brisk walking, cycling and resistance exercises would benefit him
 - (d) None of the above
3. **A 26-year-old lady with type 1 diabetes of 13 years with peripheral neuropathy, macroproteinuria, early proliferative diabetic retinopathy and poor glycemic control. She weighs 35 kg and has a BMI of 16 kg/m². All are true regarding her risk except:**
 - (a) Poor glycemic control puts the patient at risk for DKA and hypoglycemic episodes
 - (b) Proliferative retinopathy puts her at risk for developing retinal hemorrhage
 - (c) Diabetic Neuropathy puts her feet at risk for ulceration
 - (d) Physical activity like Valsalva like maneuvers should be included in her exercise regimen
4. **Exercise is described as moderate when the heart rate:**

(a) 50–70% of maximal	(b) 30–50% of normal
(c) >70% of normal	(d) When patients develops moderate dyspnea.

- 5. All the following are benefits of exercise in patients with diabetes except:**
- (a) Reduction in blood pressure
 - (b) Decrease in body fat
 - (c) Reduction in risk for osteoporosis
 - (d) Increased predilection for coronary risk factors
- 6. Which one of the following is not a potential adverse effect of exercise in patients with diabetes?**
- (a) Retinal hemorrhage
 - (b) Hypoglycemia
 - (c) Cardiac dysfunction and arrhythmias due to silent ischemia
 - (d) Renal failure
- 7. If a patient has episodes of hypoglycemia during exercise, he should be advised:**
- (a) To continue exercise as long as he can
 - (b) To eat a carbohydrate snack
 - (c) Not to stop exercise even if ill
 - (d) To always exercise alone
- 8. Exercise prescription involves:**
- (a) Medical evaluation
 - (b) Patient education
 - (c) Avoiding complications
 - (d) Realistic plan for the individual
 - (e) All of the above
 - (f) None of the above
- 9. In the mnemonic SAFE, S stands for:**
- (a) Strengthening exercises
 - (b) Stability exercises
 - (c) Sit-up exercises
 - (d) Endurance exercises
- 10. Which one of the following statements about walking in patients with diabetes is not true?**
- (a) Walking is an aerobic and weight-bearing exercise, so it is good for the heart
 - (b) Brisk walking can burn as many calories as running
 - (c) Walking is considered one of the best choices because it is easy, safe and cheap
 - (d) Walking is contraindicated in patients with Type 2 DM with cardiovascular complications

CHAPTER

5

Counseling

Ruchita Mehra Srivastava

*“Confront a patient: you are faced with his mood,
Could be focused, complacent or generally subdued,
To interact with the person, you must analyze,
The mind and its contents—we cannot compromise.”*

The biggest challenge in a chronic illness is that patients not only have to accept their disease condition but also have to live with it and adapt to it. In diabetes management, wherein the patients are required to take-up an equal share of responsibility in treatment along with their health care team, counseling plays as important a role as treatment itself. The aim of counseling in diabetes management is to help patients accept the diagnosis, know its implications, understand the importance of self-care and life-style modifications, comply with clinician advice and most importantly, have a positive approach towards their life and their treatment. Timely counseling intervention can play a vital role in enabling a patient to lead a good quality of life, and in turn delay disease progression and onset of complications.

INTRODUCTION

Diabetes is a well-known illness, yet ironically its treatment and management remain ineffective practiced. Herein lays the challenge for a clinician in not only explaining the treatment, but also motivating the patient to live with the treatment and helping him psychologically to cope with life as if nothing has happened. This challenge can be well-explained in relation to a doctor’s challenge in educating the patient and simultaneously preparing the mind through counseling. The basic difference between education and counseling is that education only gives knowledge and awareness so that the expected behavioral change is well-understood, while counseling prepares the mind to be open to receive a new belief (Table 5.1). In diabetes management, counseling and patient education go hand in hand.

Table 5.1: Differences between education and counseling.

<i>Education</i>	<i>Counseling</i>
Meaning of a diagnosis	Accepting the diagnosis
How can it be managed	How you can manage it
Why take treatment	How treatment can make you feel better
Do’s and don’ts for the family	Enabling open communication between patient and family
“This is what you need to do”	“You can do it!”

STEPS IN COUNSELING

- A. Rapport-building
- B. Identifying Counseling Goals
- C. Assessment of Patient's Level of Coping
- D. Patient Typing
- E. Practical Considerations
- F. Counseling Intervention
- G. Follow-Up

Rapport-building

Rapport-building is the most important and often overlooked aspect in counseling. In simple words, it means to strike a chord with your patients and make them comfortable. It is the building block of a counseling relationship. The aim of rapport-building is to assure your patients that they can trust you, approach you for help and can open up to you. The easiest way to build a rapport is to ask patients about themselves; where they are from, about their work and their family. If you find something in common with them, share it. If not, simply listen and respond.

Body language is also an important aspect of rapport-building. A smile on the face and eye-to-eye contact makes the patient more comfortable. However, you should always take care to adapt your behavior in accordance to the cultural norms of your setting especially when interacting with patients of the opposite sex.

Identifying Counseling Goals

A patient could have been referred to you by the doctor for counseling, or at times the patient or family would have directly approached you. If you are an educator or social worker, at times you might yourself identify a patient who requires counseling. In any of these scenarios, it is vital to begin with a counseling goal.

Counseling in a health care setting is a tool to enable desirable treatment outcomes. Therefore, some of the common counseling goals are to help:

- Patients and families accept the diagnosis
- Equip them with information on disease management
- Develop a positive and proactive approach
- Initiate and maintain life-style modifications
- Compliance to therapy
- Cope with morbidity of complications
- Treatment by socioeconomic support.

Assessment of Patient's Level of Coping

Different patients cope differently when faced with the diagnosis of diabetes. Hence, assessment of the coping level of the patient is important to decide on the counseling approach. Here, it

is also important to understand that a patient's level of coping may vary at different levels of the disease and treatment.

Stage

Stage of disease has a direct correlation with coping. As the disease progresses, patients tend to lose hope either overtly or intrinsically.

Counseling focus: At early stages of the disease, you must build hope for the patients to help them have a positive approach towards treatment. As the disease progresses, you might need to filter the information. While the nature of prognosis can be communicated to the caregiver, you must always build a positive picture to the patient.

No one can take away hope from this world, and as counselors it is our duty to always give a message of hope.

Previous Knowledge about Disease

Previous knowledge about the disease can affect coping both positively and negatively depending on:

- The amount and quality of the information
- Previous experience with the disease.

Patients equipped with complete information regarding their disease, stage and required treatment will have a proactive response to it. So also, patients with less or no knowledge might not take their treatment very seriously and would be very positive not realizing the implications of the diagnosis. Previous experience refers to a first-hand experience of the disease with a close relative/friend. For example, a patient who has limited information about diabetes, and has seen a close friend having a difficult experience will be very disturbed when diagnosed with diabetes.

Counseling focus: The first step is to evaluate what the patient knows about the disease. If information is incomplete and previous experience is unpleasant, you must explore and address any myths or misconceptions. Explain advances in treatment and how it is possible to treat diabetes and live with it well. If patient is not at all informed, you should share information on the disease and treatment, but in a nonthreatening way so as not to demotivate the patient.

Age

Age can affect coping both positively and negatively. However, age alone cannot determine the coping level of a patient and is interrelated with the stage of disease, previous knowledge, socioeconomic status and family support. A middle aged person would cope well if they have the right family support and the means to take treatment. However, for bread winners of the family, it could also affect negatively as they would be restricted by diabetes in their productive years which can lead to economic constraints. Elderly patients are likely to become fatalistic as age progresses and, therefore, easily accept the disease. But some might get extremely panicky if they do not have adequate family and economic support.

Counseling focus: We will first have to map the patient, and then decide the counseling focus after taking into account the interdependence between age, stage of disease, previous knowledge, socioeconomic status and family support. For example, a 24-year-old person with type 2 diabetes has been diagnosed at initial stages, has poor socioeconomic status and no family support.

In this case, patient will be affected badly as he is in his productive years and belongs to lower socioeconomic status. Untreated disease might not allow him to work, and with no income he will not be able to take any treatment. Also, family will now see him as a burden. Herein, the counselor should first reassure the patient that the disease can be treated, and he can live a normal life and carry on with his work. Family would also have to be counseled on the nature of the disease and how their support to the patient is essential.

Sex

Men and women could be affected differently. For a man, disease takes away a sense of control and brings in dependency resulting in anger and irritability. Some male patients try to mask their hidden fear by way of denial. For a vast majority of women in the Indian setting, a disease brings in concern for the family and guilt on the diversion of resources towards one's treatment.

Counseling focus: Counseling approach for men should focus on bringing back the control, and for women to place greater value to their own self-care. For both the sexes, importance of diabetes self-management for the benefit of themselves and their families should be stressed upon.

Socioeconomic Status

Socioeconomic status has a direct correlation with coping primarily because of the cost of treatment and the loss of income due to the disease.

Counseling focus: For economically disadvantaged patients, a team effort is required by the counselor, doctor and social worker to ensure that affordable treatment options are given to the patient, and also on the ways and means of seeking financial assistance. In the Indian setting, health care costs are very high and there is no social security. Therefore, seeking treatment is equally expensive for middle and high income groups adversely affecting the initiation and compliance to treatment. Here, the counseling focus needs to be on changing their health beliefs, emphasizing the importance of health care and its inter-relation with all the other facets of life, and also how timely treatment can save them from long-term costs.

Family/Peer Support

Family/Peer support has a direct correlation with coping. A patient who has the support of family and friends will cope better as compared to a patient who has no support and/or is looked at as a burden by the family.

Counseling focus: Here, the counselor should play a major role by becoming a support for the patient, especially for someone who has no family and peer support. The patient must be made independent and self-reliant through confidence-building, reassurance and motivation.

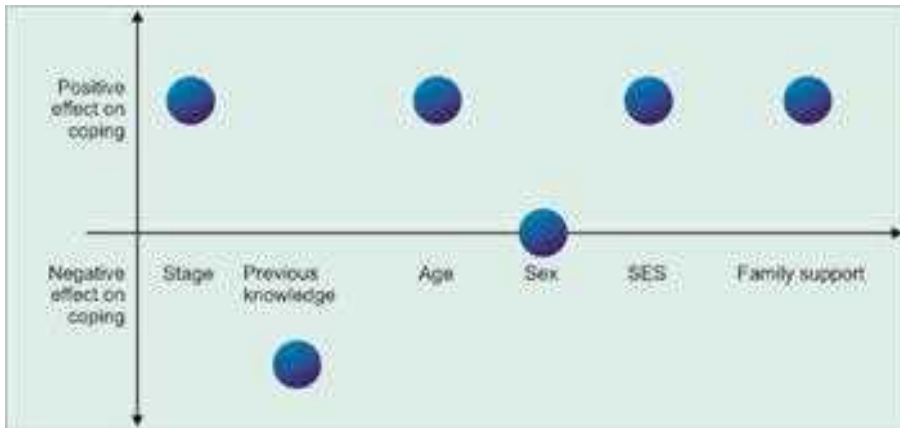


Fig. 5.1: Mapping of patient Mrs. S.
(SES: Socioeconomic status).

As you can see, all the above factors are inter-related. Hence in order to assess the overall coping level, these factors are to be mapped to see how each of these positively or negatively affects coping. For example:

Mrs. S who has been mapped above knows she has an early stage disease which can be controlled. However, she is very fearful of treatment which she has heard is very painful. She is young, has a good socioeconomic support so can afford the treatment, and has a very caring husband (Fig. 5.1).

Therefore, the counseling will focus on clearing her myths about treatment, telling her about the importance of timely treatment since it is an early stage disease and emphasizing on her age and favorable prognosis and how much her family needs her. She needs to get better for them and is lucky to have the means to do so.

Patient Typing

The patient types identified commonly among diabetics are described in Table 5.2.

Recognizing the patient type is helpful to understand their responses to the advised treatment and, therefore, to design the counseling intervention.






Practical Considerations

Certain practical considerations too need be kept in mind especially in our setting wherein awareness about counseling is low, and also the counselor does not have much time with the patient.

- *Time Per Patient*

The time given to each patient depends on the counseling goal identified. Conversely too, if time available at hand with the patient is less, the counseling goal has to be accordingly tailored. For example, in an out patient department (OPD) setting wherein a large number of patients are to be counseled, the first task will be to give basic health education.

Table 5.2: Patient types.

<i>Patient type</i>	<i>Characteristics</i>	<i>Attitude to diabetes</i>	<i>Attitude to controlling diabetes</i>
A. Proactive patient 	Knows severity of the disease Independent and curious by nature Motivated for self-care Well-informed	“I will keep my diabetes under control” “I have a serious problem, but it is not the end of the world.—I just have to make adjustments” “This will actually help me discipline my life”	Fully involved Optimistic Regular for follow-up Follows dietary restrictions Take drugs regularly and on time Exercises regularly
B. Overconfident patient 	Low awareness—claims that he knows it all Self-medication Relies on friends and relatives for advice rather than on his doctor Stubborn Life-style changes inconsistent	“This is not serious—I can manage” “This drug has not worked—let me try the other drug”—tends to experiment “I would not see the doctor this month—I am doing okay!”	Needs flexibility in outline—prefers not to be bound by fixed dietary regimen Does not feel the need for follow-up with the doctor after initial diagnosis and prescription Likes to choose his own medications
C. Skeptical patient 	Wants good results with low inputs Low awareness Lives for today—short-term benefits more important than long-term benefits Looks for low-effort, convenient options	Postpones treatment “I do not want to take Insulin”—looks for alternate drugs/home remedies even though insulin is essential. “Doctor, can you tell me when I can stop treatment?”	Average involvement Irregular for follow-up Lenient in following dietary restrictions Comfortable with OHA; avoids insulin Exercises sporadically; tends to give excuses
D. Resigned patient 	Fear drives him to treatment—“Diabetes will kill me silently” Curses fate “Why me?” Poorly aware—does not seek to know better Lacks self confidence Depends on others Goes by the rules	“This disease will affect my whole life and will finally kill me” “There is no cure—I just have to obey the doctor’s orders” “I cannot enjoy my life anymore” “I must somehow save myself from coma, heart attack and blindness”	Mechanically follows instructions “Doctor’s exercise routine” “Doctor’s medication” “Doctor’s visits” “Doctor’s diet orders”
E. Casual patient 	Not bothered about self-care, health or diabetes No drive to know more “Fate brought this disease—let fate take-care of me” Everything else is more important than self or diabetes Defeatist attitude	“This disease is nothing serious—it can be controlled easily!” “I know I need to exercise control”—but unwilling to practice it “I do not need a regimen to tackle my problem” “Treatment of diabetes is too costly for me—it is not worth the expense”	Does not practice diet control regularly Escapist attitude—gives lame excuses Health is last priority Treatment of diabetes is for getting rid of symptoms and to keep his family happy—not for self

At this time, you can identify patients who need more guidance and call them separately. Individual casework can be undertaken for inpatients.

- *Duration of Association*

In cases where inpatients will be proceeding elsewhere for further treatment, the focus should be to first equip the patient and family with basic health education. Also, enough rapport should be established, so as to assure the patient that you can be contacted for any information and guidance even from their hometown. If time and resources allow, we should follow-up at least once or twice with these patients on phone. If the patient belongs to the same city and is a regular patient to your clinic or hospital, the stepwise counseling intervention plan can be followed.

- *Information Sharing*

How much is too much!

Information sharing should be taken up very consciously with a patient. Health care professionals in their earnest attempt to make the patient realize the importance of self-care sometimes end up scaring the patient, which leads to patients not returning for follow-ups. This also affects the coping level of the patient.

Always, information should be shared in a nonthreatening manner. When information that could disturb a patient is shared, it should be immediately followed with advice on coping. Also, at times you should consider sharing information such as poor prognosis with the caregiver and not directly with the patient.

The amount of information to be given is a decision that a counselor should take after mapping the coping level of the patient as well as studying the patient type.

Counseling Intervention

- Types of Intervention
- Models of Behavior Change.

Types of Counseling Interventions

Basic health education at diagnosis stage/initiation stage: At diagnosis, multiple influences bring in a lot of confusion in the mind of the patient and family. Opinions and suggestions come in from every quarter delaying the decision-making process. Therefore, the first counseling session should include guidance on the disease, its causes and symptoms, available treatments and how it is to be managed. Also lot of fear arises from common myths, misconceptions and limited information. Once these are addressed through counseling, it immediately gives a clearer perspective. Ultimately, patients have the right and responsibility to make the final decision. Counseling can make that decision an informed decision.

Basic health education should be provided to each and every patient irrespective of the setting.

Individual casework: (at each visit to a clinic or a hospital): Individual casework means working with particular patients over a period of time. This involves helping them set their treatment goals, following their progress, addressing their problems and queries during the treatment, and also reaching out to their psychosocial needs. The number of sessions depends on the counseling goal and the patient's coping level. For example, counseling goals would differ

for a patient who is bedridden due to complications, as compared to a young diabetic who is well-informed and is showing good progress in treatment. For the former, counseling would be in-depth and long-term helping him/her slowly to adjust to the circumstances, and to develop a positive approach. For the latter, it would be basic health education followed by few weeks of regular follow-up.

In-depth casework for patients with coping difficulties: In-depth casework is undertaken for patients who face difficulty in adjusting to the demands of the disease. Mood swings, self-pity, social withdrawal, and disturbed interpersonal relationships are indicators of poor coping. In such cases, a joint effort is required from the family members/caregiver, the doctor and the counselor/educator to motivate and reassure the patient.

Referral to psychiatrist/clinical psychologist (for patients showing symptoms of psychiatric comorbidities): Diabetes is considered to be one of the most psychologically demanding of the chronic illnesses and is often associated with several psychiatric disorders. Psychiatric disorders can be a risk factor for, as well as a complication of, diabetes.

Signs of psychiatric illness such as persistent feelings of sadness, anxiety and emptiness (that continue even after three to four counseling sessions), feelings of guilt, helplessness, thoughts of death or suicide with or without suicide attempts, dramatic mood swings ranging from elated excitability to hopelessness, hallucinations, delusions, disorganized thinking and speech, are indicative of a need for referral to a clinical psychologist or psychiatrist.

Psychiatric illnesses are still considered a taboo in some parts of our society; hence this should be handled sensitively and carefully by the counselor.

Models of Behavior Change

Health belief model (to initiate desirable behavior change): The “health belief model” has been used to explain the reasons for the adoption of healthy behaviors or acceptance of preventive health practices. In this model, people’s beliefs are the key factors.

This model states that people calculate “return on investment” based on own perceptions. Factors considered important in health care decisions (Richards 1997):

- Perceived severity
- Perceived susceptibility
- Value of the treatment
- Barriers to treatment
- Cost of treatment—physical and emotional.

In studies, it has been found that cost barriers are the most important factors in making a decision to change. This means that if a change costs too much either in money or time and energy, people are less likely to implement it. It is important for a counselor to understand and address these factors.

- *Perceived severity*
 - Explore the perceived severity of diabetes
 - Ask people how much they know and how serious they think diabetes is
 - Many people do not think diabetes is a significant problem, especially if they do not have to take medication. If they do not think it is serious they are less likely to make a change to improve their health

- What can you do to help: Give some basic information, do not use scare tactics
- Although, it may be tempting to tell people all the worst possible outcomes in an effort to communicate the severity of the condition, it has been shown that scaring people does not result in long-term behavioral change.

- *Perceived susceptibility*

- Ask about perceived susceptibility
- Do they feel that the complications will happen to them?
- Do they feel that they can master this? That while it might happen to others, they will somehow be protected?

People who feel that their diabetes will not progress or that they will not develop complications may be in denial. In these cases, behavioral change is unlikely since the perception is that “nothing is going to happen anyway”.

What can you do to help: Discuss the realities without applying scare tactics. Stay positive and communicate that good management will reduce likelihood of disease progression.

- *Value of treatment*

- Ask how people perceive the value of treatment?
- Do people think that the medication or treatment will make a difference?

Sometimes people with diabetes have seen others take a medication and subsequently develop complications. They may think that, therefore, the medication does not “work”. Sometimes people are afraid of a treatment and its side effects; or, as is the case of insulin, people are afraid of administering it.

What can you do to help: Inform people about all the treatment options. Explore all their fears. If they have had a negative experience, you should encourage them to tell you about it so that you can put it into perspective. Make sure that they know what to expect from a medication.

- *Barriers to treatment*

- Explore the barriers to treatment.

The cost of a medication is an important barrier. However, other key factors include the cost in terms of time, side effects, or disruption to daily activities. People weigh-up the benefits they can expect from a medication or change in behavior against the cost. If the cost outweighs the benefits, it is unlikely that the change will be implemented.

What can you do to help: Find out the costs for the individual, not only in financial terms but also in other areas. Then help the person find ways to overcome those costs.

In summary, the health belief model focuses on people’s beliefs regarding the condition and the treatment. Your role as a health care provider is to find out what these beliefs are and help people develop realistic perceptions that will result in positive health behavior.

Now, if we correlate these health beliefs with our patient types, what would commonly emerge is shown in Table 5.3.

Empowerment model (to maintain behavior changes): This model states that our job is not to make people change, but to provide information, inspiration and support that will enable them to make the changes of their own choosing. Diabetes is primarily a self-care condition.

Table 5.3: Correlation of health beliefs with patient types.

	<i>Perceived severity</i>	<i>Perceived susceptibility</i>	<i>Value of treatment/life-style modifications</i>	<i>Cost (Tangible/Intangible)</i>
The proactive patient	High	High	High	Low
The skeptical patient	High	High	Low (as will always seek immediate answers)	High (unless it shows immediate results)
The resigned patient	High	High	High but anxiousness negatively affects approach to treatment	Low (anything to take diabetes away)
The casual patient	Unsure	Unsure	Unsure	High
The overconfident patient	Unsure but pretends otherwise	Unsure but pretends otherwise	Low	High

People with the condition, in whatever setting, make multiple and complex decisions about the way they manage their diabetes on a day-to-day basis. For example, one day people can choose to take their blood glucose-lowering medication, and another day chooses not to.

The empowerment model is based on a five-step approach to self-directed goal setting. Each step is equally and critically important.

- *Identify the problem:* The first step is to identify the problem.
 - It is important to identify any problem from the person’s perspective—not that of the counselor.
 - Ask questions which help the person to obtain clarity. Usually, asking “why is that?” several times will help you get to the root of a problem.
 - Solutions that do not address the problem itself are doomed to fail. We are not responsible for solving people’s problems; the solutions that are the most meaningful and effective must be determined by the person with the problem.
 - Our job is to ask questions that will help people to identify a solution.
- *Explore feelings:* Step two is to determine how this problem affects people with diabetes and their behavior.
 - Asking people to describe their thoughts may be less threatening than asking about feelings. Statements such as “It sounds as if you feel embarrassed about having to test your blood glucose at work” show that you are listening and attempting to understand the person’s feelings.
 - Feelings are not problems to be solved! As a counselor, you need to just listen.
- *Set goals:* The next step is to help people to decide on their objectives.
 - Asking “what” several times can help the person to obtain clarity about their intentions.
 - It is important to find out people’s level of commitment. Ask “On a scale of one to ten, with ten being the highest, how important is this for you?” If people give a low number, ask if this is truly an area that they wish to address immediately. If they indicate a high number, acknowledge their level of commitment.
- *Make a plan*
 - It is very important to help people to identify one action that they can take to initiate the steps towards their goal.

Table 5.4: Models of behavior change.

	<i>Health belief model</i>	<i>Empowerment model</i>
Basic principle	In this model, people's beliefs are the key factors; people calculate "return on investment" based on own perceptions	According to this model, we need to acknowledge that our job is not to make people change, but to provide information, inspiration and support that will enable them to make the changes of their own choosing
Suggested for	Initiating desired behavior change	Maintaining behavior change
Intervention through	Assessment and addressal of Perceived severity Perceived susceptibility Value of the treatment Barriers to treatment Cost of treatment—physical and emotional	Self-directed goal setting Identify the problem Explore feelings Set goals Make a plan Evaluate the results

- A plan should be— realistic, completely within their control, measurable and personally meaningful.

Goals such as weight loss or blood glucose readings are generally not completely within the control of people with diabetes. It would be more useful to identify behaviors that help them to reach these goals. For example, they may have control over what they choose to eat and decide to eat less servings of a chosen foodstuff.

- *Evaluate the results:* One approach is to encourage people with diabetes to think of these steps in terms of experiments rather than successes or failures. The benefit of an experiment is that you can always learn from it. In fact, our most helpful learning often comes from experiments that did not work well. The process then begins again with either the same or a new selected action. The two models are compared in Table 5.4.

In summary, the empowerment model focuses on recognizing that we cannot motivate another person but can only assist people with diabetes in selecting and attaining goals that are meaningful for them. They can empower themselves when they know what they want to achieve and have the necessary support to do so.

Follow-up

Nature of follow-up depends on type of intervention. It also important to get the family members involved.

Counseling Caregivers and Family Members

While the patient is the focus of the entire counseling intervention, it is also essential to take out time to guide the immediate attendant (spouse/children/parents/friends) of the patient. The counseling process herein could involve:

Basic Health Education

To equip them with information related to managing the patient with regard to treatment.

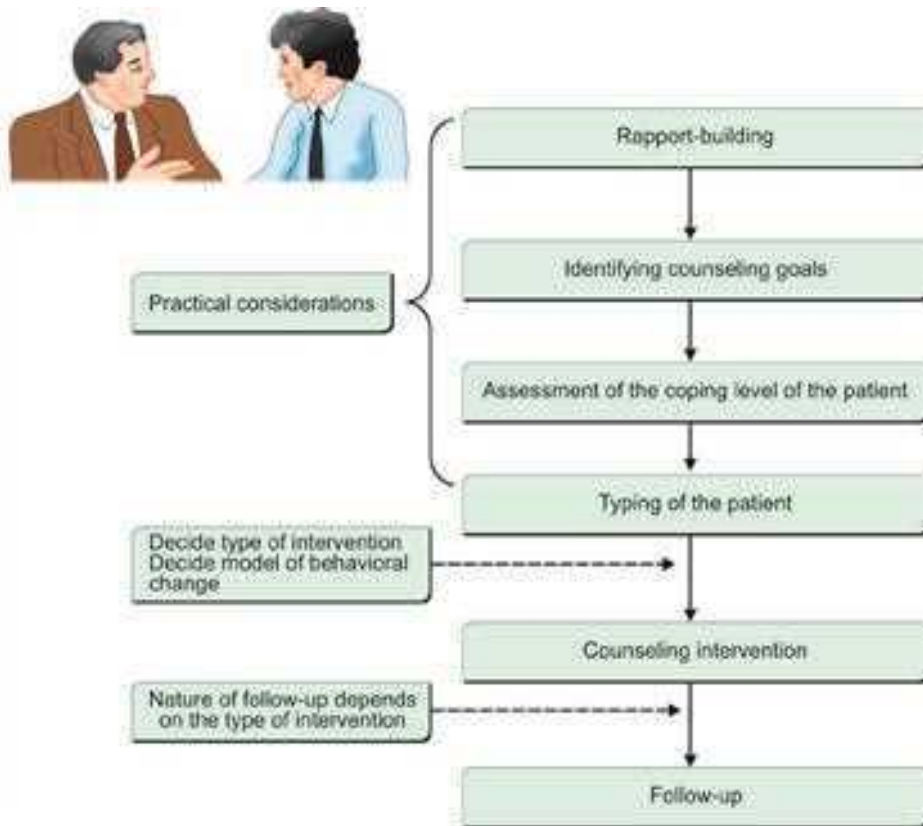


Fig. 5.2: The counseling process.

Individual Casework for “Caregiver Stress”

Caring for their loved ones can make caregivers forget themselves. They feel guilty if they leave the patient unattended, they stop going out due to social pressure, and this leads to burnout or “caregiver stress.” This also brings in feelings of guilt in the patient. Therefore, counseling on the importance of self-care is a must.

Family Therapy

Involves opening-up communication channels between patients and their families. When faced with a disease, at times an insecurity and fear develops in the patient’s mind regarding the acceptance of his/her condition by the family. At this stage it is very important for them to feel the family’s unconditional love and care, as that will motivate them to want to get well again. Family members need to be counseled to trust the patient and, hence, avoid constant nagging. This becomes especially important in the case of patients who have been independent and in control of their lives before being diagnosed. There is a time to care, and a time to just let the other person be. The counseling process is depicted in (Fig. 5.2).

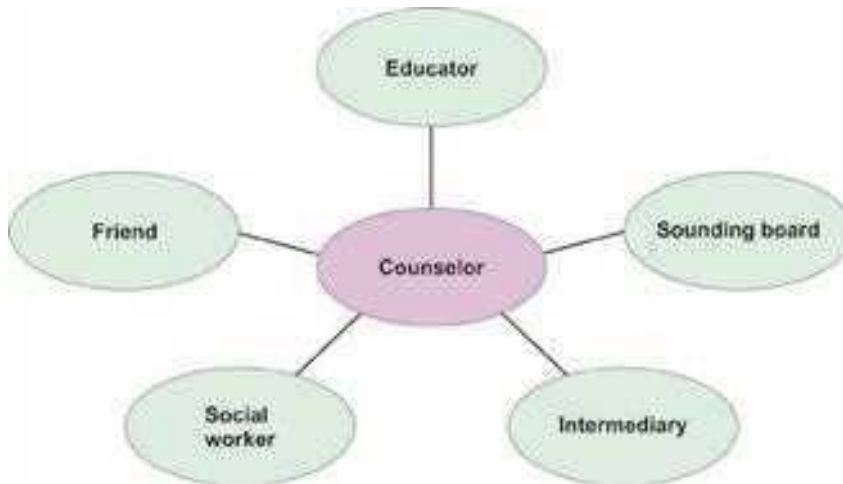


Fig. 5.3: Role of the counselor.

CONCLUSION

Health care in today's world is moving over from pharmacotherapy to a more patient-centric treatment approach wherein the "patient's will" is of prime importance. Relying on counseling is relying on one's own will-power. Counseling brings in confidence, confidence brings in will-power and we all know that "where there is a will, there is a way". The role of the counselor is depicted in Figure 5.3.

CASE STUDIES

Case 1

Mr. V, age 43, a jeweler by profession, has just got diagnosed with diabetes. His father was also a diabetic and died of a heart attack. He has come to the local hospital and has been prescribed insulin. His wife has shared that the patient does not want to start therapy and instead wants to consult a local healer.

The doctor has sent Mr. and Mrs. V to you for counseling.

- What is the counseling goal?
- How will you map this patient's coping level?
- What is your patient type?
- What type of counseling intervention would you undertake?
- What model of behavior change would you use?
- Are there any practical considerations that you have to account for?
- Design your step-wise counseling plan for this patient?

Discussion

Most of the time, this is all the information that a counselor receives about a patient during a referral. From the available information, we have some cues (Table 5.5).

Table 5.5: Cues and their interpretation.

Cues	What they mean
Referred by doctor	Probable goal is to help the patient and to initiate the therapy
Newly diagnosed patient	Initial shock, anger and fear
Jeweler by profession	Will be able to afford treatment
Family history of diabetes	Previous experience may impact the coping level
Hesitation to start therapy	Has some misconceptions regarding treatment and therefore fears it

Mr. V, age 43, a jeweler by profession, has just got diagnosed with diabetes. His father was also a diabetic and died of a heart attack.

He has come to the local hospital and has been prescribed insulin.

His wife has shared that the patient does not want to start therapy and instead wants to consult a local healer.

The doctor has sent Mr. and Mrs. V to you for counseling.

Before meeting the patient, the counselor should have a meeting or a telephonic discussion with the referring doctor to identify the counseling goal.

Step 1: Rapport-building

Mr V might not be so keen to meet a counselor since he does not want to start treatment and therefore, will be against any person who suggests otherwise. Your rapport-building process should focus on making him understand that you are on his side, and you can answer any queries regarding why the doctor has prescribed the said treatment. It would help to have a quiet place for the first session, have a smiling face, maintain eye-to-eye contact and use open-ended questions to know the basic demographic details, disease history, and family background.

Step 2: Identifying Counseling Goals

The probable counseling goals in this case are:

- Help Mr. V and his wife accept the diagnoses
- Equip them with information on disease management
- Encourage them to initiate the therapy
- Help develop a positive and proactive approach.

Step 3: Assessment of Patient's Level of Coping

A lot of interaction is required to assess the coping level of a patient (Fig. 5.4). This should be done during the course of rapport building through open-ended questions, observing the body language and the interaction between the patient and the accompanying caregiver. Some examples of open-ended questions are:

To assess understanding of the stage of disease: What did the doctor tell you about your illness?

To Assess Previous Knowledge

Have you seen any close person having diabetes? How are they now? What treatment did they take? Did it help them? What do you know about diabetes and its treatment?



Fig. 5.4: Mapping of a patient, Mr V.

Socioeconomic Status

Do you have health insurance? How will you be bearing the cost of the treatment? Will treatment be causing financial strain to you?

Assumptions for Mapping

Mr. V has been prescribed insulin at diagnosis. This, for him could be an indicator of advanced stage of disease and could have a negative effect on coping. He is not keen to start treatment and his father had diabetes and died of a heart attack. From the former, it appears that the patient is not well-equipped with information on the disease and importance of treatment and from the latter we gather that previous experience with the disease has been unpleasant. He appears to be able to afford the treatment; therefore, financial burden will not be there. The presence of his wife and her willingness to seek a counselor's help indicate positive family support.

Step 4: Patient Typing

The type of patient cannot be assumed without meeting a person. From the information available, he could be a skeptical patient or a resigned patient.

Step 5: Practical Considerations

The first interaction in this case has to be the most effective as this is the time that the patient will be making the decision whether to start treatment or not. Hence, the counselor should give sufficient time; *at least 30 minutes*, if not more. Information should be shared in a nonthreatening way with a focus on removing myths and misconceptions. The importance of treatment for a healthy disease—free life as well as to reduce the risk of complications should be shared.

Step 6: Counseling Intervention:

Type of intervention: Basic health education followed by Individual casework at each visit to the hospital.

Model of behavior change: health belief model: to find out the patient's belief regarding his disease and condition and to help him develop realistic perceptions for positive health behavior.

Step 7: Counseling to Caregiver:

The counselor should take out some special time for Mrs. V. The counseling process should touch on. Basic health education, individual casework and family therapy.

Case 2

On your ward rounds, you have come across Mr. M, a known diabetic since the last 10 years. He has come to your hospital with a fasting of 250 and postprandial of 380. He has already developed retinopathy and neuropathy. His past history shows that he has changed over 15 doctors. His compliance to treatment had been poor as he has never followed doctor's advice over 6-8 months. On two occasions in the past, he himself discontinued treatment. Even though, yours is the most prominent hospital in the city, he has come to the diabetologist here for the first time. The patient is to be discharged the next day.

Design your step wise counseling plan for this patient?

Discussion in Brief

The counseling goal for this patient which is essential for a desirable treatment outcome is—to help compliance to therapy, initiate and maintain life-style modifications and to help develop a positive and proactive approach to treatment. Assessment of this patient's coping level has to be done very thoroughly to understand the hurdles making this patient switch treatment. This patient could be the *casual patient or the overconfident patient*. The counseling intervention should involve basic health education followed by in-depth casework. A combination of both the models of behavior change should be used; the health belief model to understand the patient's beliefs behind his health behavior and the empowerment model to make the patient take responsibility of his actions and help him make the change as per his choosing. Since this patient resides in the same city, the counselor should take in-depth casework across many sessions. We have to understand here that a health behavior practiced for 10 years will not go away in 3-4 sessions. Some fear would have to be induced in the patient. Also, follow-ups will play a key role towards compliance to treatment and suggested life-style modifications.

Also, the counselor should identify a family member and make them a partner in this process because he/she would be with the patient all the time.

ACKNOWLEDGMENT

The models of behavior change featured in this Chapter have been adapted from a publication titled 'Diabetes Education Modules' (Educational resources supporting the content of the

International Curriculum for Diabetes Health Professional Education) by International Diabetes Federation: *Behavioral change Section 1. 3 of 4 Curriculum Module I-4 | Psychosocial and behavioral approaches, International Diabetes Federation, Brussels, 2006.*

SUGGESTED READING

1. Mitchell C, Catalan J, McIntosh C, et al. Joint liaison psychiatry-diabetes clinic: a new specialist service. *Diabet Med.* 2000;17(6):481-3.

SELF-ASSESSMENT

1. **Steps in counseling include all *except*:**
 - (a) Rapport-building
 - (b) Clinical examination
 - (c) Patient typing
 - (d) Assessment of patient's level of coping
2. **Identify patient type:**
 - Well-read and well-informed
 - 'Diabetes is serious but can be controlled'
 - Regular visits to the doctor and check-ups

(a) The skeptical patient	(b) The over-confident patient
(c) The proactive patient	(d) The casual patient
3. **Identify patient type:**
 - Laid back attitude towards self-care, health and diabetes
 - Does not realize the seriousness of the disease
 - There is no regular control that is practiced

(a) The over-confident patient	(b) The skeptical patient
(c) The Proactive patient	(d) The casual patient
4. **For a patient facing difficulty in adjusting to the demands of the disease and showing poor coping, which type of counseling intervention would you use**

(a) Basic health education	(b) In-depth casework
(c) Referral to clinical psychologist	(d) All of the above
5. **For the above patient, which model of behavior change is applicable and why?**

(a) Health belief model	(b) Empowerment model
(c) None of the above	(d) All of the above
6. **According to the Health Belief Model, people calculate 'return of investment' based on all *except*:**

(a) Perceived severity	(b) Value of treatment
(c) Cost of treatment	(d) Previous family history
7. **For an over-confident patient, all of the following are true *except*:**

(a) Low perceived severity	(b) Low perceived susceptibility
(c) Low value of treatment	(d) Low cost of treatment

CHAPTER

6

Oral Antidiabetic Agents

Senthil Vasan K, Nitin Kapoor, Nihal Thomas

*“Metformin-foundation, can reduce your weight,
Sulphas cause hypos, don't take them too late,
Glitazones, problems with regards to weight
Gliptins are safe, taken in any state.”*

The mainstay of treatment of type 2 diabetes includes diet, modifications of lifestyle and oral antidiabetic agent (OAD) therapy. The major aims are not only to improve glycemic control and reduce the weight of obese patients but also to reduce the risk of cardiovascular disease, reduce adverse effects and improve compliance. The specific medications used in patients with type 2 diabetes are determined by clinical judgment about the likely balance between beta-cell impairment and insulin resistance. Preventing hypoglycemia and improving compliance through less frequent dosing are the other important targets. The menu of medications has expanded greatly over the last decade and even more in the pipeline, this is especially because of a greater understanding of the pathogenesis of type 2 diabetes mellitus (T2DM) at least eight organs being implicated in the pathogenesis (Fig. 6.1).

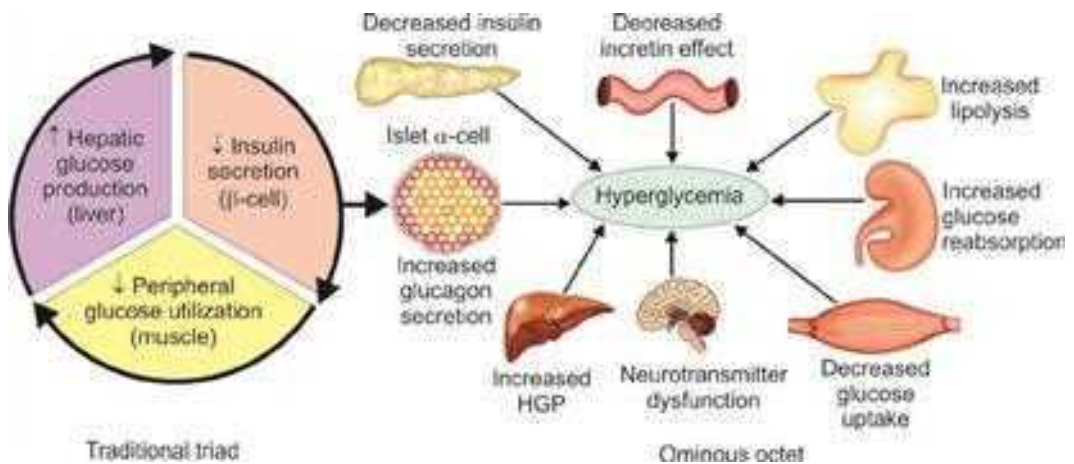


Fig. 6.1: Diabetes pathophysiology: Traditional triad to ominous octet.¹
(HGP: Hepatic glucose production).

ROLE OF ORAL ANTIDIABETIC AGENT THERAPY IN TYPE 2 DIABETES MELLITUS

Oral antidiabetic agents follow diet and exercise in the management of an individual with frank diabetes mellitus (Table 6.1). While trying to use OADs in the control of diabetes mellitus, one should also try and attempt to:

- Conserve islet cell function and thereby delay subsequent use of insulin
- Decrease the prevalence of hypoglycemic episodes
- Improve patient compliance with medications (attempting to reduce the frequency of dosing)
- Consider the cost factor when the affordability of the patient comes into play.

The mechanism of actions of various classes of OADs is summarized in Figure 6.2.

BIGUANIDES

The underlying mechanism of biguanides in glycemic control includes:

- Reduction in hepatic gluconeogenesis
- Reduction in appetite

Table 6.1: Oral antidiabetic agents.

<i>Class</i>	<i>Medications</i>	<i>Target pathogenetic factor</i>	<i>Mode of action</i>
Sulfonylureas (SU)	Glibenclamide, Glipizide, Gliclazide, Glimepiride	Reduced beta cell function → ↓ insulin secretion	Stimulates insulin release (secretagogue)
Meglitinides	Repaglinide, Nateglinide		
Biguanides	Metformin	Hepatic insulin resistance (elevated hepatic glucose output)	Inhibits hepatic glucose production → Insulin sparing
Alpha glucosidase inhibitors	Acarbose, Miglitol, Voglibose	Excess calorie intake—intestinal absorption of glucose	Delays/inhibits carbohydrate absorption in the gut
Thiazolidinediones	Pioglitazone	Adipocyte and peripheral muscle insulin resistance	Improves peripheral insulin sensitivity
Dipeptidyl peptidase (DPP) inhibitors	Vildagliptin, Sitagliptin, Saxagliptin, Linagliptin	Incretin mediated insulin secretion, Excess calorie intake—intestinal absorption of fat	Glucose induced insulin response
Dopamine agonists	Bromocriptine	Insulin release under vagal control	Hypothalamic dopamine release
Quinine derivatives	Hydroxychloroquine	Augment insulin release and action	Increase affinity of insulin to insulin receptor
Sodium-glucose cotransporter 2 (SGLT2) inhibitors	Dapagliflozin Canagliflozin Empagliflozin Ipragliflozin	Enhanced glucose excretion	Inhibits SGLT2 receptors and reduces glucose reabsorption

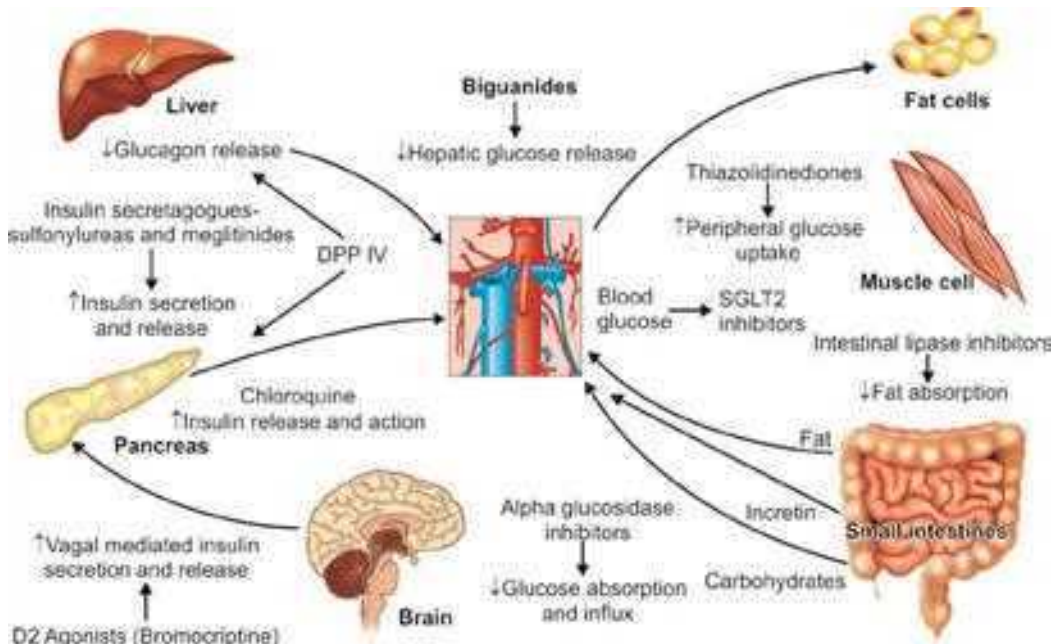


Fig. 6.2: Mechanism of action of oral antidiabetic agents (OADs).
(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors).

- Inhibition of intestinal absorption of glucose
- Increase in insulin-mediated glucose utilization in peripheral tissues such as muscle and liver.

Besides the abovementioned functions, biguanides also help in lowering triglycerides by decreasing the hepatic synthesis of triglycerides.

Adverse Effects of Biguanide Therapy

- Nausea and diarrhea (< 5%): Diarrhea may be a transient phenomenon and may subside in 3–4 days. Start with a lower dose and increase gradually to minimize gastrointestinal side effects
- Vitamin B12 malabsorption (< 0.2%) and more than 10% in the elderly more than 60 years
- Lactic acidosis when prescribed in renal failure (metformin does not interfere with mitochondrial inhibition of lactate formation and therefore spontaneous lactic acidosis is rare as compared to phenformin. Moreover, it is more hydrophilic unlike the lipophilic phenformin and is not dependent on hepatic degradation).

Dose

Metformin can be used up to 1 g thrice a day and it is also available as extended release (or sustained release) form. It is important to inform patients who are on the sustained release form that the active principle is absorbed and the vehicle is excreted in the stool and this does not interfere in the action of the drug.

Therapeutic Application

- Drug of choice in obese T2DM
- As an add on to dietary therapy in T2DM
- Failure to achieve optimal glycemic status with sulfonylureas (SUs).

Contraindications

Metformin is contraindicated in the following situations:

- *Renal impairment:* Plasma creatinine values more than 1.5 mg/dL for men and more than 1.4 mg/dL for women. More recently there is evidence to suggest that it can be advocated with a creatinine of up to 1.7 mg/dL
- Cardiac and respiratory insufficiency that is likely to cause central hypoxia or reduced peripheral perfusion. However, there are studies to show that it can be tolerated in class IV cardiac failure, provided renal functions are normal
- History of lactic acidosis
- Severe infection that could lead to decreased tissue perfusion
- Liver disease, including alcoholic liver disease. Interestingly, there are studies to show that it may inhibit hepatitis C viral replication
- Use of intravenous radiographic contrast material (relative contraindication).

SULFONYLUREAS

Sulfonylureas augment insulin response by binding to the receptor on the extracellular domain of ATP modulated K^+ channels and causes its closure (Table 6.2). This depolarizes the membrane leading to the entry of calcium through voltage dependent calcium channels (VDCC) and the resultant increase in intracellular Ca^{2+} concentrations lead to fusion of insulin-containing vesicles to the plasma membrane and subsequent rapid exocytosis of insulin from β cells. In addition to this, some SUs are now known to directly activate the cAMP sensor Epac2 (exchange protein activated by cAMP 2) to induce Rap1 signaling which can induce the exocytosis of insulin-containing vesicles (Figs. 6.3A and B). The distinct effects of various SUs appear to be because of their differential actions on Epac2/Rap1 signaling as well as K_{ATP} channels. Kir 6.2/SUR2A is present in the cardiac cell membrane (sarcolemmal) channel which closely mimics the SUR1. First-generation SUs like glibenclamide prevent cardioprotection induced by ischemia by interacting with mitochondrial K_{ATP} channels, whereas second generation SUs are thought not to interfere with ischemic preconditioning.

Table 6.2: Drug profile: Sulfonylureas.

<i>Sulfonylurea</i>	<i>Duration of action</i>	<i>Mode of metabolism</i>	<i>Daily maximum dose</i>
Glibenclamide	Up to 24 hours	Hepatic and renal	10 mg BD
Glipizide	Up to 2 hours	Hepatic	10 mg BD
Gliclazide	10–20 hours	Predominantly renal	160 mg BD
Glimepiride	Up to 24 hours	Hepatic	8 mg OD

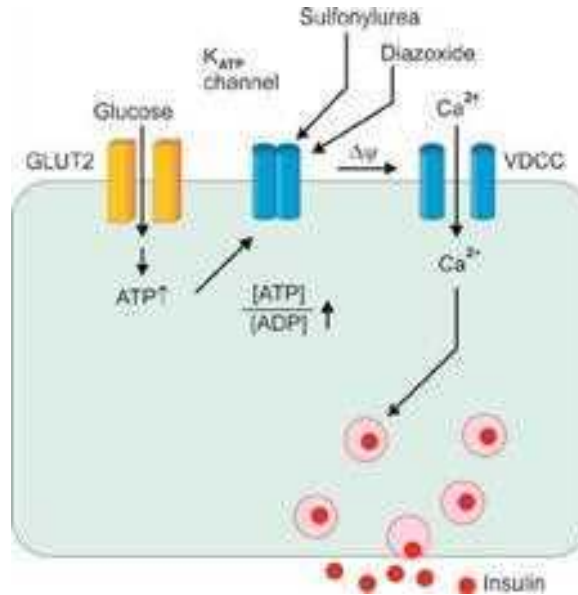


Fig. 6.3A: Mechanism of action of sulfonylurea.

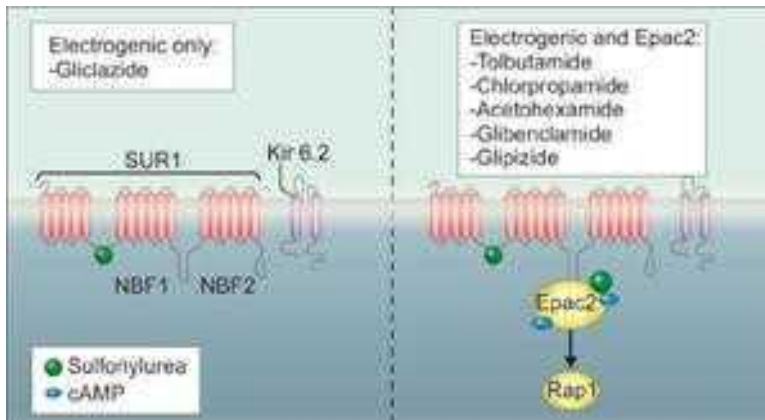


Fig. 6.3B: Differential effects of sulfonylureas on SUR and Epac2.

Source: Hinke SA. Epac2: a molecular target for sulfonylurea-induced insulin release. *Sci Signal*. 2009;2(85):pe54.

Available Agents

Glibenclamide

This is the most commonly used OAD available as a micronized formulation with consistent bioavailability. Its efficacy in reducing hyperglycemia is equal to other SUs but, it is associated with high rates of side effects including its long duration of action causing serious hypoglycemia and modest weight gain.

Glipizide

Glipizide is available in both short-acting and extended release forms. Its shorter duration of action necessitates multiple doses a day. Better control of postprandial blood glucose is achieved with glipizide. With long term use it maintains an insulinotropic action. It can be used in patients with mild to moderate renal impairment (creatinine clearance > 30 mL/min).

Gliclazide

Besides its role as an antidiabetic, it has a favorable influence over platelet aggregation and fibrinolysis. Several studies have shown that gliclazide has antioxidant properties, reduces markers of endothelial inflammation, and prevents glucose-induced apoptosis of endothelial cells. These positive antioxidant effects are not confined to the vascular wall but they are effective also in the β cells. Weight gain is usually not observed in subjects with gliclazide. A sustained release form of gliclazide also is available.

Gliclazide also reduces the adhesion of monocytes to endothelial cells, and does not interfere with ischemic preconditioning.

Glimepiride

It has rapid onset and prolonged duration of action.

It has more selectivity for beta-cell K_{ATP} channels. It binds to the 65 kDa receptors leading to more rapid onset and longer duration of glucose lowering effects (other SU target 140 kDa proteins) (Fig. 6.4). It has an insulin mimetic effect in the peripheral tissues possibly mediated by glucose transporter type 4 (GLUT-4).

Glimepiride does not restore first phase insulin secretion and it increases second phase insulin secretion, whole body glucose uptake and increases insulin sensitivity. Glimepiride treatment is associated with lower rates of hypoglycemia than other sulfonylureas.

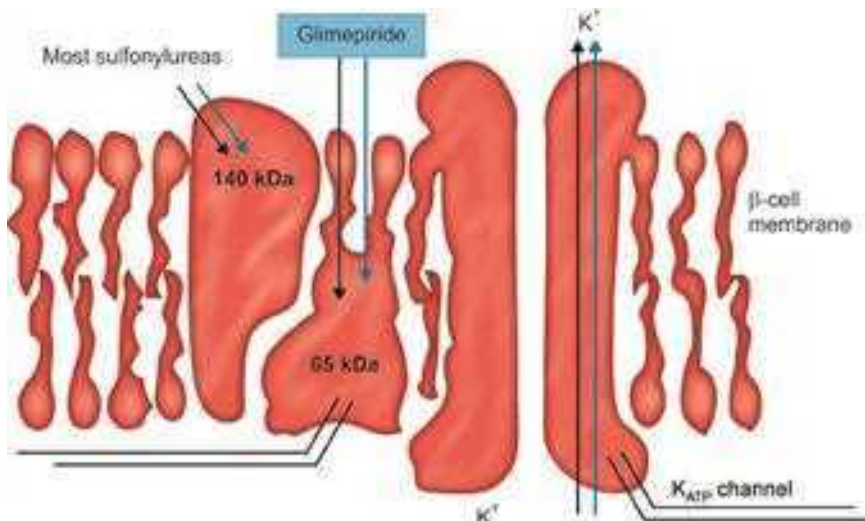


Fig. 6.4: Mechanism of action of glimepiride versus other sulfonylureas.

Glimepiride versus other Sulfonylureas

Glimepiride is therapeutically more advantageous because:

- Prevents postexercise insulin release and therefore has a reduced risk of hypoglycemia
- Does not accumulate in the body with reducing renal function and its hydroxy metabolite has negligible effects on blood glucose, hence can be safely used in mild renal failure and the elderly
- Does not exhibit any drug interaction and due to poor binding to cardiac tissue, the interference with ischemic reconditioning is less compared to other SUs. However, the clinical impact of ischemic reconditioning is now considered to be insignificant.

Therapeutic Applications of Glimepiride

- Single daily dosing, generally
- Comparable hypoglycemic side effect profile to glipizide
- Safer in cardiac disease
- Peripheral action conserves endogenous insulin
- Safer to use in physically active.

MEGLITINIDE

Meglitinides are nonsulfonylurea insulin secretagogue.

Mechanism

The insulinotropic action of meglitinides is mediated via the inhibition of ATP dependent potassium ion channels in the beta cell membrane which results in depolarization of the cell membrane and influx of calcium ions through voltage-gated channels. Intracellular calcium concentration is thus increased leading to increased degranulation and subsequent insulin release. Though the action is similar to SU, the receptors are different.

Available Agents and Dosing

- Repaglinide: 0.5 mg/1 mg/4 mg per meal
- Nateglinide: 60 mg/120 mg per meal.

Therapeutic Application

- Low incidence of hypoglycemia
- Flexibility in mealtime dosing
- No significant increase in body weight
- Can be used in mild to moderate renal failure.

Disadvantages

- Frequent dosing
- Mainly for mild diabetes mellitus
- Generally as a first line single agent with minimal adjuvant potential.

ALPHA-GLUCOSIDASE INHIBITORS

These agents are primarily used to reduce postprandial hyperglycemia without increasing the insulin levels. They have a minimal effect on the fasting glucose concentration and therefore, will lower glycated hemoglobin (HbA1c) levels by usually 0.5 to 1.0%

Complex carbohydrates are cleaved by amylases in the small intestines into oligosaccharides. These oligosaccharides are poorly absorbed and are therefore broken into monosaccharides by a variety of alpha-glucosidase enzymes to facilitate rapid absorption. The cleavage of the oligosaccharides by the alpha-glucosidase enzyme involves binding of the oligosaccharides to a binding site on the enzyme, followed by hydrolytic cleavage. Alpha-glucosidase inhibitors compete with the oligosaccharides and delay the absorption of complex carbohydrates.

Side effects of alpha-glucosidase inhibitors are:

- Flatulence
- Diarrhea
- Abdominal discomfort.

Available Agents

Acarbose inhibits pancreatic amylase. The usual dose is 50 mg per day with the first bite of each meal. Maximum dose per day is 200 mg/day.

Voglibose inhibits most alpha-glucosidase enzymes (glucoamylase, sucrase, maltase, and isomaltase). The usual dose is 0.2–0.3 mg/day with each meal.

Miglitol has no effect on pancreatic amylase but exerts an inhibitory effect on nonintestinal alpha glucosidase present in other cells of the body. It mildly interferes with glucose absorption by interacting with the intestinal sodium dependent glucose transporter. The starting dose is 25 mg thrice daily with the first bite of meal. Maximum dosage is 100 mg.

Clinical Use

Alpha-glucosidase inhibitors must be given at the start of each meal and are effective only if the diet consists of at least 40–50% carbohydrates. These drugs are extremely effective in the treatment of severe hyperglycemia following gastrointestinal surgery and other forms of reactive hyperglycemia.

Contraindications

- Diabetic ketoacidosis
- Chronic intestinal diseases characterized by marked digestive or absorptive disorders
- Hypersensitivity to miglitol
- Inflammatory bowel disease or other conditions which may deteriorate with increased gas formation
- Intestinal obstruction.

Precautions

- Serum creatinine above 2 mg/dL
- Concurrent use of miglitol and a SU may result in hypoglycemia
- Since miglitol delays the absorption of sucrose, oral glucose (dextrose) should be used if hypoglycemia occurs.

THIAZOLIDINEDIONES

Thiazolidinediones are ligands for an orphan nuclear receptor peroxisome proliferator-activated receptor (PPAR gamma). They exert insulin sparing action by activation of PPAR gamma. They increase insulin sensitivity by increasing peripheral uptake of glucose in muscle and adipose tissue. They also lower hepatic glucose production to a lesser extent and stimulate oxidation and lipogenesis in adipose tissue. They increase GLUT 4 transporters in adipose tissue (Fig. 6.5).

Therapeutic Applications

- Important second/third line OAD
- Potential single daily dose (with pioglitazone)
- Decreases arterial blood pressure minimally
- Progressive increase in high-density lipoprotein (HDL)
- Safer in moderate to severe renal failure
- Decreases microalbuminuria
- Decreases vascular intimal thickening
- Thiazolidinediones can also be used in patients with renal insufficiency and polycystic ovary syndrome (PCOS).²

Adverse Effects

- Weight gain (20%) (2–4 kg)
- Ankle edema
- Fluid overload
- Hepatotoxicity (0.6%)
- Potential, however low risk of bladder carcinoma.

Contraindications

- New York Heart Association (NYHA) Class II, III, IV of ischemic heart disease
- Volume overload states
- Hepatitis (acute or chronic)
- Macular edema
- Dysthyroid ophthalmopathy
- Osteoporosis (caution)
- Bladder cancer.

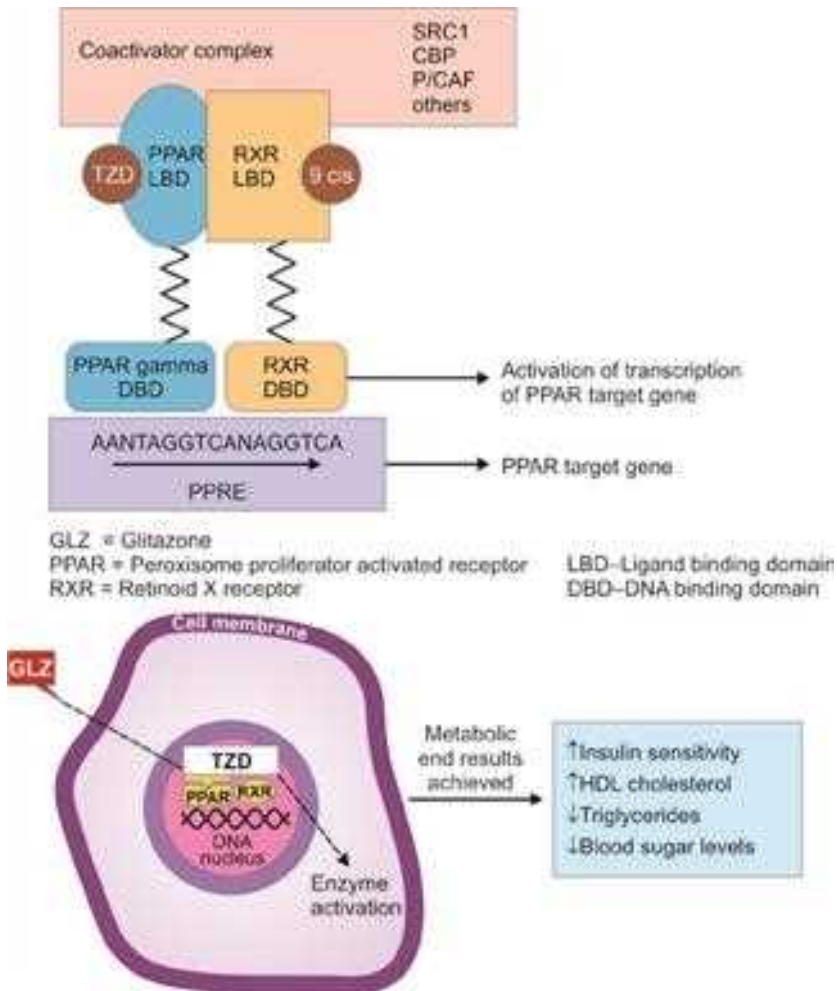


Fig. 6.5: Mechanism of action of thiazolidinediones.

Available Agents

Pioglitazone: 30/45 mg once daily.

From the available literature in light of the current debates and controversies, pioglitazone appears to be marginally safer to use with relation to its impact on the cardiovascular system compared to rosiglitazone. Rosiglitazone had been banned by the US Food and Drug Administration (FDA).

Recent Controversies

In 2012, after a French publication on the association of pioglitazone and bladder cancer, there was a spate of events happening one after the other, to the extent that the drug was banned in India for a few weeks. However more robust data from the PROactive follow-up

study revealed no possible risk of bladder cancer. At present it may only be avoided in those with past history or family history of bladder cancer.

INCRETIN EFFECT

Incretin effect implies to the release of certain substances from the gut in response to the ingested food. These substances enhance insulin secretion, beyond the release caused by the rise in glucose secondary to absorption of digested food. Incretin effect is observed in both normal healthy individuals and type 2 diabetes but the response in diabetics is diminished. This reduced effect may be due to reduced responsiveness of pancreatic beta cells to incretin hormones or impaired secretion of hormones in response to food.

An incretin hormone has the following characteristics:

- It is released from the intestine in response to food, particularly glucose
- The circulating concentration of the hormone is sufficiently high to stimulate the release of insulin
- The release of insulin in response to physiological levels of the hormone is glucose dependent.

Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase Inhibitors

Incretin hormones potentiate glucose mediated insulin response and are chiefly caused by two peptide hormones—(1) glucose dependent insulin releasing polypeptide (GIP) and (2) glucagon-like peptide (GLP-1). GIP is secreted by K cells from upper small intestine and GLP-1 is mainly produced by the enteroendocrine L cells located in the distal intestine. GIP and GLP-1 are rapidly inactivated by the enzyme dipeptidyl peptidase-IV (DPP-IV) (Table 6.3).

Dipeptidyl Peptidase Inhibitors

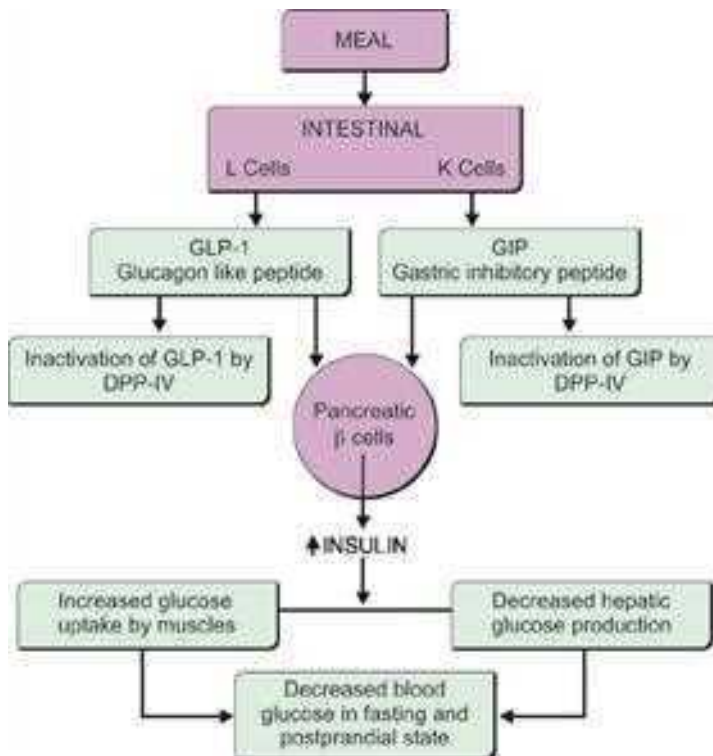
Newer therapeutic candidates for the treatment of type 2 diabetes are those drugs that enhance glucose-dependent insulin secretion called dipeptidyl peptidase inhibitors. This novel class

Table 6.3: Comparing dipeptidyl peptidase-IV (DPP-IV) inhibitors with glucagon-like peptide (GLP-1) agonists.

<i>DPP-IV inhibitors</i>	<i>GLP-1 agonists</i>
Orally available	Injectable
Multiple targets	Single known GPCR target
GLP-1, PK favorable	Higher levels of GLP-1 available, but narrow PK profile
Short acting	Long acting—days to weeks
Drug overdose—nontoxic	Drug overdose problematic
No central nervous system side effects	Nausea and vomiting
Less defined side effect profile	Well-described side effect profile

(PK: Pharmacokinetics; GPCR: G-protein coupled receptors).

Flowchart 6.1: Schematic drawing of the role of dipeptidyl peptidase-IV (DPP-IV) in the inactivation of incretins (GLP-1, GIP).



of agents includes those that inhibit the hormone (dipeptidyl peptidase inhibitors) and subsequently potentiate and prolong the endogenous incretin effect.

Mechanism of Action of DPP-IV Inhibitors

- Glucose mediated insulin secretion
- Stimulation of insulin biosynthesis
- Inhibition of glucagon secretion
- Inhibition of gastric emptying and acid secretion
- Prevents degradation of incretin hormones.

The use of DPP-IV inhibitors to improve the duration of endogenous GLP-1 activity is one method currently being investigated as a treatment for patients with type 2 diabetes. DPP-IV inhibitors exert their action in part by slowing the inactivation of incretin hormone GLP-1, leading to increase in concentrations GLP-1 which are generally decreased in patients with T2DM. DPP-IV inhibitors preferentially target postprandial glucose excursions, but have also been shown to decrease fasting plasma glucose levels. They stabilize endogenous GLP-1 at physiological concentrations, and induce insulin secretion in a glucose-dependent manner; therefore, they do not demonstrate any hypoglycemic effects (Flowchart 6.1).

Available Agents

Sitagliptin

Sitagliptin, the first approved DPP-IV inhibitor exerts its antihyperglycemic effect by slowing the inactivation of incretin hormones. Concentrations of intact incretin hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones, which ultimately leads to lowering of blood glucose both in fasting and postprandial state.

Therapeutic application: Sitagliptin is indicated as an adjunct to diet and exercise, to improve glycemia in T2DM and can be used as:

- Monotherapy
- Initial combination therapy with Metformin
- Combination as dual or triple therapy.

Sitagliptin has been reported to have reduced hypoglycemic effects and reduced weight gain when compared to SUs. Sitagliptin can also be combined with insulin to reduce the dose requirement, but this combination is not officially approved by the FDA.

Dosing: Initially as 100 mg once daily with or without food.

- If creatinine clearance is 30–50 mL/min/1.73 m², reduce dosage to 50 mg daily
- If creatinine clearance is less than 30 mL/min/1.73 m², reduce dosage to 25 mg daily.

Adverse effects: Mild gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal pain have been reported, but, are not clinically significant. Long-term consequences of DPP-IV inhibition, especially on immune function are to be borne in mind. There is a small increased risk of upper respiratory tract infection, urinary tract infection and headache but the prevalence of these infections appears to be slightly less according to the Cochrane review. Sitagliptin is associated with skin reactions which include Stevens-Johnson syndrome.

Vildagliptin

This agent has to be administered at a dosage of 50 mg twice a day. It has not been approved by the FDA for usage in renal failure. However, it has been approved by FDA for use as combination with insulin. It reduces postprandial lipemia and has a favorable effect on the blood pressure. It is not recommended for use in moderate renal failure.

Saxagliptin

The usual dose of saxagliptin is 2.5 mg or 5 mg once daily, with the 2.5 mg dose recommended for patients with moderate to severe chronic kidney disease [glomerular filtration rate (GFR) \leq 50 mL/min] and for patients taking strong cytochrome P450 3A4/5 inhibitors (e.g. ketoconazole).

Linagliptin

The usual dose of linagliptin is 5 mg once daily. No dose adjustment is needed in patients with renal or hepatic impairment. Inducers of CYP3A4 (e.g. rifampin) may decrease the efficacy of linagliptin. Therefore, patients requiring such drugs should receive an alternative to linagliptin.

HYDROXYCHLOROQUINE IN DIABETES

Antimalarials are well-tolerated and safely used therapeutic agents that are commonly utilized for disorders such as rheumatoid arthritis and systemic lupus erythematosus (SLE). Their benefit for glycemic control has been observed in patients on these drugs for immunological disorders. Hypoglycemia is one of the unusual adverse effects of these groups of drugs. Hydroxychloroquine (HCQ) in particular, was shown to be effective in lowering the HbA1c in SU refractory patients. The addition HCQ to insulin therapy causes a significant decrease in the insulin requirements.

The predominant mechanism that is involved is a reduction in insulin metabolism mediated through direct interaction with the insulin receptor, a reduced rate of dissociation of insulin from the insulin receptor, prolongation of the half-life of the insulin-receptor complex and thereby a prolonged insulin action. Other mechanisms of action include an increase in insulin production through islet cell stimulation and a reduction in hepatic gluconeogenesis.

HCQ has a beneficial effect on lipid metabolism acting by reducing triglycerides, low density lipoprotein (LDL)-cholesterol, apo-B and increasing the HDL-cholesterol. Moreover a recently published study from India showed a favorable effect of HCQ at a dose of 400 mg/day on both glycemic and lipid profile in type 2 diabetes patients who were inadequately controlled with a combination of SUs and metformin.³

Besides its glucose-lowering effect in patients with diabetes, interestingly HCQ has been found to be effective in lowering the incidence of new onset diabetes mellitus. A prospective randomized study on 4,905 patients with RA showed that patients with HCQ had 77% reduction in the risk of developing diabetes mellitus in those who had taken HCQ for more than 4 years.

Ocular toxicity is one of the less common adverse effects of long term HCQ therapy. All patients with HCQ should be routinely screened for retinal toxicity, depending on the cumulative dose and duration of therapy.

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS

The US FDA has approved two medications from a novel class called sodium-glucose cotransporter 2 (SGLT2) inhibitors for the management of diabetes.

Mechanism of Action of Sodium-Glucose Cotransporter 2 Inhibitors

The concept behind the action of these drugs is as follows:

Each day, approximately 180 g of glucose is filtered from the glomeruli of a normal adult individual, and almost all of it is reabsorbed from the glomerular filtrate and returned to the circulation. This cotransport of glucose along with sodium is brought about by the active transport of sodium out of the basolateral cells by the Na/K-ATPase pump.⁴ Glucose is also shifted out of the cell with the concentration gradient and subsequently returned to the bloodstream by glucose transporters. In T2DM, renal glucose handling and transport is

increased, likely due to the upregulation of SGLT2. Inhibition of this reduces reabsorption of filtered glucose and therefore lowers the blood glucose concentration by enhancing glucose excretion.

Available Agents

Canagliflozin

Canagliflozin became the first SGLT2 inhibitor to be approved by the FDA in 2013. It is currently indicated as an adjunct to diet and exercise in adults with T2DM. Studies have shown glycemic control benefits, weight reduction, and systolic blood pressure (SBP) lowering with monotherapy as well as in combination with other antihyperglycemic agents. Canagliflozin 100 mg and 300 mg have also been shown to significantly decrease fasting plasma glucose (FPG), weight, and SBP. It is available as 100 mg/300 mg tablets and is prescribed as a once daily dose.

Dapagliflozin

In January 2014, a second SGLT2 inhibitor, dapagliflozin, was approved by the FDA. Studies have shown benefits in glycemic control, weight reduction, and SBP reduction with dapagliflozin monotherapy and in combination with other antihyperglycemic medications. Although it is currently only approved as monotherapy, dapagliflozin has been studied in combination with metformin, glimepiride, pioglitazone, and insulin. When added to pioglitazone monotherapy, dapagliflozin attenuated pioglitazone-induced weight gain and edema. Dapagliflozin 5 mg and 10 mg, added to insulin therapy with or without other oral antihyperglycemic drugs, decreased total daily insulin doses by 6 U/day. It is available as 5 mg/10 mg tablets and is prescribed as a once daily dose.

Empagliflozin

It is available as 10 mg/25 mg tablets and is prescribed as a once daily dose.

Ipragliflozin

It is available as 50 mg/100 mg tablets and is prescribed as a once daily dose.

Therapeutic Application

The major advantages of this class of drugs is that they are simple nonspecific forms of therapy which work regardless of B-cell function and further compliments insulin dependent mechanisms. These drugs have a lower propensity for hypoglycemia, may cause weight loss and reduction in blood pressure.

However, these drugs are contraindicated in patients with ketonemia, ketonuria and end stage renal disease.

The reported side effects of these drugs include a slight increased prevalence of genital and lower urinary tract infections. Polyuria and electrolyte disturbances are also rarely described.

BROMOCRIPTINE

The US FDA had approved bromocriptine for the management of diabetes in 2009. It is a centrally acting antidiabetic agent which if given in the morning would reset the abnormally elevated sympathetic drive in the hypothalamus in patients with T2DM. This in turn would result in reducing the hepatic glucose output. It has also shown not only to augment the release of insulin but also to increase its sensitivity in the peripheral tissues. Addition of bromocriptine to poorly controlled type 2 diabetic patients treated with diet alone, metformin, SUs, or thiazolidinediones produces a 0.5–0.7 decrement in HbA1c.

The doses used to treat diabetes (up to 4.8 mg daily) are much lower than those used to treat Parkinson's disease, and apart from nausea, the drug is well-tolerated. The novel mechanism of action, good side effect profile, and its effects to reduce cardiovascular event rates make it an attractive option for the treatment of type 2 diabetes.

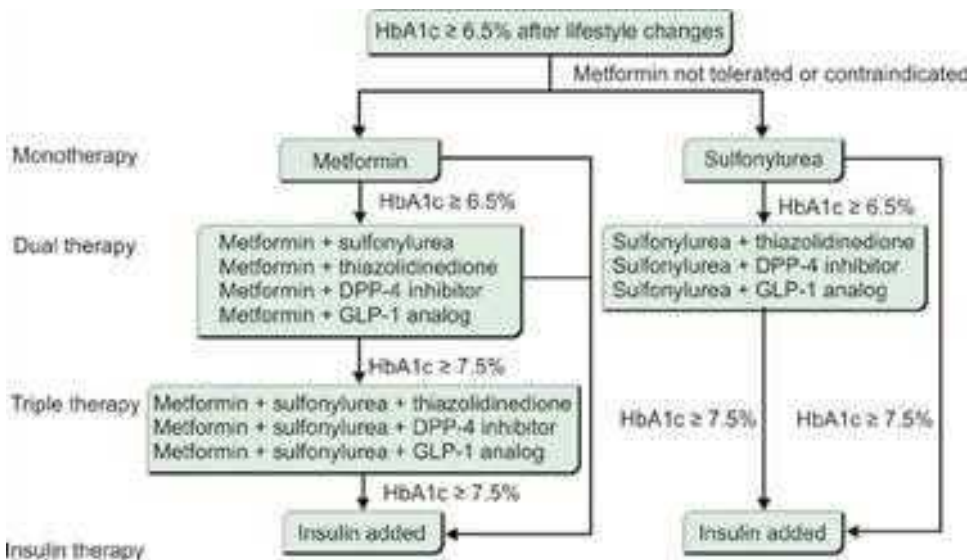
GUIDELINES FOR INITIATING ORAL ANTIDIABETIC AGENTS

National Institute for Health and Care Excellence Clinical Guidelines for the Management of Type 2 Diabetes (Flowchart 6.2 and Tables 6.4 to 6.6).

American Diabetes Association: Standards of Medical Care in Diabetes 2015 (Flowchart 6.3)

- In a subject newly diagnosed with diabetes, the first choice of management is always a calculated diabetic diet and exercise regimen.

Flowchart 6.2: NICE clinical guidelines for the management of type 2 diabetes.



Source: www.guidance.nice.org.uk/cg. Issued: May 2009; Modified: December 2014.

Table 6.4: Considerations for oral antidiabetic agent (OAD) therapy in subjects with type 2 diabetes mellitus.

<i>Drug class</i>	<i>Primary mechanism</i>	<i>Possible adverse effects</i>	<i>Monitoring</i>	<i>Remarks</i>
Sulfonylureas	Stimulates insulin release	Hypoglycemia Weight gain	Blood glucose at 2 weeks interval, until normoglycemia achieved HbA1c at 3 months interval	Response plateaus after half maximum dose Glipizide and glimepiride may be preferred in elderly patients
Biguanides	Inhibits hepatic glucose output	Dose related diarrhea (self-limiting) Lactic acidosis in patients with renal failure	Serum creatinine at initiation Blood glucose at 2 weeks interval, until normoglycemia achieved HbA1c at 3 months interval	Weight neutral, weight loss may occur; helps limit weight gain in combination therapy Maximum effective dosage is 2 g/d <i>Contraindications:</i> Serum creatinine >1.5 mg/dL (men), > 1.4 mg/dL (women), Congestive heart failure Hepatic disease, alcohol abuse
α -Glucosidase inhibitors	Delays carbohydrate absorption to decrease postprandial hyperglycemia	Dose-related diarrhea, abdominal pain, flatulence	HbA1c at 3 months interval	Administer with first bite of each meal. Use slow titration to avoid gastrointestinal adverse effects (e.g. 25 mg once daily for 2 weeks; then 25 twice daily for 2 weeks; then 25 mg three times daily for 8 weeks; maximum dosage is 100 mg three times daily)
Thiazolidinediones	Enhances insulin sensitivity	edema Weight gain	AST and ALT at baseline Monitor for signs of fluid overload	Decrease in glucose may not be apparent for 4 weeks. Maximum efficacy of dose may not be observed for 4-6 months <i>Contraindications:</i> ALT > 2.5 times the upper limit of normal, Hepatic disease, Alcohol abuse, NYHA class III and IV heart failure
Glinides	Stimulates insulin secretion	Hypoglycemia	Fasting plasma glucose at 2 weeks HbA1c at 3 months PPG at initiation	Can be given in liver and renal failure

Contd...

Contd...

Drug class	Primary mechanism	Possible adverse effects	Monitoring	Remarks
DPP-IV inhibitors	Restores GLP-1 and GIP levels	Upper respiratory tract infections especially with sitagliptin Long-term safety not established	Fasting plasma glucose at 2 weeks HbA1c at 3 months PPG at initiation	Reduce dosage in patients with renal insufficiency except linagliptin No weight gain Reduced incidence of hypoglycemia Interaction with cytochrome P459 inhibitors (saxagliptin)
SGLT 2 inhibitors	Excessive urinary glucose excretion by preventing its reabsorption	A slight increase in the risk of genital and urinary tract infections. Polyuria	Serum creatinine and electrolytes before initiations	Mild reduction weight and blood pressure

(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors; GLP-1: Glucagon-like peptide-1; GIP: Glucose dependent insulin releasing polypeptide; HbA1c: Glycated hemoglobin; PPG: Postprandial plasma glucose; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; NYHA: New York Heart Association).

Table 6.5: Guidelines for determining oral antidiabetic agent (OAD) usage.

Determinants	First choice OAD	Second choice OAD	OAD to be avoided
Body mass index (BMI) > 25 kg/m ² (Indian cardiovascular risk at BMI > 23 kg/m ² or lower)	Metformin	DPP4 inhibitors SGLT2 inhibitors Glimepiride	Glibenclamide Glipizide Thiazolidinediones
Waist hip ratio Male > 0.9 Female > 0.85	Metformin	DPP4 inhibitors SGLT2 inhibitors Glimepiride	Glibenclamide Glipizide
Presence of GI symptoms	Sulfonylurea	Thiazolidinediones	Acarbose DPP4 inhibitors
Renal dysfunction	Meglitinides Gliclazide Glipizide	Thiazolidinediones DPP4 inhibitors	Metformin
Economic constraints	Glibenclamide	Metformin	Relative to the company and agent used
Complications of diabetes	Insulin should be used in severe or progressive painful neuropathy/ proliferative retinopathy/maculopathy		

Source: ADA 2007 Guidelines.

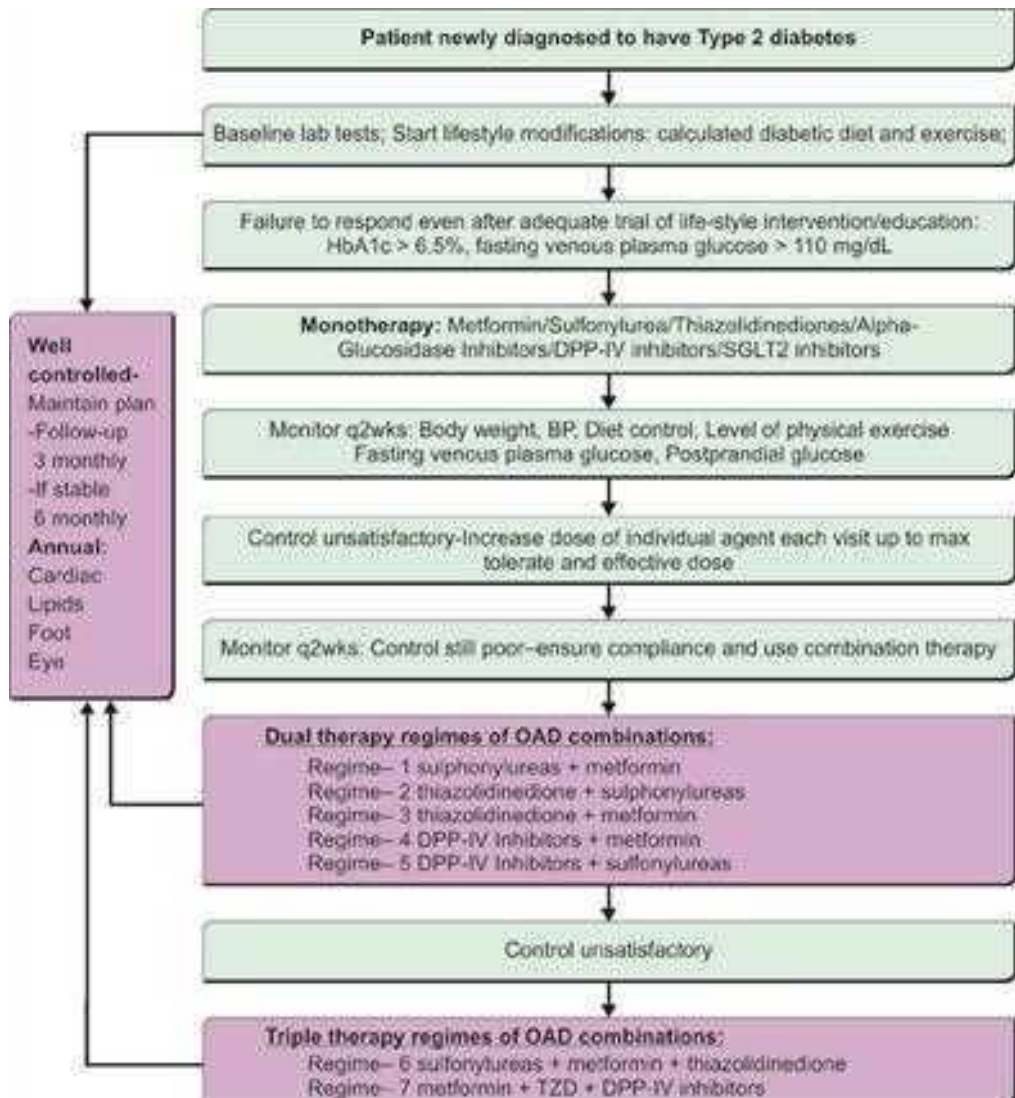
(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors; GI: Gastrointestinal).

Table 6.6: Guidelines for oral antidiabetic agent (OAD) therapy.

S. No.	OAD group	OAD	Maximum dose	Frequency	Upper limit of serum creatinine above which OAD are not indicated (mg/dL)
1.	Biguanide	Metformin	3 g/day	BD or TID	1.5
2.	Sulfonylureas	Glibenclamide	20 mg/day	BD	2.0
		Glipizide	20 mg/day	BD	2.5
		Glimepiride	8 mg/day	OD/BD	1.5
		Gliclazide	320 mg/day	BD	2.5
3.	Thiazolidinedione	Pioglitazone	45 mg/day	OD	4.0
4.	Meglitinide analogs	Repaglinide	4 mg/day	TID	4.0
		Nateglinide	120 mg/day	TID	4.0
5.	Alpha-glucosidase inhibitor	Acarbose	200 mg/day	BD/TID	1.5
		Miglitol	100 mg/day	TID	1.5
		Voglibose	0.9 mg/day	TID	1.5
6.	DPP-IV inhibitors	Sitagliptin	100 mg/day	OD	4.0
		Vildagliptin	100 mg/day	BD	—
		Saxagliptin	5 mg/day	OD	4.0
		Linagliptin	5 mg/day	OD	4.0
7.	Dopamine agonists	Bromocriptine	0.8 mg/day	OD	Not known
8.	SGLT2 inhibitors	Canagliflozin	100–300 mg/day	OD	Not known
		Dapagliflozin	5–10 mg/day	OD	
9.	Antimalarial drugs	Hydroxychloroquine	400 mg/day	OD	Not known

(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors).

- Metformin, if not contraindicated and if tolerated, is the preferred initial pharmacological agent for type 2 diabetes.
- In patients with newly diagnosed type 2 diabetes and markedly symptomatic and/or elevated blood glucose levels or HbA1c, to consider initiating insulin therapy (with or without additional agents).
- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the HbA1c target over 3 months, add a second oral agent, a GLP-1 receptor agonist, or basal insulin.
- Combining therapeutic agents with different modes of action may be advantageous.
- Use insulin sensitizers such as metformin as part of the therapeutic regimen in most patients unless contraindicated or intolerance to these agents has been demonstrated.

Flowchart 6.3: Treatment algorithm for oral antidiabetic agents.

(SGLT2: Sodium glucose cotransporter 2; DPP-IV: Dipeptidyl peptidase 4 inhibitors; TZD: Thiazolidinedione).

- Insulin is the therapy of choice in patients with OAD failure (uncontrolled glycemic response on a maximum dose of 2–3 OADs, advanced chronic renal disease, end organ failure and advanced stages of microvascular or macrovascular complications).
- The weight gain associated with thiazolidinediones in some patients may be partly offset by combination therapy with metformin.
- Assess postprandial glucose periodically to detect unrecognized exaggerated postprandial glucose excursions even when the HbA1c level is at or near target.

- A patient-centered approach should be used to guide choice of pharmacological agents.
- Considerations include efficacy, cost, potential side effects, weight, comorbidities, hypoglycemia risk, and patient preferences.
- Due to the progressive nature of type 2 diabetes, insulin therapy is eventually indicated for many patients with type 2 diabetes.

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SELF-ASSESSMENT

1. **A 55-year-old cardiothoracic surgeon with one episode of myocardial infarction is currently on diet control and exercise for diabetes. He finds it difficult to remember to take medications and is regular with meals. He has normal renal function. Which drug from this list, would you utilize in his case?**

(a) Glibenclamide	(b) Glipizide
(c) Glimepiride	(d) Metformin
(e) Repaglinide	
2. **Metformin should be preferably avoided in all of the following conditions *except*:**
 - (a) Creatinine more than 1.9 mg/dL
 - (b) Acute hepatitis
 - (c) Type I respiratory failure
 - (d) Obesity with a body mass index of more than 40 kg/m²
 - (e) Ketoacidosis
3. **A major side effect of this drug is diarrhea and flatulence:**

(a) Pioglitazone	(b) Gliclazide
(c) Metformin	(d) Acarbose
(e) Lispro	
4. **The drug most likely to precipitate prolonged hypoglycemia is:**

(a) Chlorpropamide	(b) Glibenclamide
(c) Gliclazide	(d) Glipizide
5. **The preferred medication that can be continued for better glucose control when a patient is on insulin is:**

(a) Metformin	(b) Gliclazide
(c) Acarbose	(d) Glibenclamide
(e) Glipizide	

- 6. Following is true about sulfonylureas *except*:**
- (a) Hypoglycemia and weight gain are notable side effects
 - (b) Risk of hypoglycemia is higher with glibenclamide than glimepiride
 - (c) Glimepiride may be used in early renal impairment
 - (d) Chlorpropamide has a shorter half-life than glipizide
 - (e) There is no impact on the SUR-receptor
- 7. Mrs Y is a diabetic for 8 years with mild pedal edema and a creatinine 3.2 g%. Her SGOT was 600 IU, the oral hypoglycemic agent of choice in this patient is:**
- (a) Metformin
 - (b) Rosiglitazone
 - (c) Gliclazide
 - (d) Pioglitazone
 - (e) Nateglinide
 - (f) None of the Above
- 8. In patients with type 2 diabetes mellitus, which of the following drugs act by improving insulin sensitivity:**
- (a) Pioglitazone
 - (b) Gliclazide
 - (c) Acarbose
 - (d) Repaglinide
 - (e) Nateglinide
- 9. The most common adverse effects experienced by patients on Metformin is:**
- (a) Weight gain
 - (b) Gastrointestinal
 - (c) Hypoglycemia
 - (d) Renal failure
 - (e) Hepatic failure
- 10. Which of the following are given after meals?**
- (a) Glibenclamide
 - (b) Metformin
 - (c) Glimepiride
 - (d) Pioglitazone
- 11. Which of the following can be given with a creatinine more than 2.5 mg/dL?**
- (a) Glibenclamide
 - (b) Metformin
 - (c) Glimepiride
 - (d) Pioglitazone
 - (e) Sitagliptin
- 12. Which of the following can cause hypoglycemia when used as a single agent?**
- (a) Glibenclamide
 - (b) Metformin
 - (c) Glimepiride
 - (d) Pioglitazone
 - (e) Sitagliptin
- 13. Which of the following is generally a standard multidose formulation, but is also available as a slow release?**
- (a) Glibenclamide
 - (b) Metformin
 - (c) Glimepiride
 - (d) Pioglitazone
 - (e) Sitagliptin
- 14. Which of the following can cause edema which may or may not be due to volume overload?**
- (a) Glibenclamide
 - (b) Metformin
 - (c) Glimepiride
 - (d) Pioglitazone
 - (e) Sitagliptin

CHAPTER

7

Parenteral Therapeutic Agents

Senthil Vasan K, Nitin Kapoor, Nihal Thomas

*“Fifty-one AAs it’s something that works,
Modify B-29, the shorter it lurks,
Exenatide it’s not from a wizard,
But from the saliva of a desert lizard.”*

Insulin is an anabolic hormone promoting protein synthesis, fat storage, entry of glucose into cells for energy use, and glycogen storage in muscle and liver cells. Insulin is an absolute requirement for type 1 diabetes and is used to prevent long-term complications of diabetes. It may be required in those with type 2 diabetes if other forms of therapy do not adequately control glucose levels. It is also used in gestational diabetes for those who have inadequate glucose control on diet alone. Glucagon-like peptide-1 (GLP-1) analogs like exenatide are now available and may play an adjunctive role and also serve as an alternative therapy to insulin therapy.

PATHOPHYSIOLOGY AND THE BASIS FOR INSULIN REPLACEMENT REGIMENS

Insulin secretion following a meal occurs in two phases: Phase 1 lasts about 10 minutes and is involved in suppression of the hepatic glucose production. Phase 1 also facilitates a phase 2 release which lasts 2 hours and manages the rise in blood glucose produced by the carbohydrates in the meal. A low basal secretion of insulin is present between meals that meet ongoing metabolic demands. The physiology of insulin secretory pattern forms the basis for insulin therapy. With rising blood glucose levels, the β cells respond in a linear fashion by secreting insulin. When β cells are exposed to high glucose concentrations over a prolonged period of time as in diabetes, there is a blunting in the β cell response. This is referred to as glucose toxicity.

The pathology in type 2 diabetes is that the phase 1 insulin response is absent and phase 2 release is delayed and insufficient. Initially there is an increased secretion of insulin to compensate for the insulin resistance but with progression of the disease, the β cells tire out and insulin secretion is decreased (Fig. 7.1A).

Amongst all the available antidiabetic agents, insulin provides superior reductions in glycated hemoglobin (HbA1c) as demonstrated by Figure 7.1B.

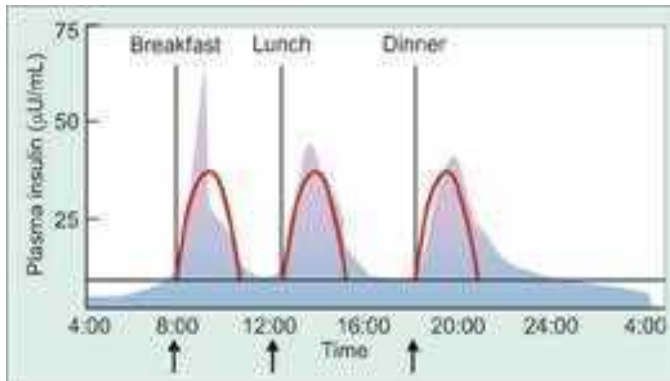


Fig. 7.1A: Ideal insulin replacement pattern.

Source: Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-83.

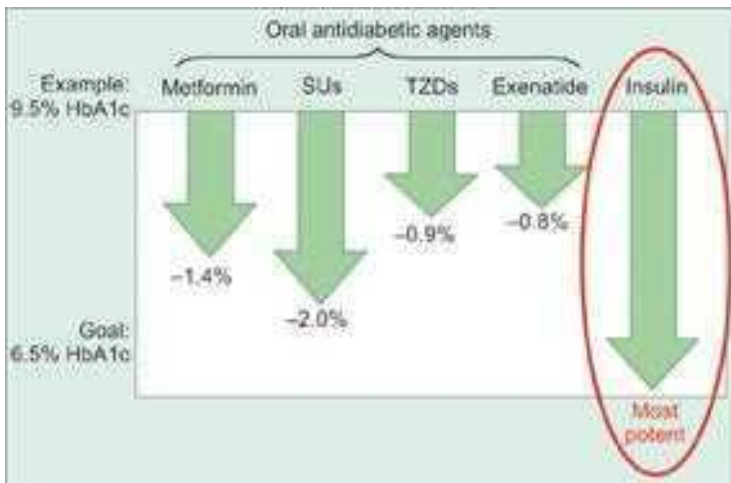


Fig. 7.1B: Insulin delivers superior glucose reductions versus other agents.

Source: American Association of Clinical Endocrinologists. AACE medical guidelines for the management of diabetes mellitus. *Endocr Pract.* 2000;6(1):43-84.

(HbA1c: Glycated hemoglobin; SUs: Sulfonylureas; TZDs: Thiazolidinediones).

HISTORY

In 1921 Banting, an orthopedic surgeon along with best hypothesized that ligation of the pancreatic ducts before extraction of the pancreas, destroys the enzyme-secreting parts, whereas the islets of Langerhans, which were believed to produce an internal secretion regulating glucose metabolism, remained intact. Their experiments produced an extract of pancreas that reduced the hyperglycemia and glycosuria in dogs made diabetic by the removal of their pancreas. The method of extraction from the entire pancreas without the need for duct ligation was introduced by them. Following this, many milestones were set in the path of insulin discovery. Beef insulin was the first commercially available preparation followed by

porcine. Recombinant DNA technique was employed in the preparation of human insulin. In 1926, John Jacob Abel (1857–1938) of Johns Hopkins University prepared the first crystalline insulin. In the mid-1950s the molecular structure of insulin was determined by Frederick Sanger (1918–1982), for which he received a Nobel Prize for Chemistry in 1958. He received a second Nobel Prize in 1980 for determining base sequences of nucleic acids. With genetic engineering it is now possible not only to make insulin in unlimited quantities, but to produce human insulin rather than to use the slightly different insulin of other species.

SOURCES OF INSULIN

Main sources of insulin are from beef, pork, human (recombinant).

Bovine insulin differs from human insulin by three amino acids (AA) and porcine insulin by only one AA. Conversion of a patient on insulin injection from animal source to human insulin may require dosage adjustment because of the shorter duration of action and lower antigenicity.

CLASSIFICATION OF INSULIN

These include meal time (bolus) and basal insulin. Mealtime insulins are rapidly acting analogs or short acting regular human insulin. These insulins have been used in an attempt to stimulate the high levels of insulin seen in individuals without diabetes after ingestion of a meal. The basal insulins are the intermediate and long acting human insulins and analogs (Fig. 7.2 and Table 7.1). They simulate the basal level of insulin occurring between meals, through the night and with fasting. Classification is primarily based upon the duration of action.

Basal Insulins

- Neutral protamine Hagedorn (NPH)
- Isophane insulin

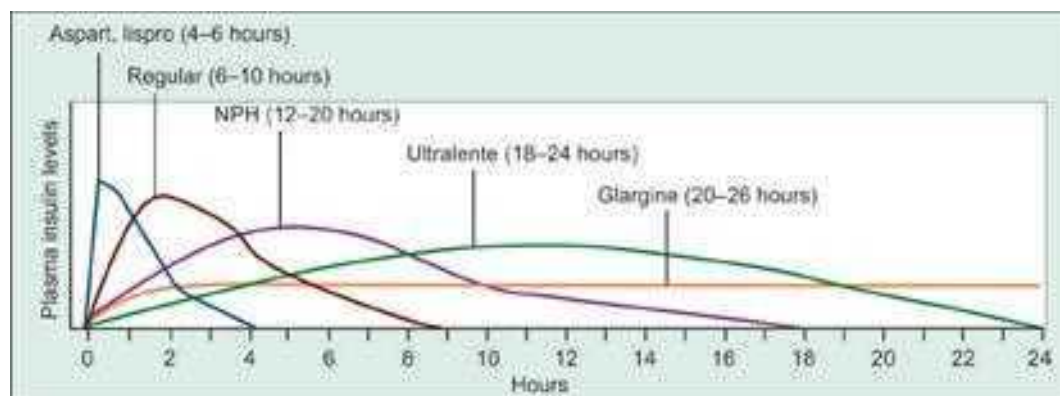


Fig. 7.2: Profiles of human insulins and analogs.

Source: Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-83.

(NPH: Neutral protamine Hagedorn).

Table 7.1: Classification of insulin.

<i>Insulin</i>	<i>Onset</i>	<i>Peak (hours)</i>	<i>Usual effective duration (hours)</i>	<i>Usual maximum duration (hours)</i>
<i>Bolus or mealtime insulin</i>				
Aspart	5–10 minutes	1–3	3–5	4–6
Lispro	< 15 minutes	0.5–1.5	2–4	4–6
Regular	30–60 minutes	2–3	3–6	6–10
<i>Basal insulin</i>				
NPH	2–4 hours	4–10	10–16	14–18
Lente (insulin zinc suspension)	3–4 hours	4–12	12–18	16–20
Detemir	2–3 hours	No peak	24	24
Glargine	1 hour	No peak	24	24
<i>Combinations</i>				
50% NPH/50% regular	30–60 minutes	Dual	10–16	14–18
70% NPH/30% regular	30–60 minutes	Dual	10–16	14–18
75% NPL/25% lispro	< 15 minutes	Dual	10–16	14–18
70% APS/30% aspart	10–20 minutes	2.4 ± 0.80	24	24

(NPH: Neutral protamine Hagedorn; NPL: Neutral protamine lispro; APS: Aspart protamine suspension).

- Ultralente (extended insulin zinc suspension)
- *Insulin analogs*: Detemir, glargine.

Bolus or Mealtime Insulins

- Regular insulin
- *Analog forms*: Aspart, lispro and glulisine.

Premixed Insulin

Premixed preparations of short and intermediate acting insulins are available in a wide range of ratios. The most commonly used premixed insulin is 30/70 which contains 30% short acting and 70% intermediate acting insulins. The use of premixed insulin prevents the potential problems of self-mixing and reduces the number of steps before injection. However, premixed insulin does not permit easy adjustment of mealtime and basal insulins.

Premixed formulations incorporate NPH and regular insulin or rapid-acting analogs.

INDICATIONS FOR INSULIN THERAPY

- Type 1 diabetes
- Type 2 diabetes who have failed to achieve glycemic goals with the maximal dose of oral antidiabetic drugs (OADs). (Metformin 2,500–3,000 mg per day + Glipizide 20 mg/glibenclamide 15–20 mg/gliclazide 320 mg/glimepiride 6–8 mg/day + pioglitazone 45 mg/day)

- Gestational diabetes
- Individuals with type 2 diabetes, during periods of physiological stress such as surgery, infection, acute illness. (OADs are to be continued simultaneously but metformin is to be stopped in case of severe infections or impending reduction in renal perfusion)
- Progressive complications threatening organ functions—proliferative retinopathy, maculopathy, severe neuropathy
- Diabetes ketoacidosis/hyperosmolar hyperglycemic nonketotic coma
- Secondary diabetes (pancreatitis, corticosteroids)
- Chronic renal failure (for all above a creatinine above 4.0 mg/dL. Cutoffs for other OADs are as follows—Metformin: 1.5 mg/dL, glimepiride/glibenclamide: 2.0 mg/dL, glipizide: 2.5 mg/dL, pioglitazone: 4.0 mg/dL)
- Use of parenteral nutrition or high calorie supplements
- Weight loss of more than 10% body weight or body mass index (BMI) < 19 kg/m².

THERAPEUTIC REGIMENS

An ideal insulin therapy regimen mimics normal physiological insulin release. The degree of hyperglycemia, associated comorbidity, affordability of the patient and patient adherence to guidelines during therapy need to be given due consideration during initiation of therapy (Figs. 7.3A and B).

Augmentation Therapy

An augmentation therapy is used when the patient has failed to achieve glycemic goals on oral medications. Its need arises in situations of residual but insufficient β cell function.

It is usually provided as basal insulin as bedtime NPH, twice daily NPH, once daily ultralente or once daily glargine. The dose adjustment is so as to maintain fasting plasma glucose levels between 90 mg/dL and 130 mg/dL.

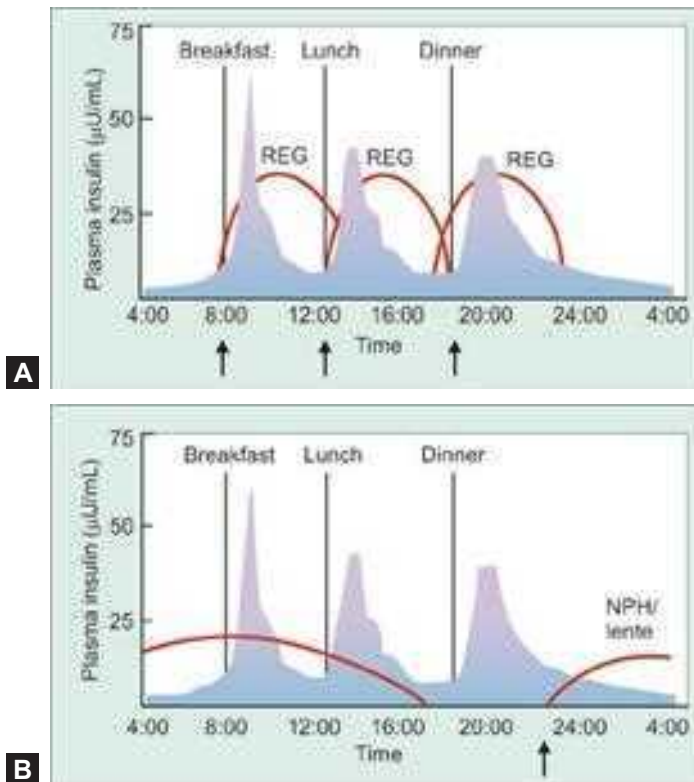
Augmentation can also be with mealtime insulin as regular insulin, aspart or lispro. Doses are adjusted so as to keep 2 hours postprandial blood glucose levels below 180 mg/dL.

Replacement Therapy

Replacement therapy is used when patients need intensive control or in those who have failed augmentation therapy. This therapy involves providing both basal and bolus insulin. A convenient regimen involves use of NPH and regular insulin before breakfast and then before dinner. This needs the patient to strictly follow mealtimes to avoid hypoglycemia. Premixed formulations are convenient for the patient to use but may not meet individual patient requirements as effective as split mixed regimens do.

Use of four injections a day of basal-bolus regimen mimics normal physiology in a better way. It has the advantage of providing a more flexible regimen to patients who find it difficult to adhere to specific mealtimes. Such regimens include NPH and regular insulin, NPH with aspart or lispro, or glargine with aspart or lispro.

Short-term rescue therapy for glucose toxicity also involves a basal-bolus regimen.



Figs. 7.3A and B: (A) Augmentation using short acting (regular) insulin; (B) Basal augmentation using intermediate acting insulin at bedtime only.

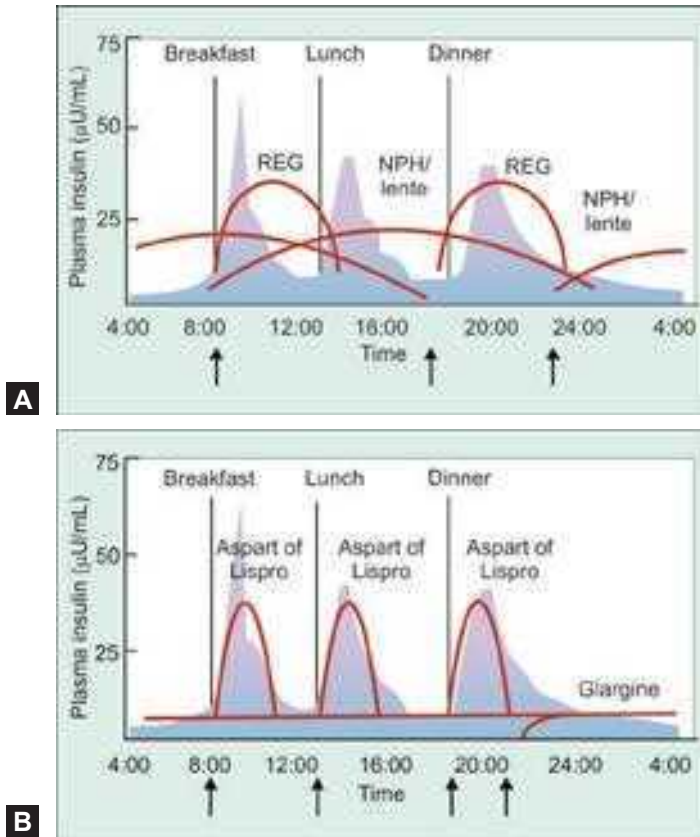
Source: Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-83.

(NPH: Neutral protamine Hagedorn).

Bolus insulin without basal insulin also commonly known as sliding scale therapy is used very commonly in hospital settings. This is associated with poor glycemic control. This does not mimic normal physiological insulin release and its use must be discouraged (Figs. 7.4A and B).

Dosing

- The starting dose for augmentation therapy is 0.15 units/kg/day
- The starting dose for replacement therapy is 0.5 units/kg/day
- Increments can be made as needed
- About 50–60% of total daily insulin requirement should be basal and about 40–50% should be bolus insulin
- Adjustments should be made to correct the fasting glucose levels first followed by preprandial and then postprandial
- Dose adjustments should also take into consideration the estimated requirement for the anticipated meal and patient's exercise schedule.



Figs. 7.4A and B: (A) Basal-bolus therapy using split-mixed regimen and bedtime intermediate insulin; (B) Basal-bolus therapy using glargine and aspart or lispro.

Source: Hirsch IB. Insulin analogues. *N Engl J Med.* 2005;352:174-83.

(NPH: Neutral protamine Hagedorn).

ORAL MEDICATIONS PLUS INSULIN

The synergistic effect of OAD medications with insulin may allow the insulin dose to be reduced by up to 50%.

Metformin with insulin decreases weight gain, hypoglycemia, and diabetes-related end points. Metformin does not need dose adjustments when administered with insulin. Metformin is best continued when renal function is normal.

Thiazolidinedione drugs administered with insulin can decrease the total insulin dose up to 50%, but this may cause edema and is contraindicated in patients with congestive heart failure. Weight gain with thiazolidinediones is accentuated with insulin usage.

Glimepirides when used in doses of 2–4 mg/day have a peripheral glucose transporter type 4 (GLUT-4) like activity reducing insulin requirement by 10–20%.

Endogenous insulin release can be stimulated with meglitinides (phase 1) or sulfonylureas (phase 2).

Coadministration of insulin with sulfonylureas may lower HbA1c levels and reduce the total daily insulin requirement if some beta-cell function remains. Sulfonylureas are absorbed better if glucose levels have been normalized with insulin.

When starting insulin in a type 2 diabetes patient who has failed to achieve glycemic goals with the maximum goals of OAD consider the following:

- Continue OAD
- Insulin starting dose at around 0.2 U/kg/day, morning two-thirds and evening one-third
- Reassess control with self-monitoring of blood glucose (SMBG) and titrate dosage
- Consider short acting premeal bolus in case of uncontrolled postprandial blood sugars
- Consider withdrawing sulfonylureas.

INSULIN ANALOGS

Standard insulins used in the treatment of diabetes mellitus frequently lead to hypoglycemia as HbA1c values approach the normal range. These added to the limitations in the pharmacokinetic and pharmacodynamics of standard insulins has led to renewed interest in producing safer insulin formulations that more closely duplicate the basal and mealtime components of endogenous insulin secretion. Insulin analogs are characterized by action profiles that afford more flexible treatment regimens with a lower risk of hypoglycemia.

Standard Insulin versus Insulin Analogs

In individuals without diabetes, insulin secretion can be divided into two basic components: (1) basal and (2) stimulated. Basal insulin is secreted continuously between meals and throughout the night at a rate of 0.5–1 U/hr in adults. Basal insulin secretion provides serum concentrations of 5–15 $\mu\text{U}/\text{mL}$. The low basal concentration reduces hepatic glucose production but allows for glucose levels sufficient for cerebral energy production. In diabetic patients, treatment with intermediate-acting or long-acting insulin attempts to mimic the basal secretory pattern (Fig. 7.5).

Normally, stimulated insulin secretion occurs in response to a meal and results in insulin concentrations of 60–80 $\mu\text{U}/\text{mL}$ from just before to 30 minutes after the meal. Concentrations return to basal levels in 2–4 hours. Regimens of regular insulin attempt to mimic the stimulated insulin secretory pattern.

Problems with Regular Insulin

Regular human insulin has a strong affinity for self-association. Thus, the hexamer is the most prevalent form in a solution of regular human insulin. The rate-limiting step in the absorption of regular insulin is dissociation to the monomeric form.

The pharmacokinetic profile of regular human insulin presents several problems for patients who use insulin. First, timing of the meal and the injection is difficult because of the lag before onset of action. Second, glucose concentrations rise rapidly after meals, whereas insulin concentrations may not peak for 3 hours (4 hours with animal insulins). Peak concentrations for intermediate-acting human insulins occur within 4–10 hours for NPH

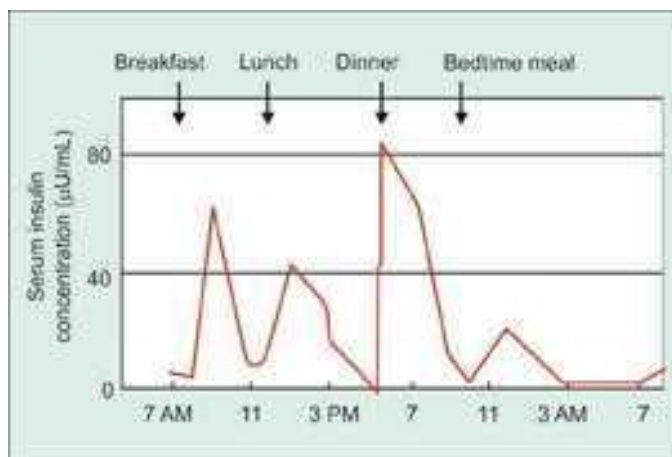


Fig. 7.5: Normal insulin secretion. In the stimulated phase, serum insulin levels increase from within a few minutes before to 30 minutes after a meal. Return to basal level occurs within 2 hours.

Source: Galloway JA, Chance RE. Improving insulin therapy: achievements and challenges. *Horm Metab Res.* 1994;26(12):591-8.

insulin and 4–12 hours for lente insulin (Figs. 7.6A and B). Human NPH insulin has an effective duration of action of 10–16 hours; lente insulin, 12–18 hours; and human ultralente insulin, 18–20 hours. Human ultralente insulin may be used as basal insulin, although two daily injections may be needed.

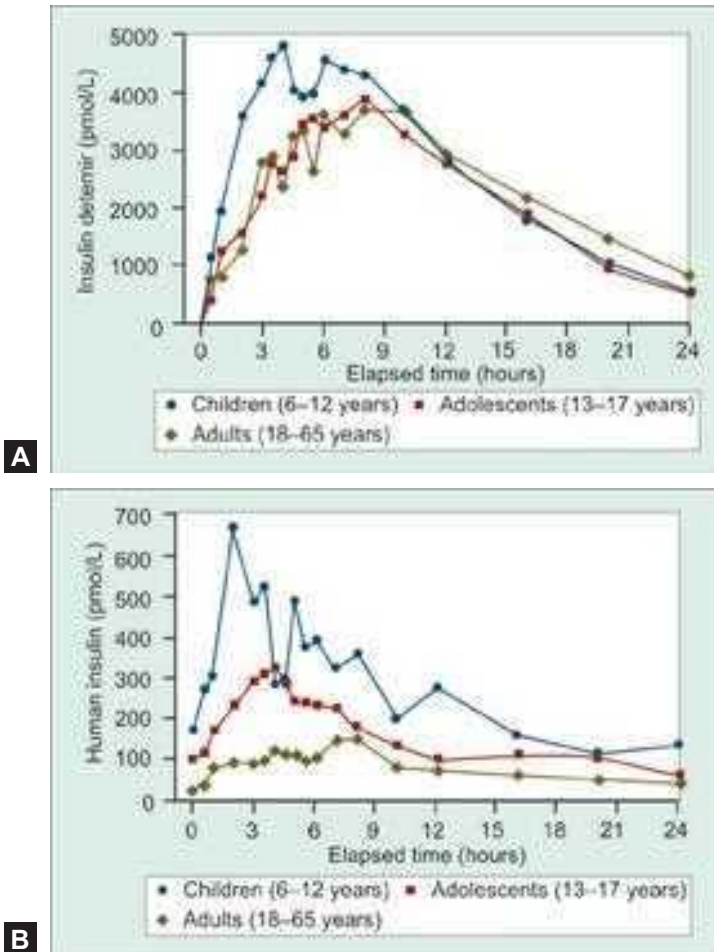
TYPES OF INSULIN ANALOGS

Rapidly-acting Analogs

The relatively slow absorption of regular insulin is attributed to the fact that when zinc atoms are added to the solution of dimers that make up regular insulin, the molecules associate to form hexamers. These larger hexamers diffuse slowly into the circulation but, insulin analogs form insulin monomers which are absorbed more rapidly.

Insulin Lispro

Insulin lispro is formed by the inversion of the lysine B29 and proline B28 of human insulin and this conformational change results in shift in the normal binding of the c-terminal portion of B-chain, which in turn reduces the formation of dimers and hexamers. Insulin lispro differs from regular insulin by virtue of its capacity to dissociate rapidly into monomers in the subcutaneous tissue. Insulin lispro is absorbed much more rapidly than regular insulin, and begins acting in 15 minutes, reaches peak biological activity in 60–90 minutes and continues to act for 4–5 hours. Lispro provides more flexibility for patients at mealtimes because it does not need to be administered 30 minutes before a meal and the doses can be readily adjusted depending on the carbohydrate content of the meal.



Figs. 7.6A and B: Mean serum concentration-time profile of insulin detemir and NPH insulin by age-group—(A) Insulin detemir; (B) NPH insulin.

Source: Danne T, Lüpke K, Walte K, Von Schuetz W, Gall MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. *Diabetes Care*. 2003;26:3087-92.

Insulin Aspart

Insulin aspart is formed by the substitution of aspartate in position 28 of the B-chain instead of proline (Fig. 7.7). Insulin aspart has closely resembles insulin lispro in its pharmacokinetic properties by virtue of its very rapid onset of action and absorption after subcutaneous administration.

Insulin Glulisine

Insulin glulisine is a rapid-acting insulin analog that differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is

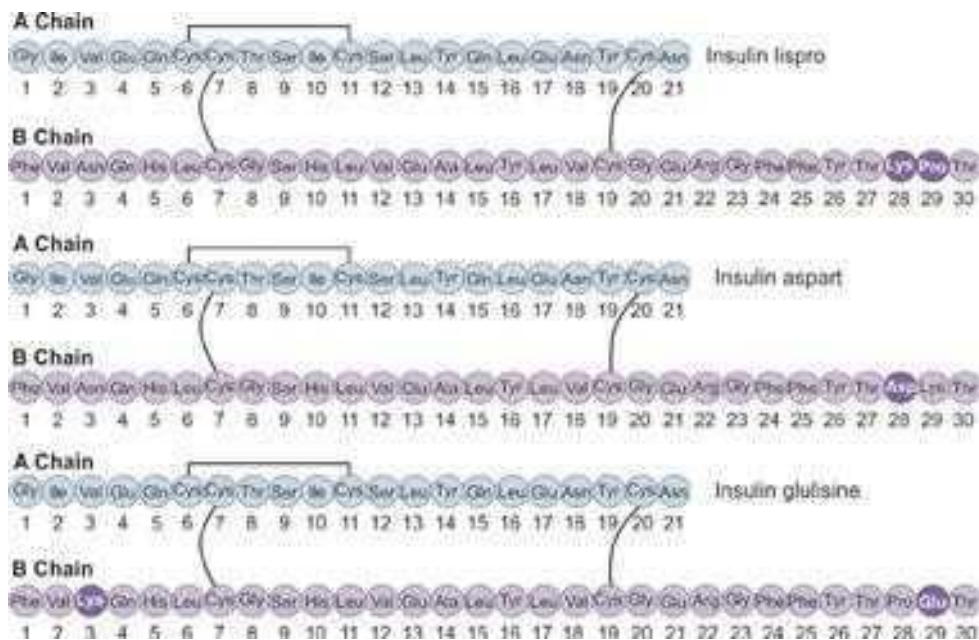


Fig. 7.7: Structure of rapid acting insulin analogs.

Source: Owens DR. Review: Insulin glulisine—the potential for improved glycemic control. *Br J Diabetes Vasc Dis.* 2007;7(2):60-6.

replaced by glutamic acid. Chemically, it is 3B-lysine-29B-glutamic acid-human insulin. When injected subcutaneously, it appears in the blood earlier and at higher concentrations than human insulin. When used as mealtime insulin, the dose should be given within 15 minutes before a meal or within 20 minutes after starting a meal.

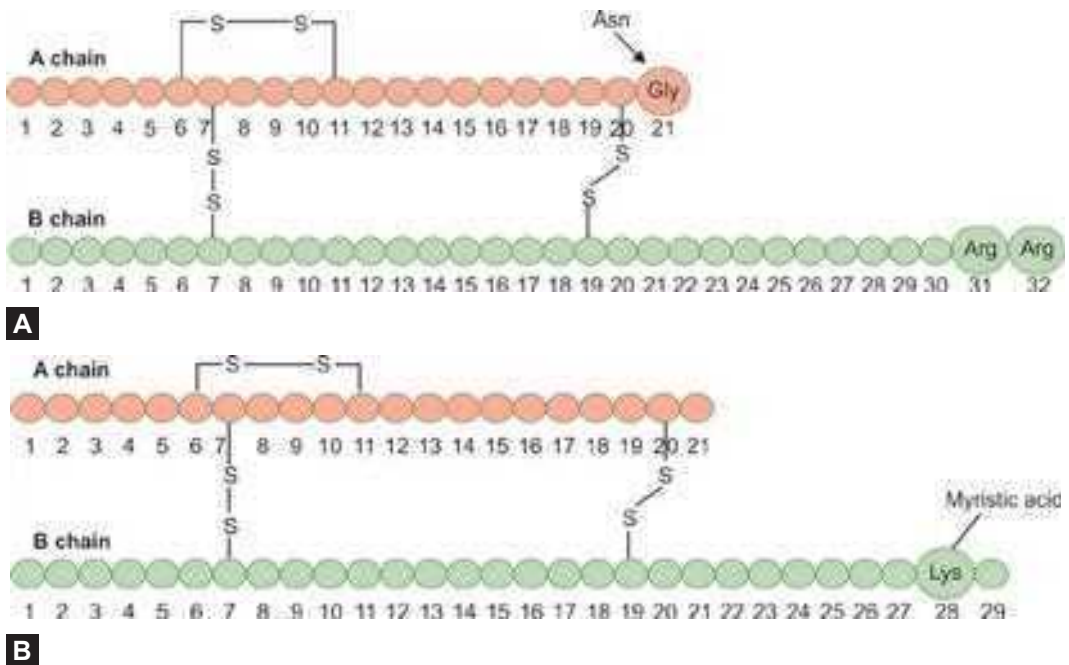
Long-acting Analogs

Insulin glargine

The first of the long-acting insulin analogs, insulin glargine, was introduced in the United States in 2001. This analog is produced by the substitution of glycine for asparagine at position A21 of the insulin molecule and by the addition of two arginine molecules at position B30 (Fig. 7.8A). These changes lead to a shift in the isoelectric point toward a neutral pH, which results in an insulin molecule that is less soluble at the injection site and that precipitates in the subcutaneous tissue to form a depot from which insulin is slowly released. Because of its slower absorption, there is no pronounced insulin peak with glargine thereby decreasing the risk of nocturnal hypoglycemia.

Insulin Detemir

Detemir is another long-acting insulin analog that was developed using a different approach—binding to albumin. An aliphatic fatty acid has been acylated to the B20 amino acid, and the



Figs. 7.8A and B: Structure of long acting insulin analogs—(A) Insulin glargine; (B) Insulin detemir.

Source: White JR. Insulin analogs: what are the clinical implications of structural differences? *US Pharm.* 2010;35(5):3-7.

B30 amino acid has been removed (Fig. 7.8B). This results in reversible binding between albumin and the fatty acid acylated to the insulin. After injection, 98% of the insulin is bound to albumin. Gradual release of the bound fraction from the albumin allows for the sustained, prolonged action of detemir.

The property of less variability in absorption is associated with a reduced risk of hypoglycemia and also less weight gain. Insulin detemir when compared to insulin glargine appears to have a shorter time action profile, which may necessitate twice daily injections in individuals with type 1 diabetes.

Insulin Degludec

The molecular structure of degludec retains the human insulin amino acid sequence, but for the deletion of threonine in the B30 position of the chain, and the addition of a 16-carbon fatty diacid attached to lysine in the B29 position via a glutamic acid spacer. Insulin degludec forms a soluble multihexamer at the injection site and is slowly released as insulin monomers, thus prolonging the duration of action. It also binds to albumin thereby causing a slow and stable release of monomers (Fig. 7.9).

The clinical pharmacology, in particular the pharmacokinetics are usually studied using a hyperinsulinemic euglycemic pancreatic clamp. The principle of the clamp is to clamp the endogenous production of hormones from the pancreas and supplement hormones from

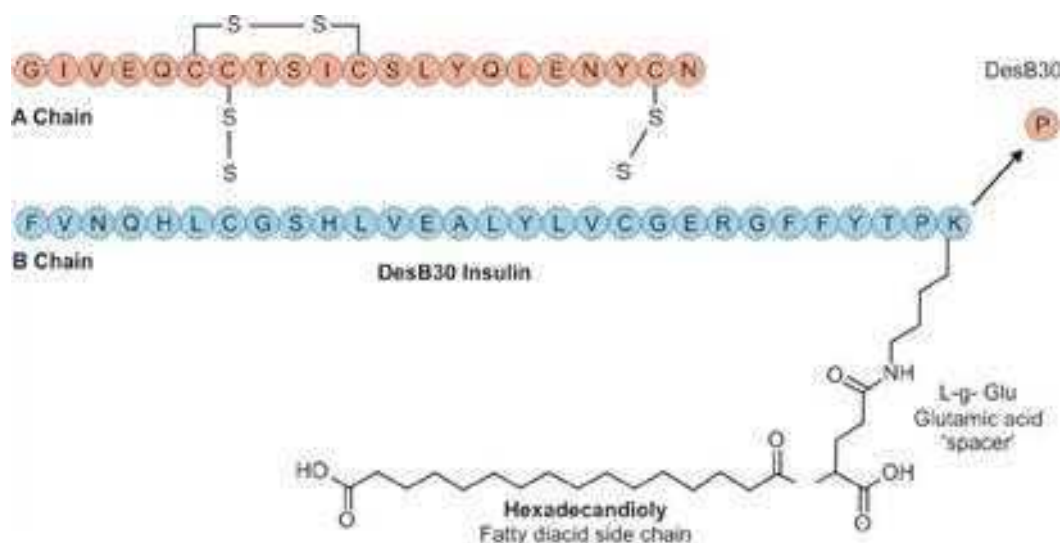


Fig. 7.9: Structure of insulin degludec.

outside so as to ascertain the level of glucose needed to achieve euglycemic state during steady state. The glucose infusion thus needed for maintaining euglycemia, after administering fixed levels of the extrinsic insulin, would be then used to ascertain the levels of the extrinsic insulin during various time periods of the study.

Degludec, on account of a smooth and stable pharmacokinetic profile at a steady state, causes less within-subject variability. As discussed earlier a drug that shows a longer duration of action and lower inter-subject variation is the need of the hour. Degludec seems to score better than glargine on this front.

A study, to compare efficacy of degludec and glargine was conducted amongst 177 type 1 diabetic subjects, by regimens of either degludec or glargine and both in combination with aspart. Those subjects between the age of 18 and 75, having type 1 diabetes for at least 12 months and on continuous treatment with insulin (any regimen) for at least 6 months were included. They were to have an HbA1c between 7% and 11%, and daily insulin dose was to be below 120 IU for inclusion in the study. No restriction was placed on the BMI for inclusion in the study. These subjects were divided into two groups: (1) Insulin degludec, and (2) one group was receiving glargine. The primary objective of the study was to assess glucose control with respect to HbA1c after 16 weeks of treatment. Secondary objectives were to compare efficacy and safety after 16 weeks of treatment in terms of frequency of hypoglycemic episodes and body weight.

The study showed that degludec was safe and well tolerated. There was a difference in rate of hypoglycemia (RR = 0.72), in particular with regards to confirmed nocturnal hypoglycemic attacks (RR = 0.42) in the two groups in favor of degludec. However there was no difference in HbA1c, fasting plasma glucose (FPG) or mean daily dose of insulin seen in the two groups, implying that degludec was as efficacious as glargine with regard to these parameters. The body weight was also maintained over the 16 weeks period.

A multicentric trial among type 2 diabetes mellitus patients was done to compare once daily glargine with once daily or thrice weekly degludec. 236 subjects in between 18 and 75 years of age, having at least 3 months duration of type 2 diabetes mellitus were included in the study. Only those who were on up to two OADs for at least 2 months were included in the study. Those who were on thiazolidines or insulins were excluded from the study. Only those with BMI between 23 and 42 and HbA1c between 7% and 11% were included in the study. The subjects were divided into three groups with one group on once daily 10 U degludec, one group on thrice weekly 20 U degludec insulin, and the third group on once daily 10 U glargine concentrations. They were then followed-up for a period of 6 weeks and HbA1c, hypoglycemic attacks, body weight and BMI over this period and the data was compared amongst the groups.

The study found no significant differences in the rate of confirmed hypoglycemic events, amongst once daily or thrice weekly degludec as compared to glargine. The efficacy outcome measures, including mean weekly insulin dose was similar across all the groups. Thus it is thought that with half the injections weekly, similar glucose control and lesser hypoglycemias could be obtained with degludec as compared to glargine.

Insulin Degludec Plus

Degludec plus (IDegAsp) is a combination of degludec and aspart in a 70:30 formulation. Studies have been done to compare degludec plus and other alternative formulations (AF) of degludec aspart (55:45) with glargine (IGlar) in type 2 diabetes mellitus, all in combination with metformin. Insulin was administered before the evening meal and dose-titrated to a fasting plasma glucose target of 4.0–6.0 mmol/L. After 16 weeks, mean HbA1c decreased in all groups to comparable levels. Mean 2 hours postdinner plasma glucose increase was lower for IDegAsp and AF than IGlar, whereas mean FPG was similar. Hypoglycemia rates were lower for IDegAsp and AF than IGlar. Nocturnal hypoglycemic events occurred rarely for IDegAsp and IGlar compared with AF. Thus no significant difference in HbA1c and FPG seen between the three groups. However those on IDegAsp had a mean decrease in postprandial sugar of 27 mg/dL as compared to those on glargine. The daily mean insulin dose was also lesser by 7 U/kg in the former as compared to the latter.

GLUCAGON LIKE PEPTIDE-1 ANALOGS

Type 2 diabetes results from two impairments: a relative insulin deficiency and insulin resistance. Insulin secretagogues are used in early stages of type 2 diabetes, when β -cell function is still viable. Although patients with type 2 diabetes may have high fasting insulin levels, they also have a blunted first-phase insulin response to a glycemic challenge. This blunting of first-phase insulin release results in prolonged postprandial hyperglycemia. Earlier agents (sulfonylureas), which were utilized to target this defect, increased overall insulin concentrations but often failed to improve first-phase insulin release.

Incretin Effect

Glucagon-like peptide is a gut hormone that stimulates insulin secretion, gene expression, and beta-cell growth. Together with the related hormone, glucose-dependent insulinotropic



Fig. 7.10: Amino acid sequences in Exendin-4 and glucagon-like peptide (GLP). Exendin-4 has partial sequence identity with GLP-1. Exendin-4 and GLP-1 are products from distinct genes in the Gila monster.

polypeptide (GIP), it is responsible for the incretin effect, the augmentation of insulin secretion after oral as opposed to intravenous (IV) administration of glucose.

Incretin effect is the ratio between the integrated insulin response to oral glucose and an isoglycemic IV glucose infusion. Incretin effect for oral glucose is approximately 20–60%. Total incretin quantity as well as incretin effect is decreased in patients with diabetes.

The two most important incretin hormones are GIP, formerly known as gastric inhibitory polypeptide, and GLP-1. Both are potent insulinotropic hormones released by oral glucose as well as ingestion of mixed meals. (See Chapter 1 for detailed information on GLP-1 and its physiology).

Exenatide

Exenatide is a GLP-1 mimetic, a synthetic form of the naturally occurring reptilian hormone exendin-4. Exendin-4 is a naturally occurring component in the saliva of the Gila monster (*Heloderma suspectum*). It has 53% homology with mammalian GLP-1. It is resistant to dipeptidyl peptidase IV (DPP-IV) because of a key difference in amino acid sequence: glycine at position two. Exendin-4 may enhance satiety and weight loss through slowed gastric emptying, as well as through centrally mediated mechanisms. Exendin-4 has been found to bind receptors in the hypothalamus and thalamus in a pattern identical to that for GLP-1 (Fig. 7.10).

Exenatide may exert either a direct or an indirect effect on β -cell mass. Indirectly, exenatide may act by reducing hyperglycemia, which is known to cause β -cell dysfunction and interfere with neogenesis. However, even normoglycemic rats have shown β -cell neogenesis in response to exenatide. Additionally, exenatide's effects on β -cell mass may simply result from the nonspecific growth factor effect of the augmented insulin supply itself. On the other hand, a direct effect on β -cell mass may also be inferred from GLP-1R knockout mice, which display deficient β -cells. Furthermore, the GLP-1R was found in pancreatic ducts, a presumed site of origin for β -cell precursors, and in animal models treated with exenatide, neogenesis appeared to be derived from these precursors. In vitro, exenatide stimulated islet progenitor cells and pancreatic tumor cells to differentiate into insulin-producing cells.

GLP-1-based therapy is a novel and complementary approach to diabetes management for several reasons. It is the first insulin secretagogue that does not cause hypoglycemia. It does not cause the weight gain that may be seen with insulin or sulfonylureas and may in

fact facilitate weight loss. It may be used as a bridge to insulin therapy or to reduce insulin requirements of insulin-resistant patients in order to avoid weight gain. Although it has not been studied in patients with renal or hepatic insufficiency, its safety profile may make it the preferred agent in these patients. GLP-1 is also unique in that it has been shown to reduce the inappropriate rise in glucagon. It may also promote β -cell rescue and theoretically halt diabetes progression, although this has not been formally examined in humans.

Dosage

- Adult minimum: 10 $\mu\text{g}/\text{day}$
- Adult maximum: 20 $\mu\text{g}/\text{day}$.

Common Dosage in Practice

- Inject 0.02–0.04 mL (5–10 μg) by subcutaneous route, two times a day before morning and evening meals
- Exenatide is provided in a single-dose tray containing one vial of 2 mg exenatide, one vial connector, one prefilled diluent syringe and two needles. It must be injected immediately after the solution is prepared and transferred to the syringe. The injection can be given in the abdomen, thigh or upper arm region. Patients should change the injection site each week when injecting in the same region.

Adverse Effects

- *Most frequent:* Diarrhea, hypoglycemia, nausea, and vomiting
- *Less frequent:* Anorexia, dizziness, dyspepsia, gastroesophageal reflux, general weakness, headache, hyperhidrosis, nervousness
- *Rare:* Abdominal swelling, acute abdominal pain, acute pancreatitis, anaphylaxis, angioedema, constipation, drowsy, dysgeusia, eructation, flatulence, pancreatitis, pruritus of skin, renal failure, urticaria.

Drug Safety

- *Pediatric:* Safety and efficacy in pediatrics has not been established
- *Lactation:* Use caution, mouse studies suggest excretion occurs, no human data available
- *Pregnancy:* Only when necessary.

Drug-Disease Contraindications

- *Significant:* Gastroparesis, pancreatitis, severe renal disease
- *Possibly significant:* Alcoholism, biliary calculus.

Liraglutide

Another GLP-1 analog, liraglutide (NN2211) 97% homologous to native GLP-1 has been designed to overcome both the effects of DPP-IV degradation and the short plasma survival

time. Acylation with a fatty acid chain in liraglutide promotes binding to albumin, thereby reducing access to the NH₂-terminal by DPP-IV and allowing the molecule to escape renal filtration. Combined with delayed absorption from the injection site, this results in a stable analog with a plasma elimination half-life of around 12 hours in humans, giving a pharmacodynamic profile suitable for once-daily dosing. Studies in type 2 diabetic patients indicated that 1-week treatment with once-daily liraglutide significantly reduces 24 hours glucose concentrations and improves β -cell function compared with placebo, and the beneficial effects appear to be maintained, with patients showing significant improvements in glycemic control and a trend toward weight reduction after 12 weeks, as compared with sulfonylurea treatment.

Not only has liraglutide been shown to be more effective than exenatide, there are other advantages:

- Less upper gastrointestinal intolerance (8%) to start with, this may reduce further in about 2 weeks
- Can be given any time during the day
- Lower tendency to form neutralizing antibodies to its structure when compared to exenatide.

The physiological impact on weight reduction is less related to its impact on slowing of gastric emptying and more related to a hypothalamic effect in contrast to exenatide.

The specific safety concerns that are harbored in connection with liraglutide are:

1. Potential C-cell hyperplasia of the thyroid gland is a concern, since it has been seen in animal models who have been administered liraglutide. The worry would be the possibility of some of the patients developing medullary thyroid carcinoma. However, the rat model that has been studied has a much greater concentration of C-cells at baseline when compared to human beings which would make the chances of this complication much lower. Hitherto, no direct case of medullary thyroid carcinoma has been reported as being due to liraglutide. As a precautionary measure, liraglutide is contraindicated in any patient who has an underlying thyroid nodule or thyroid malignancy.
2. Acute pancreatitis has been reported in a small number of patients on liraglutide, so also with exenatide. It has been argued that this has been more common in those with abnormal lipid profiles and that the medication has been used in those who are more obese. The US Food and Drug Administration (FDA) has placed a black box indicator as a warning against pancreatitis in subjects who wish to use liraglutide.

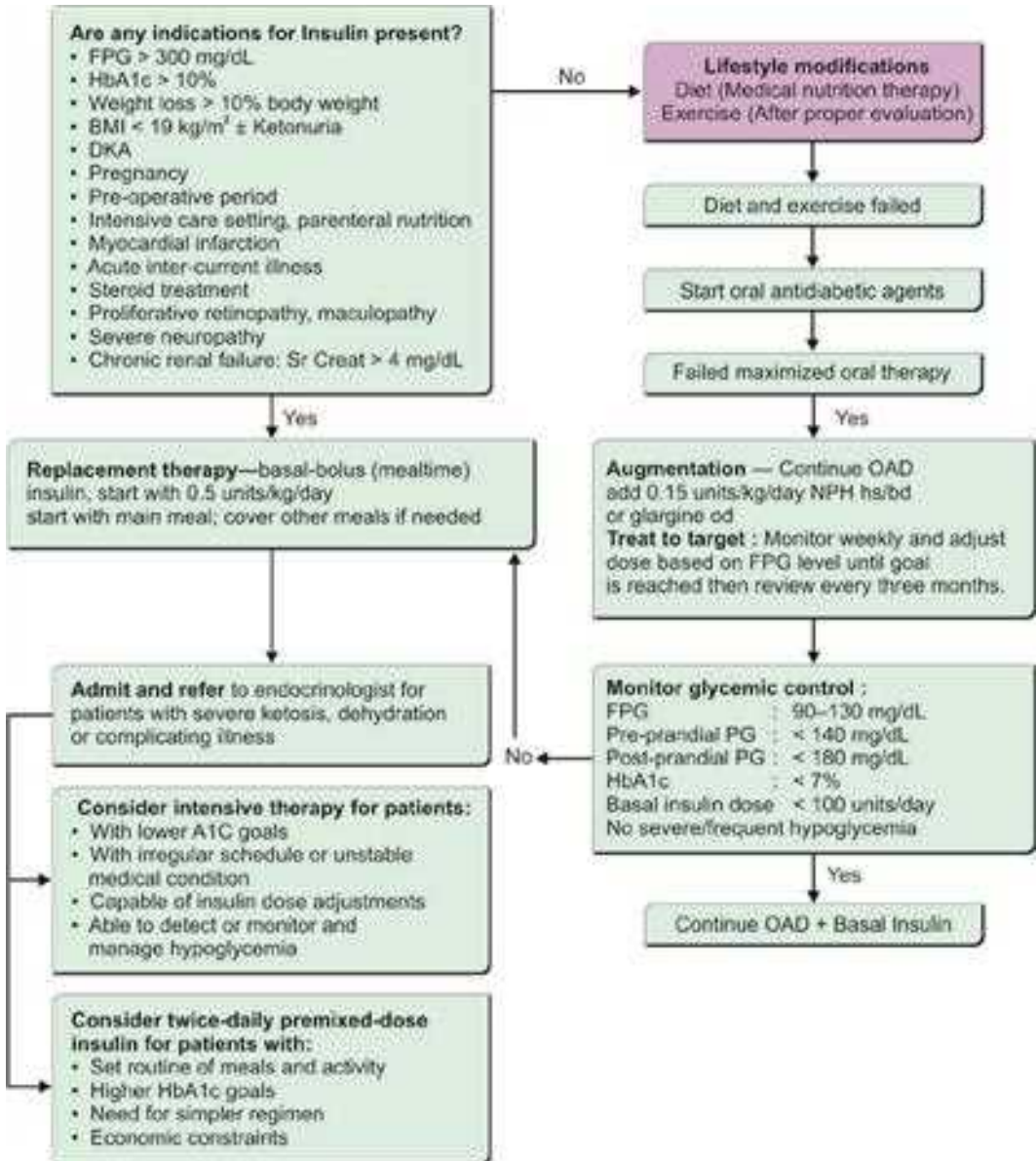
Liraglutide has been shown to be effective in a dosage of 0.6 mg a day. This can be gradually escalated in 1 or 2 weeks to 1.2 mg a day. Doses of 1.8 mg have also been tried but by and large not shown to be superior. Studies have now shown that liraglutide is effective when combined with insulin in type 1 diabetes and also in combination with detemir.

AMYLIN ANALOGS

Pramlintide

Pramlintide, an amylin analog, is an agent that reduces glucagon secretion, slows gastric emptying and improves satiety. It is a US FDA-approved therapy for use in type 1 and type 2 diabetes. It has been shown to induce weight loss and lower insulin dose; however, it is only

Flowchart 7.1: Algorithm for insulin therapy in type 2 diabetes.



(HbA1c: Glycated hemoglobin; FPG: Fasting plasma glucose; BMI: Body mass index; NPH: Neutral protamine Hagedorn; OAD: Oral antidiabetic drug; DKA: Diabetic ketoacidosis; Sr Creat: Serum creatinine).

indicated in adults. Concurrent reduction of prandial insulin dosing is required to reduce the risk of severe hypoglycemia. Gastrointestinal side effects, frequent dosing and cost are its major limitations.

In patients with type 1 diabetes mellitus, it is initiated at a dose of 15 μg prior to major meals. It is administered subcutaneously and increased in the dose of 15 μg everyday if tolerated well. It has been shown to reduce prandial insulin requirement by 50%. A maintenance dose of 30–60 μg subcutaneously per meal is recommended.

In patients with type 2 diabetes mellitus it is initiated at a dose of 60 μg prior to major meals. It is administered subcutaneously and increased to a dose of 120 μg per meal over 3–7 days. A maintenance dose of 60–120 μg per meal is recommended in these individuals. No renal dose adjustment is required for this drug.

An algorithm for Insulin therapy in Type 2 Diabetes is amended in Flowchart 7.1.

SUGGESTED READING

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SELF-ASSESSMENT

1. **A 55-year-old, Mr R who is a known patient with type 2 diabetes for 15 years presented with a history of inability to sleep at night due to persistent pricking sensation of both his feet. On examination his feet were normal, monofilament recorded 10 grams in both feet and biothesiometer read 40 volts bilaterally. Both fundi showed severe nonproliferative diabetic retinopathy (NPDR). Systemic examination was normal. He has been on glibenclamide, metformin 1 g TID. His HbA1c was >12%. All of the following are true *except*:**
 - (a) Peripheral neuropathy is an indication to start him on insulin
 - (b) Best option is to add another oral hypoglycemic agent for better control of sugars
 - (c) MCR footwear should be ideally prescribed for his neuropathy
 - (d) He would require long-term insulin therapy
 - (e) Severe NPDR is an indication for insulin therapy.
2. **The usual dose of insulin in augmentation therapy is:**
 - (a) 0.15 units/kg/dose
 - (b) 0.35 units/kg/dose
 - (c) 0.50 units/kg/dose
 - (d) 0.05 units/kg/dose.
3. **All of the following are indications to initiate insulin therapy early, *except*:**
 - (a) MODY
 - (b) LADA
 - (c) Gestational diabetes
 - (d) Fibrocalcific pancreatitis
 - (e) Secondary OAD failure.
4. **All of the following are true about insulin analogs *except*:**
 - (a) There is no pronounced insulin peak with insulin glargine
 - (b) They are superior to human insulin in preventing complications of diabetes

- (c) Insulin lispro is safe in pregnancy
- (d) Insulin detemir may be administered as twice daily injections in type 1 diabetes
- (e) Rapidly acting analogs are superior to regular insulin in lowering postprandial sugars.

5. Which of the following is *not* a short-acting insulin?

- (a) Lispro
- (b) Detemir
- (c) Aspart
- (d) Glulysine
- (e) Actrapid.

6. Which of the following is associated with weight gain?

- (a) Exenatide
- (b) Regular insulin
- (c) Detemir
- (d) Liraglutide.

7. Which of the following OAD should be ideally stopped while starting a patient on insulin?

- (a) Metformin
- (b) Glimepiride
- (c) Pioglitazone
- (d) Acarbose.

8. Which of these drugs can be used in a patient with diabetic nephropathy in renal failure (Creatinine: 4.3 mg/dL)?

- (a) Glibenclamide
- (b) Metformin
- (c) Insulin
- (d) Aminoglycoside
- (e) Detemir

9. A 16-year-old girl presents with osmotic symptoms, BMI 32 kg/m². Acanthosis nigricans is present. History of polycystic ovary disease is present. RBS—340, urine ketone—1+. Both parents have diabetes. Which of the following is true regarding this patient's immediate management?

- (a) She has type 1 diabetes, requires insulin
- (b) Has type 2 diabetes, requires insulin
- (c) Has type 1 diabetes, is in honeymoon period
- (d) Has type 2 diabetes, can manage with glimepiride
- (e) Has pancreatic diabetes.

10. A 40-year-old man presents with diabetes for 7 years duration and is on premixed insulin 120 units per day and has a BMI of 37 kg/m². He is started on exenatide 5 µg once a day. Which of the following are false?

- (a) He is likely to lose at least 3 kg of weight in 2 months
- (b) He may have nausea
- (c) The maximum dosage is 10 µg once a day
- (d) Gallstone disease is a contraindication
- (e) It is shorter acting than liraglutide.

CHAPTER

8

Insulin Therapy— Practical Aspects

ancy Jeudo, Ruth Rubyurray

*“Insulin may be injectable,
But pens are for the affordable,
The tight control it gives is good,
Always inject well before food.”*

Education is the cornerstone of diabetes treatment; the educator must possess medical competency, technical skill and psychological expertise. Insulin therapies have evolved considerably in the seven decades since its discovery. Correct insulin injection techniques are recognized as essential elements of effective insulin therapy. This chapter aims to focus on subjects with diabetes who administer insulin. Self-administration of insulin is an art which can be easily mastered by adhering to a few basic strategies.

INTRODUCTION

The United Kingdom Prospective Diabetes Study (UKPDS) showed that to keep type 2 diabetes control [glycated hemoglobin (HbA1c < 7%)]; insulin was needed within 6 years for approximately 50% of people with diabetes. There may be a change in this paradigm with the larger menu of oral hypoglycemic agents available these days—but the message conveyed is clear. Although starting insulin in clients with type 2 diabetes is safe and simple, the quantity and the number of insulin doses can be expected to increase with time as insulin resistance increases and the capacity of the pancreas to secrete insulin decreases. Hence, the practical aspects of insulin therapy become very important.

Incorrect technique, including wrong needle length, can lead to insulin being absorbed in an unpredictable manner. This may predispose to variations in glycemia leading to hypoglycemia, hyperglycemia, or even diabetic ketoacidosis (DKA) in type 1 diabetes. Nevertheless, correct injection technique is under emphasized in routine patient care. A pan-European study showed that people with diabetes do not remember receiving any education on particular topic relating to injection technique. Insulin therapy, whether using conventional method or higher technological devices is finely tuned for its peak of action and providing duration of action. If the technique is flawed, the pattern in which insulin works varies and affects glycemic

control. Hence, it is an imperative role for all healthcare providers to educate and treat people with diabetes, offer training and advice on best practices and monitor injection technique and sites at regular intervals. This chapter outlines key aspects in insulin injection technique which needs to be considered to allow injectable therapy to work as designed.

INSULIN SYRINGES

Conventional administration of insulin involves subcutaneous injection with syringes marked in insulin units. Insulin is available in strengths of U-40 and U-100 in India. To avoid dosing errors, syringes matching the concentration of U-40 and U-100 insulin is used (Figs. 8.1 and 8.2).

Each division on U-40 syringe is equivalent to 1 unit of insulin.

Each division on U-100 syringe is equivalent to 2 units of insulin.

Reuse and Disposal of Syringes

Manufacturers of disposable syringes and insulin pen needles recommend that needles should be used only once. Nevertheless, many people adopt this practice. Reuse of an insulin syringe compromises insulin sterility and can lead to bruising and bleeding due to blunted needle. Reuse is not advisable for people with poor personal hygiene, open wounds on hands and injection site, or immunocompromised patients, e.g. postrenal transplant. Recapping is important for reuse of syringes and requires manual dexterity and hand steadiness.

Most insulin preparations contain products that inhibit growth of bacteria commonly found on skin. Infection is possible if the needle is reused or when an injection is given through clothing. A far more important reason not to reuse needles has risen with the advent of new, smaller needles (30/31G). Even with one injection the needle tip can become bent to form a hook, which lacerates the tissue or breaks leaving needle fragments in the skin. Hence, clients should be instructed to discard the syringe and needle after one use. If insulin is administered by a caregiver, recapping, bending, or breaking a needle will heighten the risk for needle prick injuries. If needles become noticeably dull or bent, or come into contact with any other surface other than clean skin, they should be discarded. In a hospital setting, needles/syringes should be disposed as per the local protocol for the disposal of dangerous wastes. At home, they should



Fig. 8.1: Insulin syringe.



Fig. 8.2: Steps in subcutaneous insulin administration.

be disposed as per the local administration's rules for the disposal of medical waste. Cleaning needle with alcohol is not recommended as it removes the silicon coating which enables a less painful skin puncture. Sharing of syringes, needles or insulin pens is never acceptable (Tables 8.1 and 8.2).

Table 8.1: Client education guide 1: Subcutaneous insulin administration.

1.	Wash hands
2.	Inspect the bottle for the type of insulin and the expiration date
3.	Gently roll the intermediate-acting insulin in the palm of your hands to mix the insulin
4.	Clean the rubber stopper with an alcohol swab
5.	Remove the needle cover and pull back the plunger to draw air into the syringe. The amount of air should be equal to the insulin dose. Push the needle through the rubber stopper and inject the air into the insulin
6.	Turn the bottle upside down, now the tip of the needle should be in insulin and draw insulin into the syringe
7.	Remove air bubbles in the syringe by tapping on the syringe or injecting air back into the bottle. Redraw the correct amount
8.	Make certain that the tip of the plunger is on the line for your dose of insulin Magnifiers can be used to assist in measuring accurate dose
9.	Remove the needle from the bottle. Recap the needle if the insulin is not to be given immediately
10.	Select a site within your injection area that has not been used for the previous injection
11.	Clean the skin with an alcohol swab. Lightly grasp an area of the skin and insert the needle at a 90° angle
12.	Push the plunger all the way down. This will push insulin into the tissue. Release the skin. Hold the needle in place for 10 seconds
13.	Pull the needle straight out. Do not rub the place where you gave the shot
14.	Dispose of the syringe and needle.

Note:

- For clients with loose skin and less subcutaneous tissue, the needle is inserted at a 45° angle to avoid intramuscular injection
- Gentle pressure needs to be applied for 5–8 seconds if blood or clear fluid is seen after withdrawing the needle.

Table 8.2: Client education guide 2: How to mix a prescribed dose of 10 units of regular insulin and 20 units of neutral protamine Hagedorn (NPH) insulin.

1.	Wash hands
2.	Inspect bottle for the type of insulin and the expiration date
3.	Gently roll the bottle of intermediate insulin in the palms to mix the insulin
4.	Clean the rubber stopper with an alcohol swab
5.	Inject 20 units of air into the NPH insulin bottle. The amount of air should be equal to the dose of insulin needed. Always inject air into the intermediate-acting insulin first. Withdraw the syringe
6.	Inject 10 units of air into the regular insulin bottle. The amount of air is equal to the dose of insulin desired
7.	Withdraw 10 units of regular insulin. Be sure that the syringe is free of air bubbles. Always withdraw the shorter acting insulin first
8.	Withdraw 20 units of NPH insulin with the same syringe, being careful not to inject any short acting insulin into the bottle (a total of 30 units should be in the syringe)

Insulin doses can be loaded in prefixed syringes and left in the refrigerator for clients who have diminished vision. However, repeated dose preparation with the same syringe erases the markings on syringe due to moisture and is not generally recommended.

Syringe Alternatives

Pen-like devices and insulin-containing cartridges which deliver insulin subcutaneously through a needle are available. These devices have been demonstrated to improve accuracy of the dose and client compliance. Research shows that pen devices enhance convenience, flexibility, and clinical efficacy and users prefer pen devices over conventional syringe method. There is improvement in quality of life among clients who used insulin pen at the first initiation of insulin therapy.

Insulin Storage

Insulin preparations are stable at room temperature. However, due to loss of potency at high temperatures in India, we highly recommend that insulin be stored in a refrigerator. Extreme temperatures and excess agitation should be avoided. Insulin should be visually inspected before each use for changes such as clumping, frosting, precipitation or change in clarity or color.

In-use insulin vials, unopened vials, cartridges, and prefilled insulin pens should be stored between 2°C and 8°C (36°F and 46°F). Extreme temperatures (<36°F or >86°F, <2°C or >30°C) should be avoided to prevent loss of potency, clumping, frosting or precipitation.

Injecting cold insulin may cause pain and local irritation at the injection site and hence it is generally recommended that in-use vials be left at room temperature (<30°C), but to discard after a month. However, in a country like India, where room temperatures often exceed 30°C, it is not advisable to leave vials at room temperature. At room temperature insulin will lose 1.0% of its potency over 30 days and if refrigerated, it will lose <0.1% of its potency over the same period. Insulin can be left outside for 10 minutes before injection and rolled between palms to normalize temperature.

Insulin can be stored in earthen vessels if a refrigerator is not available. Insulin vials may also be wrapped in a polythene cover and submerged in cold water in a thermos container during travel. Pen devices should be maintained at a temperature below 30°C at all times to ensure stability of insulin. If there is uncertainty on potency of a vial, replacement of the vial in question with another of the same type is recommended. The “cold-chain” should be maintained during transportation of the vials or cartridges of insulin.

Resuspension of Insulin

A proper resuspension of cloudy insulin is required to achieve the strength of insulin delivered and results in hypoglycemia or hyperglycemia if insulin is not mixed properly. Resuspension is achieved by rolling insulin vial or cartridge in between palms 10 times and gently inverting it 10 times to ensure the insulin is milky white in color before it is injected.

Sites for Insulin Administration

Though several sites are suitable for administration of insulin, we recommend the anterior abdominal wall as the preferred site for reasons such as ease in self-administration, a larger surface area and steady rate of absorption. Insulin absorption varies depending on the injection site and proximity to the limb involved in exercise. Site of administration should be rotated within regions to promote consistent absorption. Insulin needs to be injected at a distance of 0.5–1 inches away from the previous injection site. Making an anatomical “map” for an injection rotation sites prevents repeated injection at the same site. The rotation of sites is important to prevent lipohypertrophy, which is an abnormal subcutaneous fat accumulation.

The commonly used sites for insulin administration are:

1. *Anterior abdominal wall*: The rate at which insulin is absorbed is rapid and consistent in the anterior abdominal wall as compared to arms and the thighs, in that order. The anterior abdominal wall is therefore the preferred site. Rotation of injections within this area is recommended. Insulin is injected at least four finger-breadths away from the umbilicus on all sides. Repeated injections at a particular site cause lipodystrophy and impair the nervous and vascular supply. This results in painless injection and clients prefer that particular site. Diminished vascular supply leads to decreased absorption of insulin and results in hyperglycemia.
2. *Upper outer thighs*: Injections in the thigh should be performed in the anterior and lateral aspect. The femoral vessels and nerves lie medially and can easily be traumatized. However, there is very little subcutaneous tissue laterally, sometimes less than 3 mm space. Hygiene is a special issue in India due to the tropical climate. Culturally, women sometimes find it difficult to inject on thighs considering privacy. Exercise, e.g. walking increases insulin absorption which results in hypoglycemia. Therefore, injections in the thighs are not preferred.
3. *Upper outer arms*: Like the thighs the arms have very thin layers of subcutaneous tissue and self-injection insulin in the arms is difficult.

Lifted Skin Fold Technique

To avoid injection into muscle layer in adults while using needles longer than 8 mm, a skin fold must be used. The skin should not be lifted using the whole hand and must be released gradually following injection. Otherwise, this may increase the risk of intramuscular injection. The best method is to lift the skin between thumb and two fingers with one hand, pulling the skin and fat away from underlying muscle, holding until the insulin is injected. A needle length of less than 8 mm is best suited when a lifted skin fold technique is used in very thin patients and in children.

Mixing of Insulin

Certain insulin regimens require a mixture of different insulin formulations administered at the same time. These formulations can be administered as two separate subcutaneous injections or can be mixed for a single injection. Conventional syringes allow mixing of insulin

while insulin pen do not allow mixing. During mixing of insulin in a syringe, regular insulin should be drawn up first, followed by the intermediate-acting insulin. This method prevents contamination of regular insulin with NPH insulin. NPH and regular insulin when mixed is used immediately or stored for future use (within 24 hours). Similarly, rapidly acting insulin analogs may be mixed with NPH or ultralente insulin as the pharmacokinetics of either insulin does not change on mixing. Mixing regular insulin with lente or ultralente is not recommended as the zinc in lente can bind with regular insulin, thereby delaying its onset of action in an unpredictable fashion. NPH insulin should not be mixed with lente insulin because zinc phosphate may precipitate. Insulin glargine should not be mixed with other insulin because of its acidic pH and will precipitate when mixed with the other pH-buffered insulin. The combination of the two types of insulin may result in a variable dose response. It is suggested that different brands of insulin not be mixed.

Split-Mix and Multiple Dose Regimens

A split-mix insulin regimen (twice daily mixture of regular and NPH) or a multiple dose insulin regimen (three or four injection of insulin a day with injection of short acting insulin before each meal) can be used. A twice daily split-mix is simple and attempts to match insulin peaks to the time of meals; further, each component can be independently adjusted. While preparing a split-mix dose, the regular insulin should be drawn first, followed by the long or intermediate acting insulin. Also,

- Rapid acting insulin can be mixed with NPH, lente or ultralente
- Phosphate-buffered insulin (e.g. NPH) should not be mixed with lente insulin
- Zinc phosphate may precipitate and long acting insulin will convert to short acting insulin.

FACTORS THAT AFFECT RATE OF ABSORPTION OF INSULIN

Following an insulin injection there is a breakdown of hexameric exogenous insulin to dimers and monomers that can cross into the capillaries and enter the blood stream.

Site for Injection

The duration of rate of absorption of insulin is 50% longer in the thighs as compared to the abdominal wall. Regular insulin peaks at 90–120 minutes after injection in the thigh and because of subcutaneous enzymes, only about 60–65% of insulin is absorbed. Peak bloodstream levels of insulin after injection in the arm and abdomen is achieved in 75 minutes and 60 minutes respectively. The shorter absorption time from the abdominal site also means that there is less destruction of insulin by subcutaneous enzymes.

Temperature

The warmer the area the faster is the absorption, the colder the area the slower the absorption. A warm shower should be avoided after the injection. Going out into the cold with light clothing can lead to decreased absorption and, therefore, high blood sugar.

Exercise

Exercise increases the rate of absorption of insulin by increasing the blood supply.

Needle Length

Recent research allays concerns regarding shorter needle length, demonstrating that 4–5 mm length needles minimize penetration into muscle layer and no additional leakage, even in obese patients. Glycemic control with 4 mm needle is equivalent to that of 5 mm or 8 mm length.

In summary, the factors that speed up absorption and increase the risk of hypoglycemia are:

- Warm or hot environment, increasing blood flow to injection area
- Rubbing or massaging the area
- Injection delivered into deeper layers of skin
- Exercises increase the rate of absorption.

The factors that may slow absorption and increase the risk of hyperglycemia are:

- Cold environment reducing blood flow to the injection area
- Increased volumes of insulin, as the ability to absorb larger amount is reduced
- High concentration of insulin. Recent data show that Glargine can be injected in a single dose up to 200 units with no impairment in absorption
- Unhealthy injection sites, e.g. bruised or scarred areas.

COMPLICATIONS OF INSULIN THERAPY

Insulin therapy usually does not lead to complications if the clients follow the given instructions.

Hypoglycemia

Hypoglycemia is the most frequent and feared complication of insulin treatment, with potentially serious sequelae. Previous episodes of repeated severe hypoglycemia requiring assistance or hypoglycemic unawareness are risk factors for severe hypoglycemia and this risk is inversely related to HbA1c levels.

Weight Gain

Several mechanisms have been proposed to explain the weight gain associated with insulin use. Improved glycemic control decreases glycosuria thereby decreasing the loss of calories through the urine. The direct lipogenic effects of insulin on adipose tissue may also contribute to weight gain. Also, increasing insulin doses may cause recurrent mild hypoglycemia that may manifest as hunger resulting in intake of excess calories. The result of weight gain in insulin-treated clients is further insulin resistance, leading to the need for more insulin and potentially more weight gain.

Lipatrophy/Lipohypertrophy

Injection of less-purified insulin into subcutaneous fat can sometimes lead to localized loss of fat. This is reduced by the use of more purified insulins. If insulin is injected into the area surrounding the affected sites, the subcutaneous fat will be restored over several months to years.

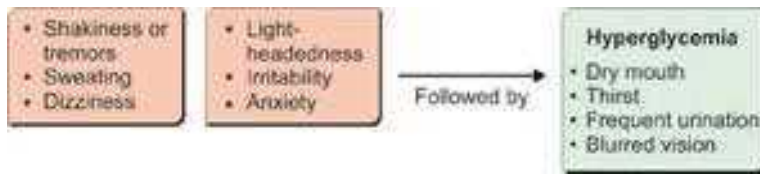
Lipohypertrophy may present as localized areas of increased swelling of subcutaneous fat on repeated injection. This reduces sensitivity to injection pain and masses of fibrous tissue develop. Insulin absorption from these sites is unreliable. Rotation injection sites prevent lipohypertrophy.

Somogyi Effect

The Somogyi effect, or rebound hyperglycemia, is another reaction to hypoglycemia. When the blood glucose levels are low certain hormones called “counter regulatory hormone” cause blood glucose levels to rise. The Somogyi phenomenon was named after a Hungarian-born professor called Michael Somogyi.

Symptoms

If someone is experiencing the Somogyi effect they may not notice the episode of hypoglycemia that triggers the hyperglycemia, they may notice following symptoms:



Eating too much food to treat hypoglycemia can cause an even greater rise in the blood glucose levels. If someone’s blood glucose levels fall less than 65 mg/dL and then rise to 200 mg/dL within the next few hours then they are probably experiencing a Somogyi effect (Fig. 8.3).

Recommendations

- The best way to treat rebound hyperglycemia is to determine what is causing the initial episode of hypoglycemia
- Check your blood sugars several times in a day
- Maintain a proper log book of your blood glucose levels and activity
- Check your blood sugars between 3 am and 4 am and then again at 7 am
- Prior snack before exercise
- An appropriate bedtime snack everyday before sleep.

Dawn Phenomenon

Dawn phenomenon, sometimes called the dawn effect, is an early-morning (usually between 2 am and 8 am) increase in blood glucose in patients with diabetes, not associated with early morning hypoglycemia (Fig. 8.4).

In the early hours of the morning, the body produces certain growth hormones. These hormones repress the action of insulin and allow the blood glucose levels to rise between 4 am and 8 am.

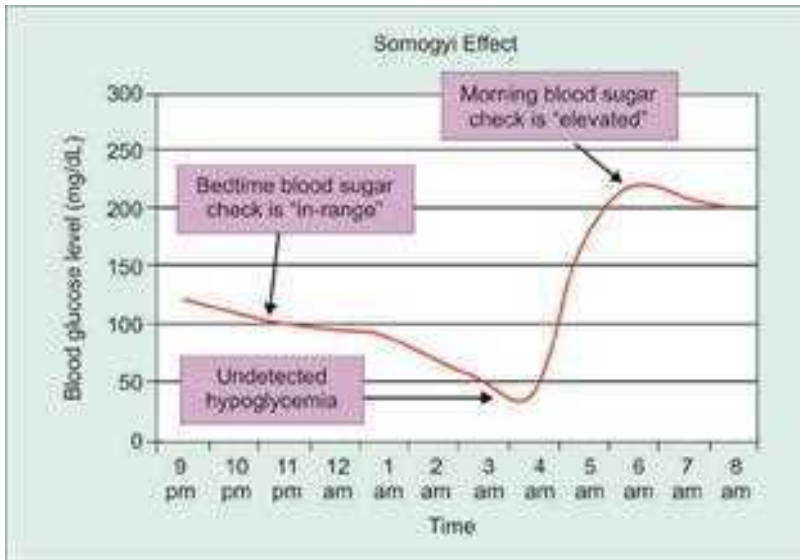


Fig. 8.3: Somogyi effect.

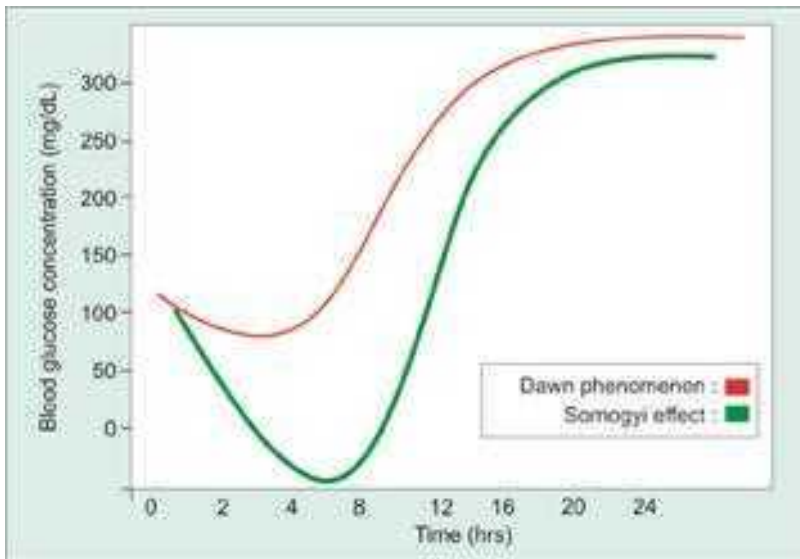


Fig. 8.4: Dawn phenomenon and Somogyi effect.

Recommendations

- Decrease the food intake at night
- Monitor blood sugars more frequently, especially between 2 am and 4 am
- If on insulin the night dose needs to be increased
- Frequent monitoring is again very important.

Pain

Perception of pain with injection therapy has shown to be related to needle length and diameter, injection technique, and accidental intramuscular injections. Short and narrow gauge insulin needles minimize pain (4 mm or 5 mm/31G). Patients who have “needle phobia” are very few, also they have true needle phobia, and psychological counseling is needed and is effective.

Measures to avoid painful injections

- Injecting room temperature insulin
- Allowing topical alcohol to evaporate if used
- Relaxing muscles at site while injecting
- Using distraction technique
- Quick skin penetration
- Avoid changing direction of needle while insertion and withdrawal
- Avoiding reuse of needles
- Using injection device that puts pressure around the injection site.

BARRIERS TO INSULIN THERAPY

Patient Barriers

- Psychological barriers
 - Fear of hypoglycemia
 - Fear of needles and pain
 - Poor self-efficacy
 - Self-blame
 - Loss of control
 - Social stigma
 - Perceived patient resistance
 - Myth based fear of insulin
 - Patient’s compliance.
- Lifestyle
 - Time-consuming, inconvenient
 - Travel issues.
- Physical and mental
 - Poor recall or cognitive impairment
 - Visual/hearing/dexterity impairment
 - Learning difficulties; low literacy/numeracy skills.

System Barriers

- Overburdened work load
- Access to education and training
- Limited to training to providers

- Underutilization of resources
- Poor follow-up system
- Suboptimal team cooperation; poor chronic care model.

Provider Barriers

- Concerns about adverse effects
- Provider time constraints: Instruction/titration
- Lack of resources, e.g. personnel to train.

Special Population

Children

Children and adolescents should use 4–5 mm needles to minimize pain and improve compliance. Skin pinching while injecting may minimize pain. To allay fear, strategies in younger children include injecting saline into stuffed animal, a diaper that stimulates skin, or a parent. A collaborative team effort is needed for emotional and psychological support in children. Education on diabetes and training should be available for parents, caregivers, and teachers.

Pregnancy

Self-blood glucose monitoring and titration of doses is essential during pregnancy especially during first trimester when hypoglycemia is common due to hyperemesis gravidarum. The skin fold should be raised while giving abdominal injections to avoid injecting into muscle layer.

Elderly Patients

Careful assessment of manual dexterity, cognition, vision, and hearing is required prior to therapy and during follow-up to determine patient's capacity to perform self-injection.

Clients with Vision, Hearing, or Dexterity Impairment

Magnifier lens and insulin pens with a dial click for each unit dialed is helpful for elderly people. Preparing prefilled syringes with desired amount of insulin by caregivers is advisable for those with dexterity impairment. Training for hearing impaired clients must happen in a calm and quiet environment. The educator should face the client, with adequate lighting to facilitate lip reading, and should speak slowly and clearly with normal intonation.

SICK DAY MANAGEMENT

Common illnesses such as tonsillitis, ear, chest or urinary tract infections can cause extra stress on the body. This increases the amount of insulin required to keep blood sugars levels under control. It is difficult to predict how an illness affects blood glucose; therefore, period blood glucose monitoring is essential. If blood sugar levels remain high for several hours the body

starts to produce ketones. Ketones are toxic and if they build up to moderate or high levels, a life threatening condition called DKA ensues. Hence, it is important to take actions during the initial clinical course of any illness.

Sick Day Guidelines

Step 1: Frequent monitoring of blood glucose, if possible to monitor for ketones in blood/urine.

Step 2: Adequate fluid intake and oral intake if possible.

Step 3: Seek assistance.

- Extra insulin is needed if blood sugars are more than 250–300 mg. It is advised to administer an extra dose of short acting insulin and not to wait until the next dose
- The dosage schedule is described in detail in the chapter on “Childhood diabetes”
- Regular and periodic monitoring of blood glucose levels
- If the client has vomiting or diarrhea and is unable to eat, oral hypoglycemic agents (OHAs) are stopped and insulin is continued in reduced doses since insulin without adequate oral intake precipitates hypoglycemia
- Urgent medical attention is required at the earliest.

Other Instructions

Advise clients to

- Carry a sick day kit containing—action plan, short acting insulin, insulin syringes, extra food, 20 g of glucose, monitoring equipment—glucometer, test strips, and ketone strips
- Carry sick day action plan—sick day guidelines, details about whom to contact, special instructions when to seek medical care, and important contact numbers
- Example for giving extra dose on a sick day:

Usual Daily Dose	Morning	Lunch	Dinner	Bedtime
Short acting	10 units	10 units	10 units	_____
Long acting/Intermediate	_____	_____	_____	10 units

If the client is on three times short acting and once intermediate acting insulin. The daily total will be $10+10+10+10 = 40$ units.

Therefore, 10% of the daily total is 4 units which is the extra dose, and further doses depend on the blood glucose levels.

ALTERNATIVE METHODS OF INSULIN DELIVERY

Insulin Pens

Insulin pens are designed for ease in subcutaneous administration of insulin. These devices are either disposable or reusable depending on the duration of insulin therapy. It is an important tool for insulin administration featuring simplicity, ease of use, reliability in clients with type 1 and type 2 diabetes. Insulin pens are proprietary and the insulins contained are company distinct. These insulin pens are manufactured only for the specific insulin for which it was designed (Fig. 8.5). The two types of insulin pen available in the market are



Fig. 8.5: Insulin pen device.

1. Reusable insulin pens
2. Disposable insulin pens

Reusable Insulin Pens

This is intended for long-term/permanent insulin therapy. These devices use small (3 mL = 300 units) prefilled cartridges that are loaded into a pen like holder. A disposable needle (30–31 G) is attached to the device for insulin injection. Insulin is delivered by dialing a dose and pushing a button for every one increment administered. A maximum of 60–70 units can be injected at one single injection. Clients using these devices still need to insert needle for each injection. Pen devices are durable, easy to use, and are designed for longer duration of use. Possible damage of pen may happen over time.

Disposable Insulin Pens (Prefilled Pens/Single Use only)

This compact unit contains a built-in, single-use insulin cartridge. It does not require loading of the insulin cartridge by the client; and it is convenient and easy to use. It is portable, durable, and light weight delivery system which is helpful for clients who have difficulty in handling cartridges in reusable pens or clients with busy schedule who prefer not to change cartridges. They are a little expensive over times, compared with reusable pens. Each delivery system has 3 mL of insulin, corresponding to 300 units of insulin. It can be dialed up to 80 units.

Advantages of Insulin Pen Devices over Conventional Insulin Syringes

- More convenient method and more accurate insulin delivery
- Less pain due to the use of smaller gauge needles
- Improved quality of life and enhanced compliance with the insulin regimen
- Simpler for specific populations to use (e.g. elderly, children, adolescents and pregnant women)
- Improved social acceptability, especially at school
- Less “medical” looking and contain all necessary parts (insulin containers and injecting device) in one unit.

Who Benefits from Pen Devices?

1. Clients with erratic eating habits may benefit. Clients who take regular or Lispro insulin before meals or snacks and NPH at bedtime usually need two pens, one for each type of insulin. Also, clients who take mixture of two kinds of insulin in one syringe (e.g. regular/Lispro and NPH or lente other than 30/70 premixed insulin) need to use two pens and two injections for each dose. This is less desirable than the single-syringe injection of mixed insulin.
2. Children often have more positive attitude regarding pen devices as compared to conventional syringes due to reduced pain perception.
3. Women with pregestational and gestational diabetes requiring pharmacologic therapy. The convenience, flexibility, and ease of use with insulin pen can simplify treatment and reduce therapy related stress for pregnant women during an existing stressful period.
4. Older clients with vision problems, air bubbles that are drawn into the syringe may go unnoticed leading to variations in insulin delivery. Not only do insulin pens improve dosing accuracy and compliance but they are also easier for clients with compromised fine-motor coordination (Fig. 8.6).

Limitations of Pen Devices

These devices are most useful for clients who need to inject only one type of insulin at a time or who can use premixed insulin. Be cautious while recommending this device for visually or neurologically impaired clients. These devices are not meant for independent use by visually impaired clients.

DETERMINING EFFECTIVENESS OF SELF-INJECTION EDUCATION

Insulin Pump: Continuous Subcutaneous Insulin Infusion

An insulin pump is a small device about the size of a small cell phone that is worn externally and can be discreetly clipped to your belt, slipped into a pocket, or hidden under your clothes (Fig. 8.7). It delivers precise doses of rapid-acting insulin to closely match your body's needs:

- **Basal rate:** Small amounts of insulin delivered continuously (24/7) for normal functions of the body (not including food). The programmed rate is determined by your healthcare professional.
- **Bolus dose:** Additional insulin you can deliver “on demand” to match the food you are going to eat or to correct a high blood sugar. Insulin pumps have bolus calculators that help you calculate your bolus amount based on settings that are determined by your healthcare professional.

Components of Insulin Pump Therapy (Figs. 8.8 and 8.9)

1. Insulin Pump: A small durable medical device that has—
 - Buttons to program your insulin
 - LCD screen to show what you are programming



Fig. 8.6: Insulin administration using an insulin pen device.

- Battery compartment to hold one AAA alkaline battery
 - Reservoir compartment that holds insulin.
2. *Reservoir*: A plastic cartridge that holds the insulin that is locked into the insulin pump. It comes with a transfer guard (blue piece at the top that is removed before inserting the reservoir into the pump) that assists with pulling the insulin from a vial into the reservoir. A reservoir can hold up to 300 units of insulin and is changed every 2–3 days.
 3. *Infusion set*: An infusion set includes a thin tube that goes from the reservoir to the infusion site on your body. The cannula is inserted with a small needle that is removed after it is in place. It goes into sites (areas) on your body similar to where you give insulin injections. The infusion set is changed every 2–3 days.



Fig. 8.7: Insulin pump.



Fig. 8.8: Parts of an insulin pump.

4. *Infusion set insertion device*: An infusion set is placed into the insertion device and with a push of a button the infusion set is inserted quickly and easily.

Example:

Mrs X, a 34 years old lady with pregestational diabetes mellitus, was on basal bolus insulin, short acting insulin 5-3-3 and 6 units of NPH, this patient was experiencing frequent hypoglycemia even when 1 or 2 units of insulin was increased, so we have planned to start on pump therapy.

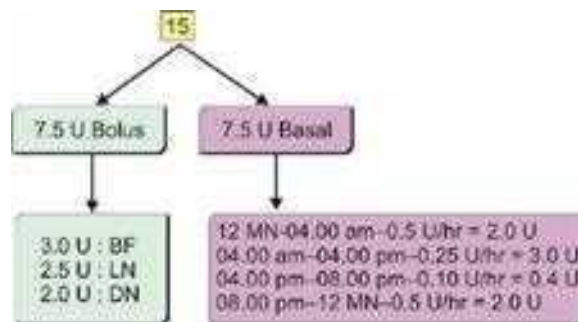


Fig. 8.9: Steps in initiating continuous subcutaneous insulin therapy.

There are some prerequisites before starting on insulin pump:

- Total daily dose (TDD) of insulin = 17 units (short acting and intermediate acting $5 + 3 + 3 + 6 = 17$ units)
- Only short acting is given, which works as basal and bolus
- Rule of 1800 for analogs and rule of 1500 for regular insulin

- Calculate ISF (insulin sensitivity factor) for Mrs X, plan to use analog
 - $ISF = Rule/TDD$
 - $1700/17 = 100$
 - This means 1 unit of insulin will bring down the blood sugar by 100 mg/dL
 - This is also called as *correction bolus*, if the patient's sugars are more based on the calculations above, we can correct the blood sugar immediately this is most important benefit on an insulin pump
- When using analogs the insulin dose is reduced by 10% from the actual dose which is 17 units to approximately 15 units
- 15 units have to be equally divided to equal halves for basal dose and bolus dose and then based on the patient



(BF: Breakfast; LN: Lunch; DN: Dinner; MN: Morning)

Basal Insulin

This is continuous infusion of small amounts of rapidly acting insulin over 24 hours. This aims to match endogenous hepatic glucose production and generally comprises 40–50% of total daily insulin dose. The rate of infusion can be individually programmed throughout the day, increasing during times of relative insulin resistance and decreasing during periods of activity. A properly set basal rate keeps the blood glucose levels stabilized in the absence of food.

- Higher basal rates for less activity periods
- Lower basal rates for more active periods.

Bolus Insulin

These are client-activated doses given with meals to correct the prandial increase in blood glucose. Some recent pump models incorporate bolus dose calculator technology. The dose calculator is programmed with both the individual client's insulin requirements per gram of carbohydrate [insulin:carbohydrate ratio (ICR)] and their insulin sensitivity factor (used to calculate correction bolus doses). Meal-time doses are calculated based on current and target blood glucose levels and the carbohydrate content of the meal. The client has the freedom to determine the amount of insulin delivered before each meal by activating the pump using the push buttons.

Client Selection for Continuous Subcutaneous Insulin Infusion

Ideal candidate for continuous subcutaneous insulin infusion (CSII) would be a patient with type 1 diabetes or a type 2 patient who is intensively managed with insulin with more than or equal to 4 insulin injections and more than or equal to 4 self-monitoring of blood glucose (SMBG) measurements daily. The candidate should be highly motivated to achieve optimal glucose controls and is willing to carry out tasks required to operate this complex and time consuming therapy. Candidates should have training in carbohydrate counting and to calculate insulin correction doses. They should be willing to keep in contact with their care providers.

Special characteristics of patients who are not good candidates for insulin pump use

- Unable or unwilling to perform multiple dose injections (≥ 3 –4 times daily), frequent SMBG (≥ 4 times daily), and carbohydrate counting
- Lack of motivation to achieve higher glucose control and/or history of nonadherence to insulin injection protocols
- History of serious psychological or psychiatric condition(s) (e.g. psychosis, severe anxiety, or depression)
- Substantial reservations about pump usage interfering with lifestyle (e.g. contact sports or sexual activity)
- Unrealistic expectations of pump therapy (e.g. belief that it eliminates the need to be responsible for diabetes management).

Proposed Clinical Characteristics of Suitable Insulin Pump Candidates

Type 1 Diabetes Mellitus

- Patients who do not reach glycemic goals despite adherence to maximum multiple daily insulin (MDI), especially if they have
 - Very labile diabetes (erratic and wide glycemic excursions, including recurrent DKA)
 - Frequent severe hypoglycemia and/or hypoglycemia unawareness
 - Significant “dawn phenomenon”, extreme insulin sensitivity
- Special populations (e.g. preconception, pregnancy, children, adolescents, competitive athletes)
- Patients with type 1 diabetes mellitus who, after investigation and careful consideration, feel that CSII would be helpful in achieving and maintaining treatment targets and improve their ability to cope with the challenges of managing their diabetes.

Type 2 Diabetes Mellitus

- Selected patients with insulin-requiring type 2 diabetes mellitus who satisfy any or all of the following:
 - C-peptide positive, but with suboptimal control on a maximal program of basal /bolus injections
 - Substantial “dawn phenomenon”

- Erratic lifestyle (e.g. frequent long distance travel, shift work, unpredictable schedules leading to difficulty in maintaining meal timing)
- Severe insulin resistance
- Selected patients with other diabetes mellitus types (e.g. postpancreatectomy).

Benefits of CSII

- Closer to normal blood glucose levels throughout the day—within the target range
- Fewer erratic swings in blood glucose and thus a decreased risk of hypoglycemia
- More appropriate matching of insulin to food intake
- Increased flexibility in lifestyle (in terms of timings and amount of meals, exercise, and travel)
- Improved chances for a long, healthy life
- Increased flexibility in coping with daily living
- Improved targeting of the “dawn phenomenon”.

Risks of CSII

Diabetic ketoacidosis: Since there is no subcutaneous depot of long-acting insulin with CSII, if the flow of the short-acting insulin is interrupted, DKA can develop more rapidly and frequently. The interruption may be intentional allowing client to participate in certain activities or unintentional, caused by catheter occlusion, disinsertion, battery failure, depletion of insulin supply and other causes such as client error and inadequate training. Clients should be trained to check their blood glucose at least four times a day.

Hypoglycemia: Generally occurs less frequently with CSII than with MDI, mainly due to unintentional insulin delivery or “Pump runaway”. Frequent blood glucose monitoring allows early recognition of hypoglycemia. The tight diabetes control associated with using insulin pump may increase the incidence of hypoglycemia unawareness because of the very gradual decline in serum glucose level from greater than 70 mg/dL to those less than 60 mg/dL.

Catheter site infection and contact dermatitis: Most common complication associated with CSII is infection at the infusion site. Occasional cases of contact dermatitis attributed to the components of the infusion site and tapes have been described. Change of catheter site every 2–3 days minimizes the risk of developing skin infections.

Weight gain: Weight gain is a common adverse effect of impaired glycemic control. Exercise and dose attention to caloric intake can result in weight maintenance and if necessary, weight reduction.

Special Consideration with CSII Therapy

Children and adolescents: Children, adolescents, and their parents prefer to use the pump because these are perceived to be the safest, easiest and the most physiologic method of subcutaneous insulin delivery to achieve near normal glycemic control. CSII has shown improvement in patient satisfaction and reduced hypoglycemia frequency. Indications in pediatric patients include:

- Elevated HbA1c levels on injection therapy
- Frequent, severe hypoglycemia
- Widely fluctuating glucose levels
- A treatment regimen that compromises lifestyle
- Microvascular complications and/or risk factors for macrovascular complications. A child from motivated family who are committed to treatment is an ideal candidate for insulin pump.

Pregnant women: Insulin pump therapy seems to be safe and effective in maintaining glycemic control during a pregnancy complicated by gestational diabetes mellitus or type 2 diabetes mellitus. Because pregnancy is a state of accelerated ketosis especially among type 1 diabetes mellitus, hyperemesis gravidarum or related to dawn phenomenon, a few hours of insulin interruption can lead to hyperglycemia and ketosis. As DKA is associated fetal demise, intensive education and monitoring of infusion sites and sets are required during the course of pregnancy. As the abdominal wall stretches and subcutaneous tissue thins, the site should be changed to offer a more secure and predictable absorption.

Training Clients on CSII

In client with type 2 diabetes mellitus CSII had shown improvements in glycemic control and beta-cell function. It also helps them to maintain glycemic parameters during exercise because of its ability to readily alter the rate of insulin delivery. Extensive training on technical aspects of insulin pump use is essential to allow safe changes in the basal infusion rate and avoid disrupting the catheter site during brisk physical activity. The use of pump may evoke psychological issues, therefore emotional and psychological assessment is necessary prior to initiation. Some clients may express difficulty with body image since pump is visible, mechanical dependency for the metabolic control may invoke feelings of vulnerability and fear of device failure.

The successful implementation of CSII is dependent on a motivated, flexible and skilled health care team. The healthcare team includes an endocrinologists/diabetologists, a diabetes educator or nurse specialists, and dietitian. Initial task of the health team is to assess the following:

- Ability to perform SMBG and maintain a glucometer
- Knowledge of premeal, postmeal, and bedtime target glucose values
- Awareness on hypoglycemia prevention, detection and treatment
- Sick day management and DKA prevention
- Ability to maintain food and physical activity records
- Basic and advanced carbohydrate counting skills.

Group training has been used more frequently in the hope that patients will receive guidance and support from each other. Training should focus on the following aspects:

1. Information about pump, infusion set operation, maintenance, and trouble shooting
2. Infusion site preparation and preventive measures such as proper insertion of catheter
3. Calculation and configuration of basal insulin infusion rates

4. Calculation of initial ICRs, boluses, and ISF
5. Filling the reservoir and tubing, button pushing, and priming
6. Frequent SMBG monitoring
7. Meaning of pump alarms (battery failure, empty syringe)
8. Back up supplies (additional infusion sets, pump batteries, insulin syringes or pens)
9. Use of injectable glucagon in case of hypoglycemia
10. Methods to minimize infection at injection sites (hand washing)
11. Contact numbers of Physician and diabetes educator
12. Pump manufacturer's emergency contact number.

CSII or insulin pumps are advancing in form as well as function. There is a clear need for educational programs taught by trained healthcare provider in insulin pump use, committed physicians providing diabetes educators/nurse specialists, and dietitians help with initial and follow-up pump use training.

DOSE ADJUSTMENT FOR NORMAL EATING

The Diabetes Control and Complications Trial (DCCT) compared intensive insulin therapy to conventional treatment. Intensive insulin was shown to reduce the progression of complications and HbA1c levels in the intensive group when compared to the normal group. Unfortunately, there was a three-fold increase in severe hypoglycemia and a 33% increase in undesirable weight gain in the intensive group and overall quality of life did not improve. The dose adjustment for normal eating (DAFNE) program balances insulin dose and carbohydrate intake in clients with diabetes.

What is DAFNE?

Dose adjustment for normal eating is a 5 day group program which is skill based and client centered. The aim of this program is to enable client to eat freely and adjust insulin to match their desired carbohydrate intake. The diabetes educator and dietitian teach group members how to adjust their insulin to their carbohydrate intake.

Dose adjustment for normal eating (DAFNE) includes a complete diabetes education program and involves workshops and discussion about individual insulin adjustments in a group setting. The basal insulin dose is either given as twice daily such as NPH, or once daily as a long acting insulin analog. This basal insulin is calculated to meet their basal insulin requirement, and is not to account for carbohydrate from meals or snacks. The preprandial quick acting insulin is calculated on the amount of carbohydrate that will be eaten for that meal or snack. Quick acting insulin must be administered at all meals containing carbohydrate. Individual ratios for each meal or snack time are calculated for each participant over 5 days. For example, a ratio is defined as 2:1 for breakfast would be 2 units of quick acting insulin per 10 grams of carbohydrate (1 carbohydrate portion). Correction boluses for variable blood sugars are also advised with main meals. 10 grams of carbohydrate equals 1 carbohydrate portion. This portion size, rather than 15 grams of carbohydrate, was selected due to ease of calculation of dose adjustment.

What are the Benefits of DAFNE?

The DAFNE study group in UK conducted a randomized control trial involving 169 clients who were divided into immediate or delayed DAFNE for 6 months. The trial showed:

- Reduction in HbA1c of 1% in 6 months post-DAFNE and 0.5% at 12 months
- No increase in severe hypoglycemia, change in weight, cholesterol or triglyceride
- An improved quality of life and treatment satisfaction
- Cost-effective due to expected reduction of microvascular complications if such positive metabolic outcomes were maintained.

SUGGESTED READING

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SELF-ASSESSMENT

1. **Mrs A aged 61 years, has type 2 diabetes for 8 years. She is now taking the maximum oral hypoglycemic agents: Metformin 1 g three times daily, Glimepiride 4 mg twice daily and Rosiglitazone 8 mg in the morning. Her weight is 76.5 kg and her height 164 cm, her BMI—29.2 kg/m² indicates that she is overweight but not obese. Her prebreakfast and postprandial sugars are between 140 mg/dL and 250 mg/dL and her HbA1c is 11%. How will you improve her glycemic control?**
 - (a) Life style modification and review after a month
 - (b) Starting her on once daily long acting insulin analogs
 - (c) Stop Rosiglitazone and start twice daily premixed insulin
 - (d) Increase the dose of Glimepiride dose to 6 mg twice a day
 - (e) Stop Rosiglitazone and add Repaglinide
2. **Mr X is 62-year-old and has type 2 diabetes for 10 years. He started taking insulin 8 months ago. His medications include intermediate acting Isophane insulin 36 units at bedtime, Metformin 1 g and Glimepiride 4 mg once a day. He apparently noticed some lumps in his abdomen. His blood sugars remained constantly high. What does Mr X most probably have and how will you treat it?**
 - (a) Lipohypertrophy which will dissolve by giving hot fomentation
 - (b) Lipoatrophy which will dissolve by massaging site

- (c) Lipohypertrophy which will resolve by just foregoing the site and injecting elsewhere in the abdomen
 - (d) Lipohypertrophy—needs surgical removal
 - (e) Lipohypertrophy—keep injecting on the same area
- 3. Mr X's wife (previous case) is seeking your advice over the phone "Mr X is sick with vomiting and diarrhea. What shall I do about his insulin? He has nausea and not eating. His blood glucose is 300 mg/dL. What will you advise her?"**
- (a) Stop giving oral fluids and insulin and monitor blood glucose
 - (b) Stop oral hypoglycemic agents and administer only insulin
 - (c) Give oral fluids, stop oral hypoglycemic agents and administer insulin
 - (d) Take him to the nearest hospital
- 4. With regard to mixing of insulin, which of the following statement is wrong?**
- (a) Insulin Glargine can be mixed with Insulin Lispro
 - (b) Rapid acting insulin can be mixed with NPH, Lente, or Ultralente
 - (c) Phosphate buffered insulins (NPH) should not be mixed with lente insulin
 - (d) Rapid + NPH insulin if mixed should be used immediately
 - (e) No diluent should be used with any insulin preparation
- 5. For a client with lipohypertrophy:**
- (a) Change the type of insulin
 - (b) Change the site of injection
 - (c) Change from 40 IU/mL to 100 IU/mL
 - (d) Use pen delivery device
- 6. A pen device delivers insulin:**
- (a) Intradermally
 - (b) Transcutaneously
 - (c) Subcutaneously
 - (d) Intraperitoneally
 - (e) Intrathecally
- 7. Which of the following insulins can be mixed?**
- (a) Glargine + Lispro
 - (b) Glargine + plain
 - (c) Plain + NPH
 - (d) Lispro + NPH
- 8. All of the following are false about insulin usage *except*:**
- (a) Insulin vials should be stored in the freezer compartment of the refrigerator
 - (b) Insulin when taken out of cold storage should be used after a minimum of 15–20 minutes
 - (c) During insulin administration the needle should be inserted tangentially
 - (d) The rate of absorption is lower when injected intramuscular as compared to subcutaneous injections
 - (e) The area after insulin administration should be massaged in order to facilitate a rapid and complete absorption of insulin

9. The following is the most preferred insulin injection site in the adult:

- | | |
|-----------------------------|---------------------------------------|
| (a) Forearm | (b) Medial aspect of the upper arm |
| (c) Anterior abdominal wall | (d) Anterolateral aspect of the thigh |

10. The current needle used in pen devices is a _____ gauge needle.

- | | |
|--------|--------|
| (a) 25 | (b) 28 |
| (c) 31 | (d) 35 |

CHAPTER

9

Blood Glucose Monitoring

Mercy Jesudoss, Ruth Ruby Murray

*“For insulin treatment there is a strong moral,
This contrasts particularly with things that are oral,
To get the control good and keep things tight,
You monitor sugars with all your might.”*

A disease like diabetes requires continuous self-care. The good news is that “diabetes self-care technology” has come a long way. Today, there are numerous gadgets and gizmos available that are supposed to make living with diabetes much easier.

INTRODUCTION

Several devices and gadgets have been designed to help people living with diabetes to lead a near-normal life (Table 9.1). They can be divided into three broad categories.






Insulin administration has been dealt in the preceding chapter. Home and hospital-based monitoring of blood glucose using various gadgets is discussed in this chapter.

SELF-MONITORING OF BLOOD GLUCOSE

Self-monitoring of blood glucose (SMBG) is a cornerstone of diabetes management. It enables the patients to make self-management decisions regarding diet, exercise, and medications.

Table 9.1: Other helpful gadgets.

<p>Extendable mirror</p> 	<p>Visual foot inspections can become more challenging with age or reduced physical mobility. There are special mirrors available to check the foot daily</p> <p><i>Insight foot care scale:</i> This is a special scale, which is equipped with a mirror through which one can know the condition of the feet standing on the scale</p>
<p>Safety device</p> 	<p>Glucose tablet case, which attaches to a key ring, backpack, purse, or belt loop are available to treat sudden episodes of hypoglycemia. A variety of gels and tablets of dextrose which is more rapidly absorbed into circulation, resulting in a quicker response</p>
<p>Wearable medical identification tags</p> 	<p>These are essential safety items for people who take hypoglycemic agents. Some options include charms for watchbands or existing jewelry, bracelets, dog tags, sports bands, bolo cords, necklaces, and rubber glow-in-the-dark shoe tags</p>
<p>Carbohydrate counting and meal planning aids</p> 	<p>The InsuCalc wheel will calculate mealtime insulin doses based on blood glucose level plus carbohydrate intake</p> <p>The wheel fits in most blood glucose meter cases and is available for a variety of carbohydrate-to-insulin ratios and correction-dose scales</p>

Good glycemic control is important to ensure good quality of life among those living with diabetes as compared to those without diabetes. It is an integral part in the management of type 1, insulin treated type 2 diabetes, and gestational diabetes mellitus.

Major landmark clinical trials clearly demonstrated the benefits of normal or near-normal blood glucose levels. Optimal glycemic control reduces the risk of microvascular complications. Several devices for self-monitoring have recently evolved and have played a major role in glycemic control and prevention of complications. It is a great educational tool which has an impact on daily life style habits, special situations like illness or stress, and medications on blood glucose levels fostering foster self-management and enable patients to make necessary changes.

There are various methods in SMBG and most of the methods involve obtaining a drop of blood using disposable lancets from finger tips, applying the blood to special reagent strip, and allowing the blood to stay on the strip for the amount of time specified by the manufacturer (usually 5–30 seconds). Newer glucometers have strips that “wick” the blood sample into the end of the strip, allowing visual inspection to assure an appropriate sample obtained. The liquefied crystal display (LCD) screen gives out a digital readout of the glucose value.

- The American Diabetes Association (ADA) recommends SMBG for patients taking insulin or oral agents. Assessment of blood glucose levels is very important for the following patients:
- Patients with any type of diabetes trying to keep glucose levels in the near normal range
- Pregnant women
- Client with a tendency to develop severe ketosis or hypoglycemia.
- Client with hypoglycemia unawareness
- Patients undergoing intensive treatment programs, especially those using insulin pumps, or taking multiple daily insulin injections.

Benefits of Self-monitoring of Blood Glucose

- It provides an objective feedback on blood glucose values which is used to make adjustments in food intake, activity patterns, and medication dosage
- Supports and enhance a diabetes care program that aims to educate people about their condition
- It also produces accurate records of daily glucose fluctuations and trends, as well as alerting patients to acute episodes of hyperglycemia and hypoglycemia
- It provides patients with a tool for achieving and maintaining specific glycemic goals.

Frequency of Self-monitoring of Blood Glucose

The frequency of monitoring depends on the following factors:

- The level of patient’s glycemic control
- The type of diabetes
- The patient’s ability to perform tests independently
- Patient’s or caregiver’s willingness to test
- Patient’s economic status and reimbursement policies.

Specific schedules for SMBG will vary with each patient. Intense SMBG for short periods before and after meal and at bedtime provides data to identify glucose patterns. This can be an important adjunct to glycosylated hemoglobin (HbA1C) to distinguish between preprandial and postprandial hyperglycemia. Patients may have staggered time of checking at various time of the day throughout the week. Testing after meals helps to see how effectively he or she judged what was eaten. If a patient is unable to afford to test frequently, then once a day may be sufficient checking at different times of the day or consecutive day (before breakfast one day, postbreakfast the next day etc.). The SMBG is useful in the following patient’s conditions:

Individuals with type 1 diabetes and those on insulin pumps typically test five times a day, before meals, at bedtime, and early morning

- Individual patients with type 2 diabetes who have more variable and individualized testing regimens. It is best measured once before breakfast, 2 hours after breakfast, lunch, and dinner, 1–2 times a week
- In pregnant women blood glucose levels are measured once before breakfast, 1 hour after breakfast, lunch, and dinner, three times a week
- If hypoglycemia is suspected (immediate action is taken if necessary)
- During acute phase of illness, to determine the effect of stressor on blood glucose level and to prevent hyperglycemia.

Bedside Monitoring

Blood glucose monitoring at bedside is performed to guide insulin dosing. In patients who receive nutrition, the timing of glucose monitoring should match carbohydrate exposure. In a patient who is kept nil by mouth, monitoring for glucose should be done every 4–6 hours. More frequent monitoring ranging from 30 min to every 2 hours is essential for patients requiring intravenous insulin infusions.

Barriers for Self-monitoring of Blood Glucose

The monitoring method should match patient's level of skill. Factors that affect the SMBG performance include visual acuity, fine motor coordination, cognitive ability, and comfort with technology, willingness, and cost. Psychological issues such as impending fear of and feeling of guilt owing to increased values impedes patient's monitoring.

Record Keeping

It is important to have a monitoring dairy, log book or some type of electronic memory device to record patterns of glycemic control and adjustments of treatment. Records of SMBG are used to titrate blood glucose lowering agents and to guide physical activity and food intake. The ADA recommends using SMBG as a guide to successful therapy and to achieve postprandial targets. The target HbA1C is less than 7% and this correlates with an average blood glucose of approximately 150 mg/dL. The ADA recommends a preprandial plasma glucose range from 70 mg/dL to 130 mg/dL, and peak postprandial levels targeted at less than 180 mg/dL. The use of SMBG is helpful in developing a longitudinal glucose profile and an aid to making day-to-day decisions.

Patients should be asked to maintain a log book on the information regarding SMBG values, food intake, medications, and exercise. This helps to interpret SMBG results. Keeping a record helps patient to encourage to acknowledge their SMBG and to contemplate the potential adjustments they can make with activity and nutrition. The record book is useful at the time of consultation and should contain:

- Time and date
- Blood glucose levels
- Insulin dose adjustments
- Special events affecting glycemic control (e.g. illness, parties, exercise etc.)
- Hypoglycemic episodes and description of severity and measures taken.

Self-monitoring of Blood Glucose Devices

Glucometers

These are portable electronic blood glucose meters used at hospitals and by patients who perform SMBG (Fig. 9.1A). A wide variety of blood glucose monitors are available. Lancing devices with disposable lancets help to obtain blood drop with minimal pain experience. The depth of the prick is adjusted depending on the skin thickness. The auto eject facility in the lancing devices minimizes the risk for needle prick injuries (Fig. 9.1B).

Glucometers measure blood glucose by using color reflectance or sensor technology. These two principles are given in Flowchart 9.1.

Reflectance photometry: A detector captures the reflected light and converts it to an electronic signal which is translated to its corresponding glucose concentration. The lower the glucose the lighter the color and vice versa.

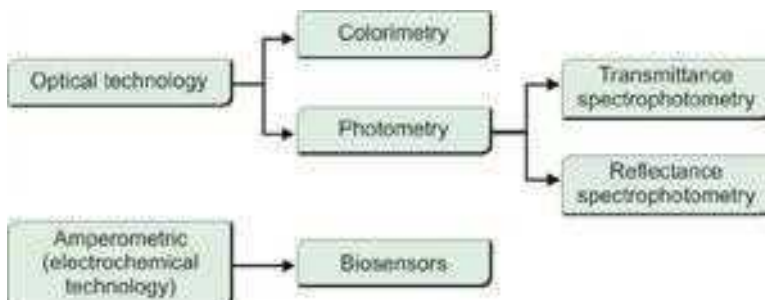
Amperometry/electrochemistry (biosensor technology):

- A biosensor is an electronic device that quantifies the number of electrons generated by the oxidation of glucose, i.e. it measures the electrical current (equal the flow of electrons)
- Using the enzyme as a catalyst, glucose is oxidized with a mediator to generate electrons



Figs. 9.1A and B: (A) Different glucometers use different technologies to measure blood glucose; (B) Lancing devices with disposable lancets help to obtain a blood drop with minimal pain experience.

Flowchart 9.1: Principles of glucometer.



- The electrons are transferred to and counted at the electrodes
- A detector converts the resulting current to an electronic signal and translates that signal to its corresponding glucose concentration
- The number of electrons captured by the mediator is directly proportional to the amount of glucose present in the sample
- The higher the glucose the more the electrons and lower the glucose the fewer the electrons.

Issues to be Considered in Glucose Meter Selection

A glucometer's accuracy is reflected by how close its readings are to results generated by a reference method (laboratory method). The latter is assumed to provide "true result". There is some variation between the glucose level measured in whole blood by glucometers and that measured by clinical laboratory which measures plasma glucose levels. Due to difference in solvent volume, plasma values are about 10–15% higher than whole blood values when hematocrit ranges between 35% and 52%.

Relationship between plasma and whole blood glucose

$$\text{Plasma glucose} = \text{Whole blood glucose} / [1.0 - (0.0024 \times \text{hematocrit})]$$

The accuracy of glucometers can be affected by the interfering substances. The accuracy of SMBG by glucometers has been recommended to produce results within a 20% margin. The factors which potentially increase the accuracy of SMBG values include:

- The amount of blood on the strip—sample requirement is as small as 0.3 μL
- The glucometer's calibration to the strip currently in use
- Environmental conditions like altitude, moisture, and temperature. Extreme temperature and humidity affects the viability of enzymes on the test strip. Extreme temperature also damage components of the glucometer
- Client-specific conditions like hematocrit level, triglyceride level, and presence of hypotension. Higher than normal levels of hematocrit in the blood impairs diffusion of the sample through the test strip or delay the processes (enzymatic reaction and transduction) involved in the glucometer's calculation of blood glucose levels. Therefore, high hematocrit level yields falsely low blood glucose results and low hematocrit level falsely elevates blood glucose results
- Other substances like uric acid, glutathione and ascorbic acid also interfere with glucometer accuracy
- Contamination or insufficient blood sample due to faulty technique (e.g. unwashed hands, unclean test strips or glucometers).

Calibration Code

The manufacturing process of the glucometer includes a calibration procedure to ensure that glucometers produce accurate results. This involves measuring glucose levels from the same blood sample by both the reference method (laboratory) and glucometer. These results are compared and a "normalizing factor", called the calibration code is generated for each batch

(lot) of test strips. These codes enable the glucometer to adjust its readings to reflect values close to the reference method. The code number on the glucometer should be changed to match the strip bottle code.

Plasma samples are 10–12% higher as compared to whole blood samples. Capillary samples are expected to have 4–30% greater glucose concentration than venous samples. Some monitors are automatically calibrated to give a “plasma” test result (although whole blood sample was used) enabling home readings to readily compare with laboratory values. The literature accompanying the glucometers identifies whether a particular monitor is calibrated to give plasma or whole blood readings.

Patients must be taught to use and interpret calibration control solutions that are a part of blood glucose monitoring kit. The control solution is the measured glucose solutions specific to each monitor and should be used whenever a new bottle of strips is used or whenever the validity of the reading is in doubt.

Once every 6–12 months, patients should conduct comparison of their glucometer with simultaneous laboratory measured blood glucose during visit to hospital.

International Diabetes Federation’s (IDF) Recommendations for Glucose Monitoring in Diabetes

1. SMBG should be considered at the time of diagnosis but should only be used when clients, their caregivers, and/or their healthcare providers have the knowledge and willingness to incorporate findings into the diabetes management plan.
2. SMBG should be considered a part of ongoing diabetes self-management education.
3. SMBG protocols should be individualized.
4. Clients and their healthcare providers should agree on how to use SMBG data.
5. Tools used to measure SMBG must be easy to use and accurate.

Training on Self-monitoring of Blood Glucose

Self-monitoring of blood glucose is an empowering tool that allows patients to be an active partner in the treatment of diabetes. Achieving the desired level of client and family participation does require time and effort from the healthcare professional. The diabetes educators involved in this aspect of management should anticipate a close working relationship with patients and their family. This helps to refine their techniques and learn appropriate decision making as they manage their diabetes. It is essential to provide initial training on SMBG, equally important to evaluate and review techniques of patients who are experienced in self-monitoring. Patients should be discouraged from purchasing SMBG products that do not provide direct education. A tendency to discontinue SMBG is more likely to occur when patients do not receive instructions on using test results to alter treatment regimen. Patients on insulin therapy will require instructions to use algorithms for insulin dose adjustments based on patterns of values greater or lesser than the target range and amount of carbohydrate consumption. A client who is visually impaired, cognitively impaired, or limited in manual dexterity requires careful evaluation of the degree to perform independent SMBG. The educator has to identify caregivers or significant others in the family who can assume this responsibility.

Client Education Guide Self-monitoring of Blood Glucose

1. Wash hands with warm water. It is not necessary to clean the site with alcohol, and it may interfere with test results. Fingers should dry before puncturing.
2. If it is difficult to obtain a drop of blood, warm the hands in warm water or let arms hang independently for a few minutes before the puncture is made.
3. Use the side of the finger pad rather than the center as fewer nerve endings are along the side of the finger pad.
4. The puncture should be deep enough to obtain sufficiently large drop of blood. Unnecessarily deep punctures may cause pain and bruising.
5. Follow monitor instructions for testing the blood.
6. Record results and compare to personal target glucose goals.

Note: Bedside monitoring in hospital will warrant use of alcohol wipes prior to testing. The first drop of blood is wiped off with a dry cotton swab and the second drop is used for testing.

CONTINUOUS GLUCOSE MONITORING SYSTEM

Hyperglycemia promotes the development of both long-term complications and suboptimal well-being in patients with diabetes. In our quest to optimize patients' glycemic control, there is a trade-off between normalizing blood glucose levels and increasing the risk of hypoglycemia. Glucometer readings obtained by finger pricks are at best, single "snapshots", providing readings at selected times over a 24 hour period. There may be patient bias to choose to test predominantly at times of low or high blood glucose levels, and when preparing for review appointments. Continuous glucose monitoring (CGM) enables tracking of blood glucose levels on continuous basis over 24 hour periods. This would enhance our awareness of excursions in glucose readings, particularly during nocturnal hours, when hypoglycemia may go unrecognized. It is designed to continuously and automatically monitor glucose values in subcutaneous tissue fluid within a range of 40–400 mg/dL. A 2 weeks data of glucose can be stored in the monitor's memory and then transferred to a personal computer for analysis.

Continuous glucose monitoring lowers HbA1C without increase in the incidence or severe hypoglycemic episodes in patients with type 1 diabetes who use the device frequently. Patients experience a positive quality of life. In pregnant women with diabetes, the results from CGM help to control in-hospital hyperglycemia, however requires further investigation.

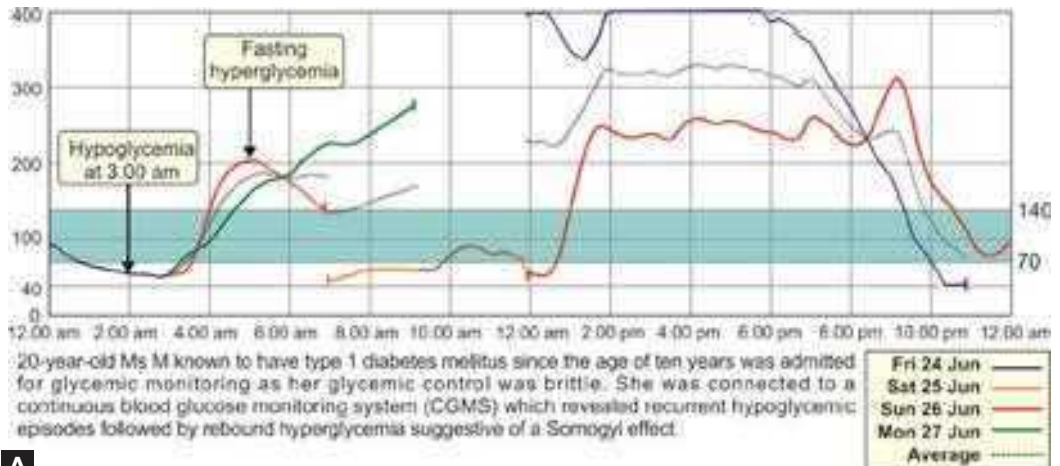
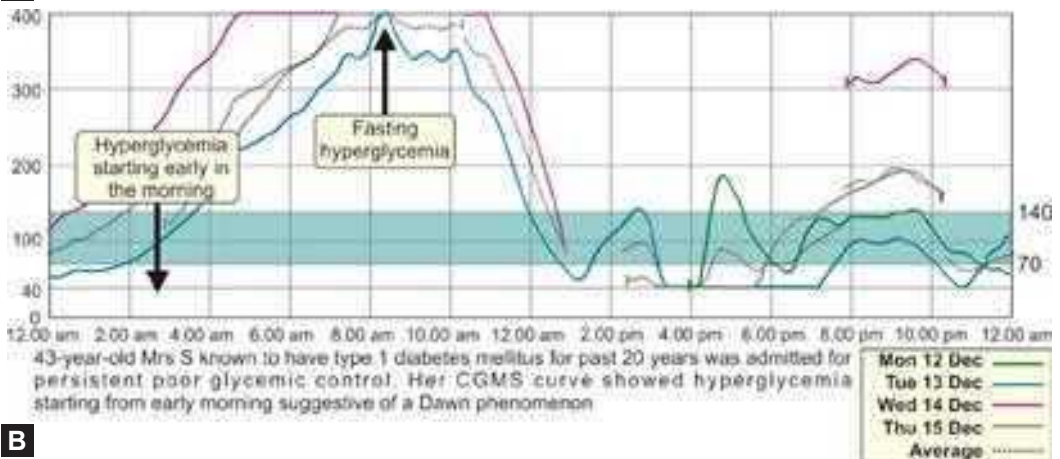
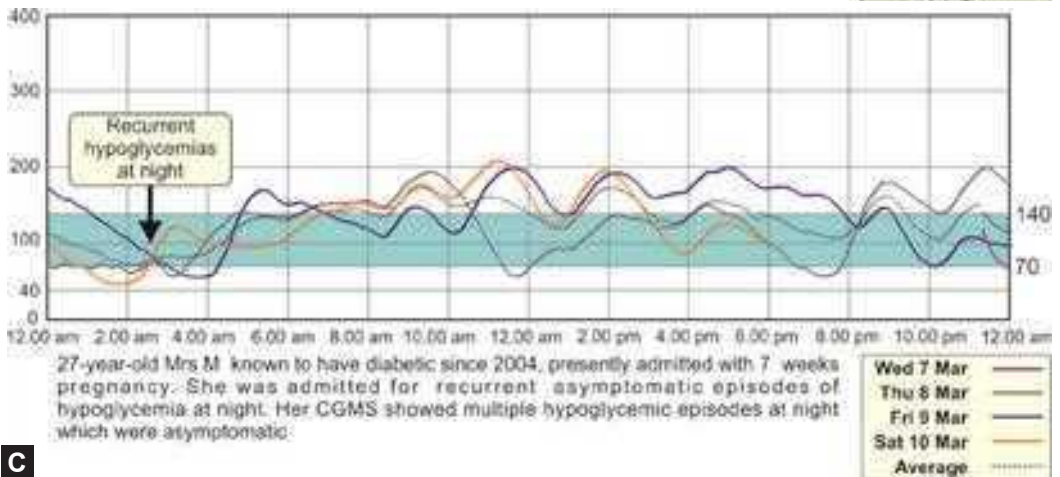
Clinical examples of using CGMS are depicted in Figures 9.2A to C.

Components

The continuous glucose monitoring system (CGMS) has four primary components (Fig. 9.3).

Continuous Glucose Monitor

A portable, pager sized device has a disposable glucose sensor attached which is inserted subcutaneously. The monitor acquires and stores electronic signals from the glucose sensor and converts these signals into clinical glucose values that are also stored. The monitor requires two (AAA) alkaline batteries which approximately last for 2 months.

**A****B****C**

Figs. 9.2A to C: (A) CGMS graph showing Somogyi effect; (B) CGMS graph showing dawn phenomenon; (C) CGMS graph showing asymptomatic multiple hypoglycemia.



Fig. 9.3: Components of continuous glucose monitoring system (CGMS).



Fig. 9.4: Newer continuous glucose monitoring system (CGMS) devices collect glucose data and send the data wirelessly to the monitor for real time use or the data can be downloaded to the computer for analysis.

Cable

It provides continuous transmission of electronic signals from the glucose sensor to the monitor.

Glucose Sensor

Glucose sensor is a small sterile flexible electrode containing the enzyme glucose oxidase. The electrode is coated with a biocompatible polyurethane polymer for sensor protection and patient comfort. The electrode is attached to a connector, which adheres to the surface of the skin and forms a tight connection with the cable. The glucose sensor is inserted just under the skin using a rigid introducer needle. The needle is then removed and the connector is secured against the skin with medical dressing.

Com-station

A data downlink communication station is established. Data is downloaded into a database file, which can be viewed and graphed using a utility program provided with the Com-station.

Measurements can be made every 5 minutes, giving 288 blood glucose readings over a 24-hour-period, or 864 readings over 72 hour. The glucose readings obtained have been validated against glucose measurements made on capillary blood. Individual glucose sensors will be worn for a maximum of 3 days. Following each patient use, data stored in the monitor is transferred to a computer for analysis and interpretation. Up to 14 days of information can be stored in the monitor (Fig. 9.4).

Beneficial Scenarios

- During stabilization of patients on insulin pumps
- When managing insulin-requiring patients with unstable diabetes
- In patients with type 1 or type 2 diabetes during pregnancy.

Limitations

- Not recommended for patients with impairment in vision or hearing, because full recognition of the monitor signal and alarms will be difficult for them
- It is very expensive
- Inconvenience associated with wearing the device for 3 days.

Warnings/Precautions

Infection, inflammation or bleeding at the glucose sensor insertion site is a possible risk of CGMS. Glucose sensor should be removed if redness, pain, tenderness or swelling develops at the insertion site.

SUGGESTED READING

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3. Hermanides J, Phillip M, DeVries JH. Current application of continuous glucose monitoring in the treatment of diabetes—pros and cons. *Diabetes Care*. 2011;34(2):S197-201.
4. Kirk JK, Stegner J. Self-monitoring of blood glucose: practical aspects. *J Diabetes Sci Technol*. 2010;4(2):435-9.

SELF-ASSESSMENT

1. **40 years gentleman, a laborer and a known type 2 diabetes mellitus on oral hypoglycemic agents and insulin has poorly controlled diabetes. Treatment advice for Mr J will include the following *except*:**
 - (a) Needs home monitoring of blood glucose and insulin titration
 - (b) Reinforcement by dietitian
 - (c) Ideal for starting on CGM
 - (d) May benefit from inhalational insulin
2. **A 26 years old Mrs R, primigravida at 28 weeks of gestation is diagnosed to have gestational diabetes. Her management will include:**
 - (a) Using reusable insulin pens
 - (b) Using disposable insulin pens
 - (c) Trial of oral antidiabetic agents
 - (d) Does not require home monitoring when started on insulin.
3. **All of the following are true regarding use of insulin pens *except*:**
 - (a) Pen should be turned though 180° for insulin mixing
 - (b) Insulin cartridges should be refrigerated when not in use

- (c) After administration, insulin pen should be immediately withdrawn
- (d) One needle for insulin pen can be used for a minimum of 5–6 times.

4. ADA recommends SMBG for the following patients *except*:

- (a) Patient on insulin pump
- (b) Pregnancy
- (c) Impaired glucose tolerance
- (d) Hypoglycemia unawareness.

5. Glucometer using reflectance photometry measures:

- (a) Light
- (b) Electric current
- (c) Magnetic energy
- (d) Electrons.

6. Glucometers usually measure.

- (a) Capillary plasma glucose
- (b) Capillary blood glucose
- (c) Venous plasma glucose
- (d) Venous blood glucose.

7. The following patient specific factors can influence glucometer readings:

- (a) Total WBC count
- (b) Blood ketones
- (c) Hematocrit
- (d) Serum creatinine

8. In gestational diabetes, blood glucose is monitored at:

- (a) 2-hour postmeals
- (b) 1½ hour postmeals
- (c) 1 hour postmeals
- (d) 5 am postmeals.

9. Plasma values are higher than blood glucose values by:

- (a) 5–10%
- (b) 15–20%
- (c) 20–25%
- (d) 10–15%.

10. In CGMS, an individual glucose sensor is worn for:

- (a) 24 hours
- (b) 48 hours
- (c) 36 hours
- (d) 72 hours

CHAPTER

10

Peripheral Neuropathy

Mahesh DM, Thomas V Paul, Nihal Thomas

*“When the night falls my feet-they hurt,
My axonal sheaths-they lose their girth,
My toes-they become insensate,
Walking in dark-I may gyrate.”*

Diabetic peripheral neuropathy is the commonest symptomatic complication of diabetes. It involves the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes. It is a clinical syndrome involving distinct regions of nervous system.

INTRODUCTION

In an outpatient study conducted in four institutions across India including CMC, Vellore—the prevalence varied from 14% to 17% using monofilaments. Hence, diabetic neuropathy is a common complication and depending on what method is used for screening, the prevalence is fairly significant. Prior to the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) era, about 50% of subjects with diabetes of 20 years duration had symptomatic neuropathy (positive symptoms like pain or burning sensation, or negative symptoms like numbness and absence of sensation). Asymptomatic neuropathy was present in about 40% (Fig. 10.1).

DEFINITION

WHO Definition of Neuropathy in Diabetes

The WHO definition for diagnosis of neuropathy is a functional one. It is characterized by a decline and damage of nerve function leading to loss of sensation, ulceration and subsequent amputation. The pathogenesis of diabetic neuropathy is largely that of a small vessel disease or microangiopathy. Diabetic peripheral neural damage is of two types. It could be largely due to axonal damage and a lesser extent due to demyelination. The axonal damage may be also associated with subsequent regeneration of the nerve fibers which cross-connect leading

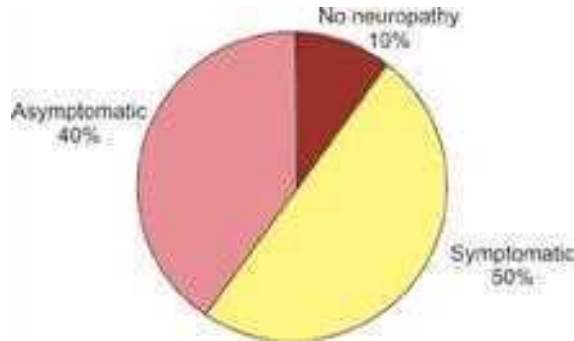


Fig. 10.1: Incidence of diabetic neuropathy as a proportion of all diabetics 20 years after diagnosis.

to positive symptoms such as paresthesias. There are number of risk factors associated with the onset of diabetic neuropathy and these include poor glycemic control and the duration of diabetes. Genetic susceptibility has also been reported in diabetic neuropathy. However, the genes, which govern the onset of diabetic nephropathy, are far more documented than those, which govern diabetic neuropathy. A combination of these symptoms with other exogenous factors like alcohol ingestion may worsen neuropathy and lead to added cofactors that perpetuate neural dysfunction. More recently, cofactors, such as smoking, increased low-density lipoprotein (LDL) cholesterol and cardiovascular disease, have been attributed to cause neural dysfunction.

RISK FACTORS

1. Poor glucose control
2. Long duration of diabetes
3. Damage to blood vessels
4. Autoimmune factors
5. Genetic susceptibility
6. Lifestyle factors:
 - Alcohol
 - Smoking
 - Low high-density lipoprotein (HDL)
 - Cardiovascular disease.

CLASSIFICATION

- Symmetric polyneuropathies
 - Sensory or sensorimotor polyneuropathy
 - Selective small-fiber polyneuropathy
 - Autonomic neuropathy
- Focal and multifocal neuropathies
 - Cranial neuropathy
 - Limb mononeuropathy

- Compression and entrapment neuropathies
- Nerve infarction
- Trunk mononeuropathy
- Mononeuropathy multiplex
- Asymmetric lower limb motor neuropathy (amyotrophy)
- Mixed Forms

PATHOGENESIS

Metabolic Hypothesis

Persistent hyperglycemia and insulin deficiency precipitate alteration of the sorbitol pathway, increased AGE (advanced glycosylated end products) formation, increased oxidative stress leading onto nerve dysfunction.

Immune Hypothesis

A number of autoantigens that induce immune responses like antiphospholipid antibodies and autoantibodies to gangliosides have been described in patients with neuropathy in diabetes.

Microvascular Hypothesis

Microvascular insufficiency due to impaired vasoconstriction and vasodilatation causes absolute and relative ischemia in the nerves of subjects with diabetic neuropathy.

Neurotrophic Hypothesis

Neurotrophic factors like nerve growth factor (NGF), neurotrophin-3, neurotrophin-4/5 and insulin-like growth factor (IGF)-1, which are necessary for survival of neurons are deficient in hyperglycemic individuals.

Oxidative Stress Hypothesis

Increased free radical formation resulting from hyperglycemia causes endothelial cell dysfunction and neurotoxic effects leading to nerve damage (Fig. 10.2).

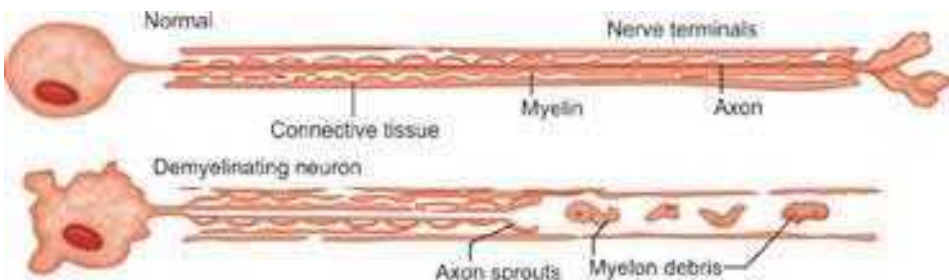


Fig. 10.2: Peripheral nerve damage in diabetes.

CLINICAL PRESENTATION

There is a common misconception that diabetic neuropathy is a phenomenon limited largely to the lower limbs, which is not really true. About 40% of patients with diabetic neuropathy have upper limb involvement in addition and the associated symptoms could be positive with that of pain, paresthesias and dysesthesias. The diagram in Table 10.1 illustrates the typical glove and stocking distribution and one should bear in mind that physical examination should extend up to the thighs and shoulders. It is important to look for motor involvement like wasting and weakness in the fingers and palms. Small fiber neuropathy is generally less common, involves the alpha and C fibers and may be burning or stabbing in nature. It tends to be more severe at night and is basically the opposite of what might happen in a venous insufficiency wherein the patient may have more pain while standing during the day. Large fiber neuropathies lead to symptoms like electrical tingling sensation or a snug-like band around the ankles or feet. The patient may have a sense of imbalance with prominent gait instability (Fig. 10.2).

A reversible form of neuropathy may occur in recently diagnosed diabetes with predominantly sensory symptoms. It may be difficult to detect unless the clinician is vigilant and performs regular examination of the feet (Fig. 10.1). Good glucose control usually reverses the nerve dysfunction.

Acute painful sensory neuropathy may occur with poor glycemic control or with rapid control of blood sugars. Patients report severe burning deep pain and hyperesthesia in the feet with accompanying electric shock like sensations in the lower limbs. There may be accompanying cachexia, weight loss and erectile dysfunction in males. Allodynia may be the only finding on clinical examination. The staging and types of diabetic neuropathy are summarized in Tables 10.2 and 10.3.

Symmetric Polyneuropathies

Distal Symmetrical Polyneuropathy (DSPN): There is usually a stocking like distribution of the sensory deficit in both lower limbs and involves the hands in severe cases. All sensory modalities may be affected. Ankle reflex may be reduced or absent and wasting of small and in severe cases large muscles may occur.

- *Small fiber neuropathy:*
 - Acute painful, distinctive variant of DSPN where pain is the outstanding complaint (constant burning, severe hyperesthesia or shock-like sensations) and usually associated with poor glycemic control
 - Chronic painful
 - Chronic small fiber.
- Large fiber neuropathy.

Proximal Motor Neuropathy

Focal and Multifocal Neuropathies:

- Cranial neuropathy
- Limb mononeuropathy

Table 10.1: Distal symmetrical polyneuropathy (DSPN).



	<i>Small fiber neuropathy</i>	<i>Large fiber neuropathy</i>
Fiber	C-fiber type	Delta type ($A\delta$)
Sensory loss	0 to + (Warm thermal perception) Pinprick hypoesthesia Light touch sensation $\downarrow\downarrow$ Monofilament testing—1 and 10 g)	0 to +++ (touch, vibration perception)—checked with biothesiometer and tuning fork (128 Hz) \downarrow position sense and muscle strength \downarrow sharp-dull and two-point discrimination.
Prominent symptoms	Hyperalgesia-superficial pain (+ to +++) Constant burning Allodynia— \downarrow sweating \rightarrow dryness Severe hyperesthesia Shock-like sensations Hypoalgesia—late	Deep-seated, dull aching pain (+ to +++) Sensory ataxia \rightarrow falls \rightarrow minor trauma/fractures \rightarrow ulcers/amputation
Areas affected	 Glove and stocking anesthesia	
Deformities	None	Small muscle wasting of feet \rightarrow hammertoes
Motor deficit	Absent	0 to +++
Tendon reflexes	Normal to \downarrow	Normal to $\downarrow\downarrow\downarrow$
Risks	Foot ulceration Gangrene	> 25 mV \rightarrow 7 times more risk for foot ulcers Charcot arthropathy Falls and fractures (because of ataxia and incoordination)

Table 10.2: Staging severity of diabetic polyneuropathy.

	<i>Symptoms</i>	<i>Signs (Sensory impairment on examination)</i>	<i>Test abnormalities</i>	<i>Description</i>
N0	-	-	-	No objective evidence of diabetic neuropathy
N1	Asymptomatic polyneuropathy			
N1a	-	-	+	
N1b	-	+	+	

Contd...

Contd...

	Symptoms	Signs (Sensory impairment on examination)	Test abnormalities	Description
N2	Symptomatic polyneuropathy			
N2a	+	+	+	
N2b	+	+	+	Plus significant ankle dorsiflexion weakness
N3	Disabling polyneuropathy			

Table 10.3: Neuropathy disability score.

Neuropathic disability score		Right	Left
Vibration perception test—tuning fork—128 Hz	Normal = 0 Abnormal = 1		
Temperature perception—dorsum of foot	Normal = 0 Abnormal = 1		
Pin prick	Normal = 0 Abnormal = 1		
Ankle jerk	Present = 0 Present with reinforcement = 1 Absent = 2		

- Compression and entrapment neuropathies
- Nerve infarction
- Trunk mononeuropathy
- Mononeuropathy multiplex
- Asymmetric lower limb motor neuropathy (amyotrophy)

Cranial Neuropathies

Cranial neuropathies affecting extraocular movements occur more frequently in diabetic than nondiabetic patients. Patients are usually greater than 50 years of age. The onset is typically abrupt, and may be painless or associated with a headache. A lesion of oculomotor nerve (CN III) is the most common single cranial neuropathy in diabetes, often sparing the pupil. Dysfunction of the trochlear nerve (CN IV) is less common. The abducens nerve (CN VI) is rarely involved alone, but may be involved with other cranial nerves. While facial palsy (CN VII) and other cranial neuropathies occur in patients with diabetes, their relationship to the diabetes is uncertain (Asbury 1987, Thomas and Tomlinson 1993). There is no specific treatment, although gradual recovery typically occurs.

Limb Mononeuropathies

Compression and entrapment neuropathies are common in patients both without and with diabetes, and it is uncertain if these are causally related to diabetes. The most commonly

involved nerve is the median nerve at the wrist (carpal tunnel syndrome). Symptomatic carpal tunnel syndrome occurs in 11% of patients with type I diabetes and 6% of patients with type II diabetes. Asymptomatic carpal tunnel syndrome is much more common. Ulnar neuropathy at the elbow occurs commonly as well. Typically, such neuropathies are slowly developing lesions characterized by variable amounts of pain and weakness. Treatment has been empiric, and may be conservative or surgical. The presence of a superimposed generalized polyneuropathy does not preclude surgical intervention in such patients, but the degree of polyneuropathy, which is contributing to the patient's symptoms, must be taken into account when making decisions regarding surgery. Dysfunction of some nerves may be abrupt and painful, likely secondary to nerve infarctions. Common examples include the radial nerve (wrist drop), peroneal nerve (foot drop), femoral nerve (quadriceps weakness) and lateral femoral cutaneous nerve ("meralgia paresthetica"). Electrodiagnostic tests reveal axon loss. Recovery typically occurs over months or years, and depends on the extent of axon loss and the site (proximal vs distal) of the lesion. Distal muscle strength is often recovered incompletely. If multiple nerves are affected in this way, a mononeuropathy multiplex will result. There is no specific treatment for these abrupt limb neuropathies, though some have advocated immunomodulating therapy when there is multiple nerve involvement.

Diabetic Truncal Mononeuropathy

This is typically characterized by pain around the abdomen or lower chest. Cutaneous hyperesthesia may occur, as may abdominal wall weakness. Some cases appear to be a restricted form of diabetic radiculopathy, and demonstrate paraspinous muscle denervation on electromyogram (EMG) (Thomas and Tomlinson 1993). Once structural abnormalities have been ruled out, treatment consists of pain management. Gradual improvement generally occurs.

Asymmetric Lower Limb Motor Neuropathy (Diabetic Amyotrophy)

There are many names for this syndrome, including proximal diabetic neuropathy, diabetic polyradiculopathy, diabetic femoral neuropathy, diabetic lumbar plexopathy and diabetic lumbosacral plexus neuropathy. Affected individuals have type II diabetes mellitus, and are usually males greater than 50 years of age. The initial symptom is pain in most patients, usually in the territory of the lower thoracic and upper lumbar nerve roots. The pain typically is worst at onset, and gradually subsides. Paresthesia and hyperesthesia are common. Weakness, generally in the upper legs, commonly follows the pain. Weight loss is common. On examination, weakness is most common in the L2-L4 distribution. Thus, the weakness primarily affects the iliopsoas, quadriceps and adductor muscles, usually sparing hip extensors and hamstrings. The weakness may be unilateral or bilateral, and when bilateral it is frequently asymmetric. Sensory loss is mild and mainly distal in most patients, consistent with a coexisting distal sensory or sensorimotor polyneuropathy. Knee and/or ankle jerks are lost in most patients. Progression of symptoms and signs occurs over a very variable period of time; as short as 1-2 weeks, and

as long as a year or more. Most patients experience improvement or resolution of pain or dysesthesia. Recovery of motor function is often incomplete and usually slower, proceeding for up to 18 months. Nerve conduction studies often reveal evidence of a sensory or sensorimotor polyneuropathy. The needle examination typically reveals fibrillations and positive sharp waves in lower extremity muscles and in thoracic and/or lumbar paraspinal muscles. Most commonly affected are the L2-L4 levels, although low thoracic and L5-S1 levels are abnormal in some patients. The etiology appears to be microscopic vasculitis producing nerve ischemia, with multifocal involvement of lumbosacral roots, plexus and peripheral nerves. This has led to the recent use of the term “diabetic lumbosacral radiculoplexus neuropathy” to characterize this type of neuropathy. Typically, no treatment is given other than controlling the diabetes.

Chronic Inflammatory Demyelinating Polyneuropathy

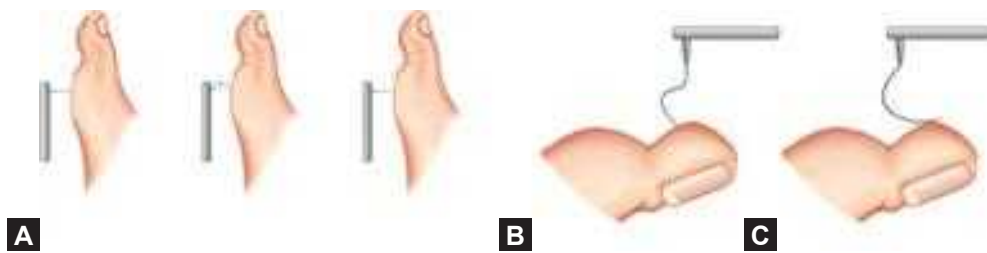
Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the peripheral nervous system. The disorder is sometimes called chronic relapsing polyneuropathy (CRP) or chronic inflammatory demyelinating polyradiculoneuropathy (because it involves the nerve roots). These patients have a chronically progressive or relapsing symmetric sensorimotor disorder with cytoalbuminologic dissociation and interstitial and perivascular endoneurial infiltration by lymphocytes and macrophages. It can be considered the chronic equivalent of acute inflammatory demyelinating polyradiculoneuropathy, the most common form of Guillain-Barré syndrome. These patients often present with limb weakness (both proximal and distal) which is often preceded by an infective illness. A proportion of patients in addition also have sensory and autonomic dysfunction. CIDP must be treated to prevent accumulating disability that necessitates physical and occupational therapy, orthotic devices and long-term treatment. The mainstay of treatment is immunosuppressive or immunomodulatory intervention.

Assessment of DSPN

Severe peripheral neuropathy in the absence of significant retinopathy warrants assessment for causes other than diabetes.

Nylon Monofilament Test

The Semmes-Weinstein monofilament: The standard American Diabetes Association (ADA) criteria will mention that it is only necessary to do a 2 g and a 10 g monofilament testing. In leprosy, up to 300 g may be utilized. Performing a monofilament test is an absolute essentiality in a diabetic patient on an annual basis. A loss of protective sensation is apparently detected when a 10 g monofilament cannot be felt; we feel that this is rather late in the course of the disease. We perform a sliding assessment of 2, 4 and 10 g monofilament assessment. The monofilament is held at 90° to the skin surface and then slowly bent with just enough pressure to bend the filament (Fig. 10.3A). Monofilaments out after repetitive use which reduce their ability to accurately detect peripheral neuropathy (Fig. 10.3B). There is a risk of ulcer formation if the patient is unable to feel the monofilament.



Figs. 10.3A to C: Using a monofilament (A) The correct way of applying pressure (For performance of the 10 g monofilament test, the device is placed perpendicular to the skin, with pressure applied until the monofilament buckles. It should be held in place for 1 second and then released); (B) Monofilament which is worn out after use; (C) Incorrect method of applying pressure.



Figs. 10.4A and B: The monofilament test should be performed at the highlighted sites while the patient's eyes are closed.

Nylon monofilaments are constructed to buckle when a 10 g force is applied; loss of the ability to detect this pressure at one or more anatomic sites on the plantar surface of the foot has been associated with loss of large-fiber nerve function. It is recommended that four sites (1st, 3rd and 5th metatarsal heads and plantar surface of distal hallux) be tested on each foot. The patient is asked to say “yes” each time he or she feels the filament. Failure to feel the filament at any of the four sites (Fig. 10.4A) is considered as loss of protective sensation (LOPS). On using a monofilament there are ideally nine positions on the plantar surface and a tenth one the dorsal surface for assessing neuropathy (Fig. 10.4B). Failure to feel the filament at four of the 10 sites (Fig. 10.4A) is 97% sensitive and 83% specific for identifying LOPS.

Color coding for monofilaments:

- 0.5 g = Light blue
- 2.0 g = Purple
- 4.0 g = Red
- 10.0 g = Orange



Figs. 10.5A and B: Biothesiometer

QST–Quantitative Sensory Testing

Vibration threshold measurements are typically done using biothesiometry. However, detection of impairment of vibration sense using tuning fork (128 Hz) is adequate, when a biothesiometer is not available. The biothesiometer is essentially a glorified tuning fork and can be used for assessment of vibration in a graded manner using the dial up to a maximum 50 mV. If there is neuropathy, the recording is usually more than 15 mV when it is mild, more than 25 mV when it is moderate and more than 40 mV when it is severe. In patients who are elderly beyond the age of 70, one may be permitted to say that there is neuropathy when the millivoltage is more than 25 mV (Figs. 10.5A and B).

Electrophysiology

Nerve conduction velocity (NCV): It provides a sensitive but nonspecific index of the onset of DSPN and can trace the progression of DSPN. It is not indicated in all subjects (as it is not cost-effective or necessary) with diabetes but in selective cases where the etiology of neuropathy cannot be attributed to diabetes mellitus (DM) (example, severe neuropathy in the

absence of retinopathy). It can clearly differentiate between axonal disease (reduced amplitude of wave transmission) and demyelination (reduced velocity of transmission).

Skin biopsy: In recent times, it has been used as an important minimally invasive and easy tool to study small nerve fibers that may miss evaluation by nerve conduction studies. Antibody staining techniques are used to quantify small epidermal nerve fibers. Such a small nerve fiber syndrome has been recognized as a part of impaired glucose tolerance and the metabolic syndrome.

Proximal Motor Neuropathy

It primarily affects the elderly and is of gradual or abrupt onset. It usually begins with pain in the thighs followed by weakness of the proximal muscles of the lower limbs with inability to rise from sitting posture. It begins unilaterally and spreads to become bilateral and usually coexists with distal neuropathy. It has to be differentiated from chronic inflammatory demyelinating neuropathy, which occurs rarely in subjects with diabetes and is potentially treatable with immunomodulators.

MANAGEMENT

General Management

Small Fiber Neuropathy

- Daily foot inspection
- A mirror to inspect the soles of the feet
- Microcellular rubber (MCR)
- Shoes should fit well
- Avoid exposure to heat
- Creams for skin drying and cracking
- After bathing, feet should be dried
- Nails should be cut transversely.

Large Fiber Neuropathy

- *Gait and strength training:* Diabetic patients with large fiber neuropathy have an increased predisposition to falls due to ataxia, incoordination, weakness and muscle wasting. Improving muscle strength by high intensity strength training, coordination and balance by techniques such as yoga helps to reduce falls and resultant fractures
- MCR footwear.

Medical Management of DSPN

Management Aimed at Pathogenesis

Control of hyperglycemia: Good glycemic controls of sugars play an important role in the management.

Treatment should also aim at control of blood pressure, dyslipidemia and lifestyle modifications such as exercise and cessation of smoking and alcohol.

Other therapies aimed at pathogenesis are dubious and have not been shown to be of much help in clinical trials or have not been tried adequately. Many of these include Aminoguanidine (inhibitor of advanced glycation end products), Benfotiamine is a transketolase activator that reduces the formation of advanced glycation end products, gamma-linolenic acid (however not proven to be effective in controlled trials), aldose reductase inhibitors like epalrestat. These reduce the flux of glucose through the polyol pathway and inhibit the accumulation of sorbitol and fructose in tissues (by and large not helpful) and alpha-lipoic acid has been used for its antioxidant properties. However, it is not recommended to use these in routine practice.

Management Aimed at Symptoms

Superficial—Paresthesia and Dysesthesia

1. *Tricyclic antidepressants (amitriptyline)*: It is one of the common drugs and probably one of the most cost-effective drugs to be used in DSPN. It is started in the doses of 25 mg and increased by increments of 25 mg usually up to 75 mg. It causes sedation in many and cardiac conduction defects in a few. Relatively contraindicated in cardiovascular disease, prostatic hypertrophy and in narrow angle glaucoma (in the view of the anticholinergic effect). Anticholinergic effects, orthostatic hypotension and erectile dysfunction limit their usage. They can be used in renal failure.

It is probably the most cost-effective and powerful agent in therapy of painful neuropathy. Other norepinephrine reuptake inhibitors, such as desipramine and nortriptyline, have also been shown to be beneficial.

2. *Anticonvulsants*:

- a. Carbamazepine is the other drug commonly used in the symptomatic management of DSPN. It is used in the doses of 200 to 800 mg per day. In higher doses, it can cause ataxia. It rarely causes Stevens-Johnson syndrome.

It is especially useful in patients with shooting or electric shock like pain.

- b. *Gabapentin*: With a minimum dosage of 300 mg/day up to 1800 mg/day.

Gabapentin has been shown to improve sleep, which may be impaired in a patient with chronic pain.

In short, anticonvulsants have a major impact on neuropathy. However, sodium phenytoin should be avoided since it may worsen hyperglycemia.

- c. *Pregabalin*: This agent has been found to be marginally superior to gabapentin.

Pregabalin and gabapentin have a similar mechanism of action in that they bind to a subunit of the voltage-sensitive calcium channel and thereby decrease calcium influx at nerve terminals modulating neurotransmitter release.

Pregabalin is used in dosages of 150–600 mg/day. Dizziness, somnolence and peripheral edema are frequently reported adverse effects. Sustained release forms of pregabalin are now available in the market.

- d. Topiramate has shown promising results in trials with an effect on causing growth of intraepidermal nerve fibers and is used in a dose of 25–50 mg per day.

Table 10.4: Drugs used to treat symptomatic DSPN.

Class	Examples	Doses
Tricyclic drugs	Amitriptyline Nortriptyline Imipramine	10–75 mg at bedtime 25–75 mg at bedtime 25–75 mg at bedtime
Anticonvulsants	Gabapentin Carbamazepine Pregabalin	300–1200 mg BD 200–400 mg TID 100 mg BD
5-HT and norepinephrine reuptake inhibitor	Duloxetine	60–120 mg OD
Substance P inhibitor	Capsaicin cream	0.025–0.075% TID
Antipyretics	Paracetamol	500–2500 mg
Semisynthetic opioids	Tramadol	50–100 mg

Besides the above list of drugs, analgesics, NSAIDs and opioids are also used in addition to treat symptomatic painful neuropathy, however no advantage of NSAID's over paracetamol has been noted.

3. *Selective serotonin reuptake inhibitor (SSRI) and Serotonin-norepinephrine reuptake inhibitors (SNRIs):* Fluoxetine has some impact on neuropathic pain. However, more recently duloxetine has been found to be more effective.

Duloxetine hydrochloride is a selective and potent norepinephrine and serotonin reuptake inhibitor in the brain and spinal cord that has been approved in the treatment of painful neuropathy.

Deep-seated Pain

- *Opioid derivatives:* Tramadol in combination with acetaminophen is effective in curbing pain and is less addictive than other opioid derivatives.
- *Transcutaneous electrical nerve stimulation (TENS):* It is effective in therapy of deep-seated pain.
- *Local application of capsaicin ointment:* In randomized trials, it is found to be useful as an adjuvant therapy.

The drugs used to treat DSPN are summarised in Table 10.4.

Nonpharmacological Treatment of Diabetic Neuropathy

Whilst pharmacotherapy is the mainstay of therapy for the relief of painful diabetic neuropathy (PDN), alternative nonpharmacological treatments, such as acupuncture, TENS, spinal cord stimulation, percutaneous electrical nerve stimulation (PENS), low-intensity laser therapy (LILT) and monochromatic infrared light are used in patients who are unresponsive or cannot tolerate pharmacotherapy; however, the evidence for these approaches is limited and needs to be carefully reviewed (Table 10.5).

Transcutaneous Electrical Nerve Stimulation

In a study of diabetic patients with mild to moderate neuropathic pain, TENS showed an improvement in pain, numbness and allodynia. Another study showed cyclic doses of electrical

Table 10.5: Nonpharmacological symptomatic treatment options for diabetic neuropathy.

<i>Mechanism of effect</i>	<i>Type of treatment</i>	<i>Comment</i>
Physical therapy	Transcutaneous electrical nerve stimulation (TENS)	Useful
	Electrical spinal cord stimulation	Highly invasive Limited data
	Percutaneous electrical nerve stimulation (PENS)	Limited data
	Magnetic field therapy	Limited data
	Low-intensity laser therapy (LILT)	Limited data
	Monochromatic near-infrared treatment (MIRE)	Limited data
	Dressings	Limited data
	Electroacupuncture	Limited data
Others	Psychological support	Limited data

Source: Adapted from Tavakoli et al *Ther Adv Endocrinol Metab.* Apr 2010; 1(2): 69–88.

stimulation through a contact-stocking electrode may be effective in alleviating neuropathic pain. However, pain relief was maintained after discontinuation of therapy, questioning the direct efficacy of this treatment and invoking the ‘placebo effect’. In a recent analysis from the American Academy of Neurology, the effectiveness of TENS was assessed from two Class II studies and given a Level B recommendation for the treatment of PDN. We commonly use this form of therapy and find it highly effective in reducing pain in refractory cases.

Electrical Spinal Cord Stimulation

Spinal cord stimulation has been used over the last 40 years and the original idea was pioneered in the late 1960s by Dr Norman Dhealy, a neurosurgeon, who implanted the first dorsal column stimulator in a patient suffering from terminal metastatic cancer. Currently, it is widely used for the management of different types of chronic neuropathic or intractable pain. A simplistic explanation for the mode of action of electrical spinal cord stimulation (ESCS) is that of the production of an electrical field on the dorsal horns of the spinal cord. However, recent data generated in an experimental mononeuropathy model using tactile thresholds has demonstrated that ESCS may activate the descending serotonergic pathways, thus inhibiting spinal nociceptive processing. Two small studies have shown ESCS to be effective in 6/10 patients with chronic intractable PDN, to achieve relief within 3 months of implantation followed by continued relief for a mean of 3.3 years in the six patients who achieved an initial response. The expense and invasive nature preclude recommendation as a routine option for treatment.

Percutaneous Electrical Nerve Stimulation

Three weeks of treatment with PENS showed a significant improvement in neuropathic pain for more than 6 months, questioning the direct benefit of this treatment and again raising the intriguing role of the ‘placebo effect’. In addition to decreasing extremity pain, PENS

therapy improved physical activity, sense of well-being and quality of sleep while reducing the requirement of oral nonopioid analgesic medication.

Magnetic Field Therapy

Magnetic field therapy (MFT) has been employed in a range of medical problems including arthritis, chronic pain, wound healing, insomnia and headaches. Static MFT delivered by wearing a constant multipolar sole in the shoe significantly reduced neuropathic pain in a multicenter parallel group study. However, pulsed low-frequency electromagnetic fields delivered in a repetitive and cumulative manner failed to show a benefit in neuropathic pain.

Low-intensity Laser Therapy

Low-intensity laser therapy (LILT) has been shown to be beneficial in several pain models including patients with neuropathic pain. The exact mechanism of pain relief is not established but increased release of serotonin and endorphin as well as anti-inflammatory effects has been suggested. There is only one clinical trial in which the administration of biweekly therapy over 4 weeks in 50 diabetic patients showed a reduction in weekly mean pain scores.

Monochromatic Near-infrared Treatment (MIT)

Several studies have shown that temporary application of monochromatic near-infrared photo energy (MIRE; Anodyne Therapy System) increases foot sensitivity and reduces neuropathic pain and this has been attributed to the release of nitric oxide.

Electroacupuncture

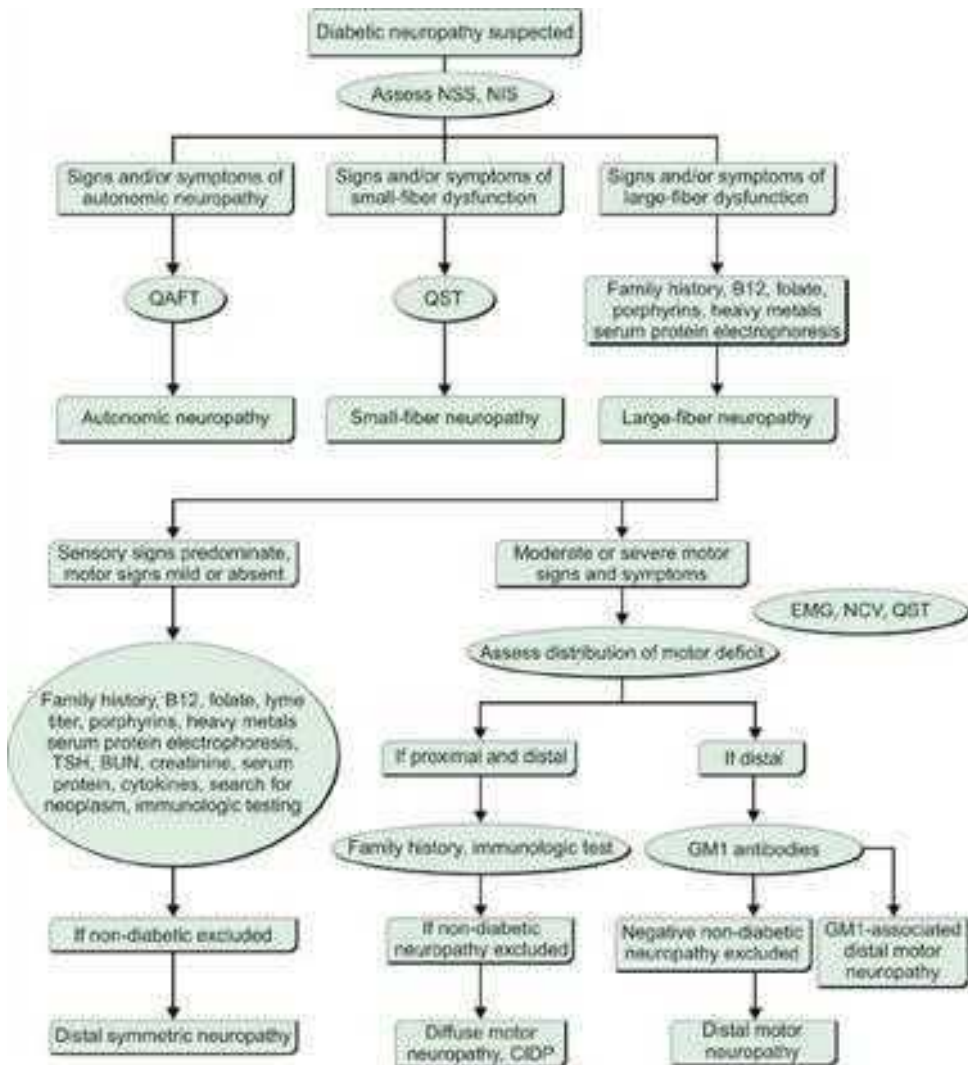
Acupuncture, developed in Chinese medicine in the fifth century BC was first brought into Europe in the 17th century. Its major attraction is that it is relatively inexpensive, painless and free from side effects. A recent modification of this ancient therapy, electroacupuncture (EA) has been shown to be efficacious via the release of a number of neuropeptides depending on the frequency of stimulation, with 2 Hz releasing enkephalin, beta-endorphin and endomorphin, whilst 100 Hz releases dynorphin.

Exercise

Specific exercise, such as Tai Chi Chuan has been shown to improve fasting blood glucose and peripheral NVCs in patients with type 2 diabetes. Patients with mild to moderate neuropathic pain have demonstrated an improvement in symptoms after 30–40 minutes of yoga for 40 days. In a study of 149 patients with type 2 diabetes, 40 days of yoga therapy improved blood glucose in 104 patients, particularly those with a short duration of diabetes and good glycemic control.

Psychological Therapy

Depression among diabetic patients is reported to be almost twice in comparison to nondiabetic patients. In a recent longitudinal study, neuropathy itself has been shown to be a

Flowchart 10.1: Algorithm for management of diabetic peripheral neuropathy.

Source: Figure modified from Medscape—endocrine practice, 2007 American association of clinical endocrinologists.

(B12: Vitamin B12; BUN: Blood urea nitrogen; CIDP: Chronic inflammatory demyelinating polyneuropathy; EMG: Electromyogram; GM1 antibodies: Ganglioside GM1 antibodies; NCV: Nerve conduction velocity studies; NIS: Neurologic impairment score (sensory and motor evaluation); NSS: Neurologic symptoms score; QAFT: Quantitative autonomic function tests; QST: Quantitative sensory tests; TSH: Thyroid-stimulating hormone).

risk factor for depressive symptoms by generating pain and unsteadiness, with the latter being particularly related to a perception of diminished self-worth due to an inability to perform normal social roles. Thus, psychological treatment may be another nonpharmacological

treatment for this group of patients and has been shown to have a positive effect on the quality of life and emotional well-being in diabetic patients. It is also important to identify depression and treat that independently.

Focal Neuropathies

Mononeuropathy

- Usually in older population
- Generally acute with pain
- It can involve truncal and cranial nerves (III and VI)
- Self-limiting and resolving in 6–8 weeks
- Usually due to vessel occlusion
- *Treatment:* Symptomatic for pain and physiotherapy.

Entrapment Neuropathy

- Starts slowly and progresses slowly.
- Commonly involves median (carpel tunnel), ulnar, radial, femoral and lateral cutaneous nerve of thigh.
- Treated with splints, NSAIDs, local injection
- In some cases surgery to decompress.

The therapeutic algorithm to manage diabetic neuropathy is summarised in Flowchart 10.1.

CONCLUSION

Diabetic peripheral neuropathy is an important complication of uncontrolled hyperglycemia in diabetes needs careful evaluation and assessment. Measures like good metabolic control, patient education and emphasis about foot care play a vital role in preventing foot ulcers and complications like amputations.

SUGGESTED READING

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2. Viswanathan V, Thomas N, Tandon N, et al. Profile of diabetic foot complications and its associated complications—a multicentric study from India. *J Assoc Physicians India.* 2005;53:933-6

SELF-ASSESSMENT

1. **All of the following medications are used in the treatment of diabetic neuropathy except:**
 - (a) NSAID
 - (b) Carbamazepine
 - (c) Capsaicin
 - (d) Gabapentin
 - (e) None of the above

2. All of the following are symptoms of diabetic neuropathy except:

- (a) Numbness or insensitivity to pain or temperature
- (b) Tingling, burning or prickling sensation
- (c) Sharp pains or cramps
- (d) Tremors
- (e) Loss of balance and coordination

3. Signs of diabetic neuropathy include:

- (a) Muscle weakness
- (b) Loss of reflexes
- (c) Changes in gait
- (d) Collapse of midfoot
- (e) None of the above

4. Diabetic neuropathy can present as any of the following except:

- (a) Diarrhea
- (b) Urinary retention
- (c) Weakness of lower limbs without pain
- (d) Burning sensation in a band of area in chest
- (e) None of the above

5. The protective sensation of the foot is absent in diabetic patients:

- (a) When the patients complain of pain following injury
- (b) When the patient does not appreciate 10 g monofilament testing
- (c) When the patient complains of slipping of *chappals* while walking
- (d) All the above.

6. Tuning fork used to test vibration sense is:

- (a) 128 Hz
- (b) 256 Hz
- (c) 512 Hz
- (d) 126 Hz

7. The biothesiometer measures:

- (a) Visual perception threshold
- (b) Vibration
- (c) Touch pressure sensation
- (d) Continuous long fiber stimulatory sensation (CLFSS)
- (e) Autonomic dysfunction

8. In a patient with diabetic neuroarthropathy of the feet, which of the following exercises would be the safest?

- (a) Skipping
- (b) Jogging
- (c) Swimming
- (d) Treadmill
- (e) None of the above.

9. A 44-year-old patient with diabetes of 12 years duration presents with burning sensation over the feet, which is accentuated at night. All of the following are true except:

- (a) Amitriptyline is highly effective in treating these symptoms
- (b) Demyelination is a feature of this condition
- (c) Tramadol may not be as effective as Amitriptyline in treating this sort pain

- (d) Methylcobalamin tablets are effective in ameliorating nerve regeneration
- (e) Pregabalin has only a marginally better effect than gabapentin in treating such patients with pain.

10. A 55-year-old gentleman who is a known patient with type 2 diabetes for 15 years presented with a history of inability to sleep at night due to persistent pricking sensation of both his feet which was worrying over 6 months. On examination, his feet were normal, monofilament recorded 10 g in both feet and biothesiometer read 40 volts bilaterally. Both fundi showed severe nonproliferative diabetic retinopathy (NPDR). Systemic examination was normal. He has been on Glibenclamide 10 mg twice daily and Metformin 1 g thrice daily. His HbA1c was more than 12%. All of the following are true *except*:

- (a) Peripheral neuropathy is an indication to start him on insulin
- (b) Best option is to add another oral hypoglycemic agent for better control of his sugars
- (c) MCR footwear should be ideally prescribed for his neuropathy
- (d) He might require long-term insulin therapy
- (e) Severe NPDR is an indication for insulin therapy

CHAPTER

11

Feet, Foot Care and Neuroarthropathy

PART A: FOOT CARE AND NEUROARTHROPATHY

□ukhabandhu □aik, Bhara'hi S, Suni'ha R, □d□in Ste□hen, Jubbin Jagan Jacob, □ihal □homa□

*“Cutting nails and washing feet are mundane things as such,
Checking between toes for fungus is not very much,
The hardened callus on the sole can problems aggravate,
But much beyond that problem may make it ulcerate.”*

Foot problems are a leading cause of hospitalization for patients having diabetes mellitus all over the world. Foot ulcers in diabetes precede 85% of nontraumatic lower-extremity amputations (LEAs). Fifteen percent develop foot ulcers during their lifetime. The risk of LEA increases by a factor of 8 once an ulcer develops. Approximately 3–4% of individuals with diabetes have foot ulcers or deep infections. Individuals who develop foot ulcers have a decidedly decreased health-related quality of life and consume a great deal of healthcare resources. Neuroarthropathy is a frequently missed diagnosis and a focus in this area of medical education has never been optimal despite its frequency of presentation.

INTRODUCTION

The vast majority of diabetic foot related complications resulting in amputation can be prevented by early detection and appropriate treatment of these ulcers by the primary caregiver. Unfortunately, several studies have found that primary care physicians infrequently perform foot examinations in diabetic patients during routine visits to the hospital.

ULCERATION

Etiology of Foot Ulceration

The etiology of diabetic foot ulcers is usually multifactorial. Majority of diabetic foot ulcers are due to the critical triad of peripheral sensory neuropathy, trauma, and deformity. Other factors in ulceration are ischemia, infection, callus formation, and edema. Infection plays a major role in countries like India where bare foot walking is prevalent. Many of the risk factors

for foot ulcer are also predisposing factors for amputation, because ulcers are the primary causes leading to amputation. Recognized risk factors for diabetic foot ulceration and LEA are as follows:

- Absence of protective sensation due to peripheral neuropathy
- Arterial insufficiency
- Foot deformity and callus formation resulting in focal areas of high pressure
- Autonomic neuropathy causing decreased sweating and dry, fissured skin
- Limited joint mobility
- Obesity
- Impaired vision
- Poor glucose control leading to impaired wound healing
- Poor footwear that causes skin breakdown or inadequate protection from high pressure and shear forces
- History of foot ulcer or LEA.

Pathobiology of Foot Ulceration

Neuropathy whether sensory, motor or autonomic may lead to ulceration through various mechanisms.

Diabetic foot ulceration occurs through either of the two pathways described in Figures 11.1 and 11.2.

- Fissures + Infection + Abscess = Ulcer
- Pressure/Trauma + Dermal Callus + Dermal Hematoma = Ulcer.

Pressure over bony prominences often has been cited as the cause for skin breakdown in patients with diabetes. Pressure could be either minimal over a long time, as in an ill-fitting shoe, or large over a short period of time, as in stepping on a sharp object. Skin breakdown occurs at far lesser loads when the pressure is applied by shear forces. The accompanying loss of protective sensation prevents the patient from being warned that intolerable loads have been applied. This leads to blister formation and full-thickness skin loss. The process is heightened in the presence of severe venous edema, which further lowers the injury threshold. Shoes become tight due to swelling, thus increasing the direct pressure and shear forces applied to skin overlying bony prominence. Thickened hypertrophied nails increase pressure to the soft tissues surrounding the nails. The common result is tissue failure and ulcer formation.

Once the skin barrier is broken, wound healing can be impaired by abnormally functioning white blood cells. These patients are often malnourished. Many have marginal vascular supply, with less ability to achieve resolution of infection and achieve wound healing.

Structural Deformity and Limited Joint Mobility

Foot deformities, which are common in diabetic patients, lead to focal areas of high pressure. When an abnormal focus of pressure is coupled with lack of sensation, a foot ulcer can develop. Most diabetic foot ulcers form over areas of bony prominences, especially when bunions, calluses or hammer-toe formations lead to abnormally prominent bony points. Foot deformities are believed to be more common in diabetic patients due to atrophy of the intrinsic musculature responsible for stabilizing the toes.

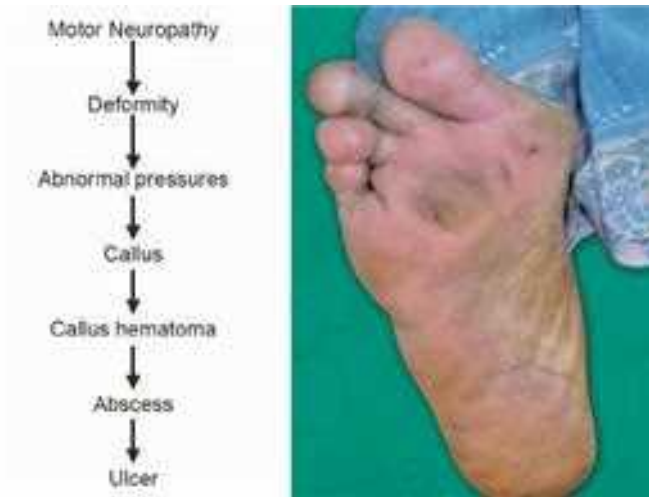


Fig. 11.1: Callus story (Origin: Motor).



Fig. 11.2: Fissure story (Origin: Dysautonomia).

Rigid deformities or limited range of motion at the subtalar or metatarsophalangeal joints have also been associated with the development of diabetic foot ulcers. Other mechanisms of skin breakdown in the insensate diabetic foot include puncture wounds and thermal injuries from, e.g. walking barefoot in the midafternoon (Fig. 11.3).

Evaluation of a Foot Ulcer in Diabetes

A thorough evaluation of any ulcer is critical to plan management. An adequate description of ulcer characteristics, such as size, depth, appearance, and location, is important for mapping the progress during treatment (Fig. 11.4A).

After describing the dimensions and appearance of the ulcer, the ulcer should be probed with a blunt sterile probe (Fig. 11.4B). Gentle probing can detect sinus tract formation, undermining of ulcer margins, and dissection of the ulcer into tendon sheaths, bone, or joints. A positive probe-to-bone finding has a high predictive value for osteomyelitis. Failure to



Fig. 11.3: Usual locations of ulcers in the diabetic foot. Ulceration is particularly likely to occur over the dorsal portion of the toes and on the plantar aspect of the metatarsal heads and the heel.



Figs. 11.4A and B: (A) Describing an ulcer: A thorough evaluation of any ulcer is critical in deciding management. Examining the ulcer characteristics such as size, depth, appearance and location aids in management. (B) Probe test: Gentle probing using a blunt sterile probe has high sensitivity for detecting underlying osteomyelitis.

diagnose underlying osteomyelitis often results in failure of wound healing. The existence of odor and exudates, and the presence and extent of cellulitis must be noted.

Limb-threatening infections can be defined by (1) cellulitis extending beyond 2 cm from the ulcer perimeter, (2) deep abscess, (3) osteomyelitis, (4) critical ischemia. Aerobic and anaerobic cultures should be taken when signs of infection, such as purulence or inflammation, are present. Cultures are best taken from purulent drainage or curetted material from deep within the wound. Fungal infections are common in the diabetic foot and should be attended to when examining the feet (Figs. 11.5A and B).

Classification of Diabetic Foot Ulcers

The classification system developed by Wagner and modified by Brodsky is commonly followed. The classification along with the management plan is given in Table 11.1.



Figs. 11.5A and B: Examining the interdigital area is important to look for fungal infestation. (B) Fissuring with fungal infestation. A thorough examination is vital as most fungal infestations are symptom free.

Table 11.1: Depth-ischemia classification of diabetic foot lesions.

Depth classification	Definition	Treatment
0	At-risk foot, no ulceration	Patient education, accommodative footwear, regular clinical examination
1	Superficial ulceration, not infected	Offloading with total contact cast (TCC), walking brace or special footwear
2	Deep ulceration exposing tendons or joints	Surgical debridement, wound care, offloading, culture-specific antibiotics
3	Extensive ulceration or abscess	Debridement or partial amputation, offloading, culture-specific antibiotics
<i>Ischemic classification</i>		
A	Not ischemic	
B	Ischemia without gangrene	Noninvasive vascular testing, vascular consultation if symptomatic
C	Partial (forefoot) gangrene	Vascular consultation
D	Complete foot gangrene	Major extremity amputation, vascular consultation

Source: Brodsky J. The Diabetic Foot. In: Coughlin MJ, Mann RA (Eds). Surgery of the foot and ankle. St. Louis: Mosby Inc.; 1999. p. 911.

Treatment of Foot Ulcer in Diabetes

The primary goal in the treatment of diabetic foot ulcers is to obtain wound closure. Management of the foot ulcer is largely determined by its severity (grade) and vascularity, and the presence of infection. A multidisciplinary approach should be employed because of the multifaceted nature of foot ulcers and the numerous comorbidities that can occur in these patients.

Role of Debridement

The mainstay of ulcer therapy is debridement of all necrotic tissues, calluses, and fibrous tissue. Unhealthy tissue must be sharply debrided back to bleeding tissue to allow full visualization of the extent of the ulcer and detect underlying abscesses or sinuses. Topical enzymes have not been proved effective for this purpose and should only be considered as adjuncts to sharp debridement. Soaking ulcers is controversial and should be avoided because the neuropathic patient can easily be scalded by hot water (Figs. 11.6A to F).

Although numerous topical medications and gels are promoted for ulcer care, relatively few have proved to be more efficacious than saline wet-to-dry dressings. Topical antiseptics, such as povidone-iodine, are usually considered to be toxic to healing wounds. Generally, a warm, moist environment that is protected from external contamination is most conducive to wound healing. This can be provided by a number of commercially available special dressings, including semipermeable films, foams, hydrocolloids, and calcium alginate swabs (Figs. 11.7A to E).

Role of Antibiotics

When infection is present, aerobic and anaerobic cultures should be obtained, followed by initiation of appropriate broad-spectrum antibiotic therapy. Antibiotic coverage should subsequently be tailored according to the clinical response of the patient, culture results, and sensitivity testing. Surgical drainage, deep debridement, or local partial foot amputations are necessary adjuncts to antibiotic therapy of infections that are deep or limb-threatening.

Underlying osteomyelitis is frequently present in patients with moderate to severe infections and requires aggressive bony resection of infected bone and joints followed by 4–6 weeks of culture-directed antibiotic therapy. The presence of deep infection with abscess, cellulitis, gangrene, or osteomyelitis is an indication for hospitalization and prompt surgical drainage.

Role of Amputation

The concept of function-preserving amputation surgery is vital to diabetic foot management. Partial and whole foot amputations frequently are necessary as treatment for infection or gangrene. The goal of treatment is preservation of function, not just preservation of tissue. Amputation surgery should be the first step in the rehabilitation of the patient. The principle of direct construction of a residual limb for weight bearing with prosthesis, when performing debridement or partial foot amputation should be employed.

The major value of partial foot amputation is the potential for retention of plantar load-bearing tissues, which are uniquely capable of tolerating the forces involved in weight bearing.



Figs. 11.6A to F: Diabetic foot problems. (A) Charcot's foot with neuropathic ulcer: The lack of protective sensation combined with foot deformities exposes the foot to undue sudden or repetitive stress that leads to eventual ulcer formation; (B) Abscess: Presenting with pain, swelling and pus discharge with obvious signs of infection. It needs thorough drainage and exploration as these can often extend deeper along the fascial planes; (C) Wagner's grade 2B ulcer; (D) Wet gangrene: Wet gangrene usually develops due to blockage of venous and/or arterial blood flow. The affected part is saturated with stagnant blood which promotes the rapid growth of bacteria; (E) Dry gangrene: Dry gangrene begins at the distal part of the limb due to ischemia. Macroscopically, the affected part is dry, shrunken and dark black, resembling, mummified flesh. The dark coloration is due to liberation of hemoglobin from hemolyzed red blood cells which is acted upon by hydrogen sulfide produced by the bacteria, resulting in formation of black ferrous sulfide that remains in the tissues; (F) Necrotizing fasciitis: Necrotizing fasciitis is an infection of the deeper layers of the skin and subcutaneous tissues, easily spreading across the fasciae within the subcutaneous tissue. Many types of bacteria can cause this condition, the most common being group A streptococcus.



Figs. 11.7A to E: Diabetic foot problems—preprocedure and postprocedure. (A) Fissures before and after debridement; (B) Ulcer before and immediately after paring; (C) Ulcer before and 1 week after paring; (D) Ulcer in the medial malleolus before and 1 month after paring; (E) A patient with ulcer in the stump after transmetatarsal amputation (picture on the right) was offloaded with patellar tendon bearing orthosis (middle picture). The ulcer shows good healing after 3 months (picture on the left).

The soft tissue envelope should be capable of minimizing these forces. The use of split-thickness skin grafts in load-bearing areas should be avoided. Deformity should be avoided as much as possible. Tendo-Achilles lengthening to avoid equinus deformity and increased loading of the residual forefoot in partial foot amputations is beneficial. Retention of a deformed foot with exposed bony prominence leads only to decreased walking ability and recurrent ulceration.

History of Previous Ulceration and Amputation

A patient with diabetes and a history of previous ulceration or amputation is at increased risk for further ulceration, infection and subsequent amputation. Alterations in foot dynamics

due to ulceration, joint deformity or amputation can cause the abnormal distribution of plantar pressures and result in the formation of new ulcers.

Prevention

Prevention of an initial or subsequent foot lesion is crucial in preventing the progression to amputation. The best approach is to make use of a team of multidisciplinary professionals who are committed to limb salvage. Centers that have instituted teams specifically for this purpose have subsequently reported dramatic reductions in LEA and improved rates of primary-ulcer healing. Patient education has a central role in treatment and should include instruction on foot hygiene, daily inspection, proper footwear, and the necessity of prompt treatment of new lesions.

Regular foot-care examinations, including debridement of calluses and ingrown toenails, provide an opportunity to reinforce appropriate self-care behaviors and allow for early detection of new or impending foot problems.

Care of calluses and fissures with a goal to prevent progression to ulcer should be emphasized. The patient can be advised to rub pumice stone in one direction after a shower or bath or after soaking the foot in lukewarm water for about 10 minutes. Six percent salicylic acid topical application can be used over these areas. If the callus is thick a scalpel may be used to trim it down.

Care of toenails is an important aspect of care of the diabetic foot that is often neglected by both physicians and patients. The patient should be advised to soak feet in lukewarm water for about 10 minutes which softens the nails. The nails should be trimmed straight across and then the corners filed so that no nail is left hanging off. Thick toenails may have to be filed down with an emery board. Thicker toenails may have to be clipped with toenail clipper or razor.

The patient who wears shoes should be asked to choose woolen or cotton socks over nylon socks. Nylon socks do not absorb sweat which could hamper foot care in the diabetic. The socks should not be very tight around the top as this could block circulation and cause swelling and softening of the feet. Care should be taken to see that the socks do not wrinkle inside the shoes which could cause pressure points. Therapeutic shoes with pressure-relieving insoles are an essential element of ulcer prevention and have been associated with significant reductions in their development.

NEUROARTHROPATHY

Distal symmetric polyneuropathy is the most common complication affecting the lower extremities of patients with diabetes mellitus. This lack of protective sensation, combined with foot deformities, exposes the foot to undue sudden or repetitive stress that leads to eventual ulcer formation with a risk of infection and possible amputation.

Autonomic neuropathy has several common manifestations. First, denervation of dermal structures leads to decreased sweating. This causes dry skin and fissure formation, which predispose the skin to infection. In patients with adequate vascular competence, this “autosympathectomy” may lead to increased blood flow, which leads to the development of Charcot’s joint and severe foot deformity.

The Semmes-Weinstein monofilament test is a simple outpatient investigation to diagnose patients at risk for ulcer formation due to peripheral sensory neuropathy.

The clinical presentation of Charcot arthropathy can vary widely depending on the stage of the disease. Thus, symptoms can range from mild swelling and no deformity to moderate deformity with significant swelling.

Acute Charcot arthropathy almost always presents with signs of inflammation. Profound unilateral swelling, an increase in local skin temperature, erythema, joint effusion, and bone resorption in an insensate foot are present. The local elevation in skin temperature generally is 3–7° when compared to the unaffected foot. These characteristics, in the presence of intact skin and loss of protective sensation, are often pathognomonic of acute Charcot arthropathy. This can be often mistaken for acute cellulitis and treated wrongly.

Pain can be present in a significant proportion of patients (up to 30%); however, the severity of pain is significantly less than would be expected based on the severity of the clinical and/or radiographic findings. Instability and loss of joint function also may be present. Passive movement of the joint may reveal a “loose bag of bones.” Approximately 40% of patients with acute Charcot arthropathy have concomitant ulceration, thereby complicating the diagnosis and raising concern for osteomyelitis.

Understanding the pathobiology of neuroarthropathy requires a basic understanding of the anatomical structure of the arches of the foot (Fig. 11.8).

Diabetic neuroarthropathy can be classified according to Sanders and Mrdjencovich (Fig. 11.9).

Investigations (Table 11.2)

Plain Radiography

Plain radiographs are useful to

- Stage the disease
- Determine if active disease is present or if the joint is stable (Monitor serial radiographs)
- Identify osteopenia, periarticular fragmentation of bone, subluxations, dislocations, fractures, and generalized destruction.

Here are some radiological examples of the various types of Charcot’s arthropathy.

Quite naturally, mixed forms may occur in the same patient.

Pattern 2 neuroarthropathy (Fig. 11.10A) is the most common form. The ideal X-ray that should be taken is an antero-oblique-lateral view; the standard anteroposterior (AP) view may lead to overlap of the heads of the metatarsals which could obscure dislocations and fractures.

Table 11.2: Efficacy of currently available investigations of Charcot’s neuroarthropathy.

Investigations	Sensitivity	Specificity
Plain film X-ray	60% (28–93)	66% (50–92)
99mTc-3 phase bone scan	70–90%	38–79%
111-INDIUM WBC scan	80–100%	70–90%
MRI	88–99%	83%

(WBC: White blood cell; MRI: Magnetic resonance imaging; 99mTc: Technetium-99m).

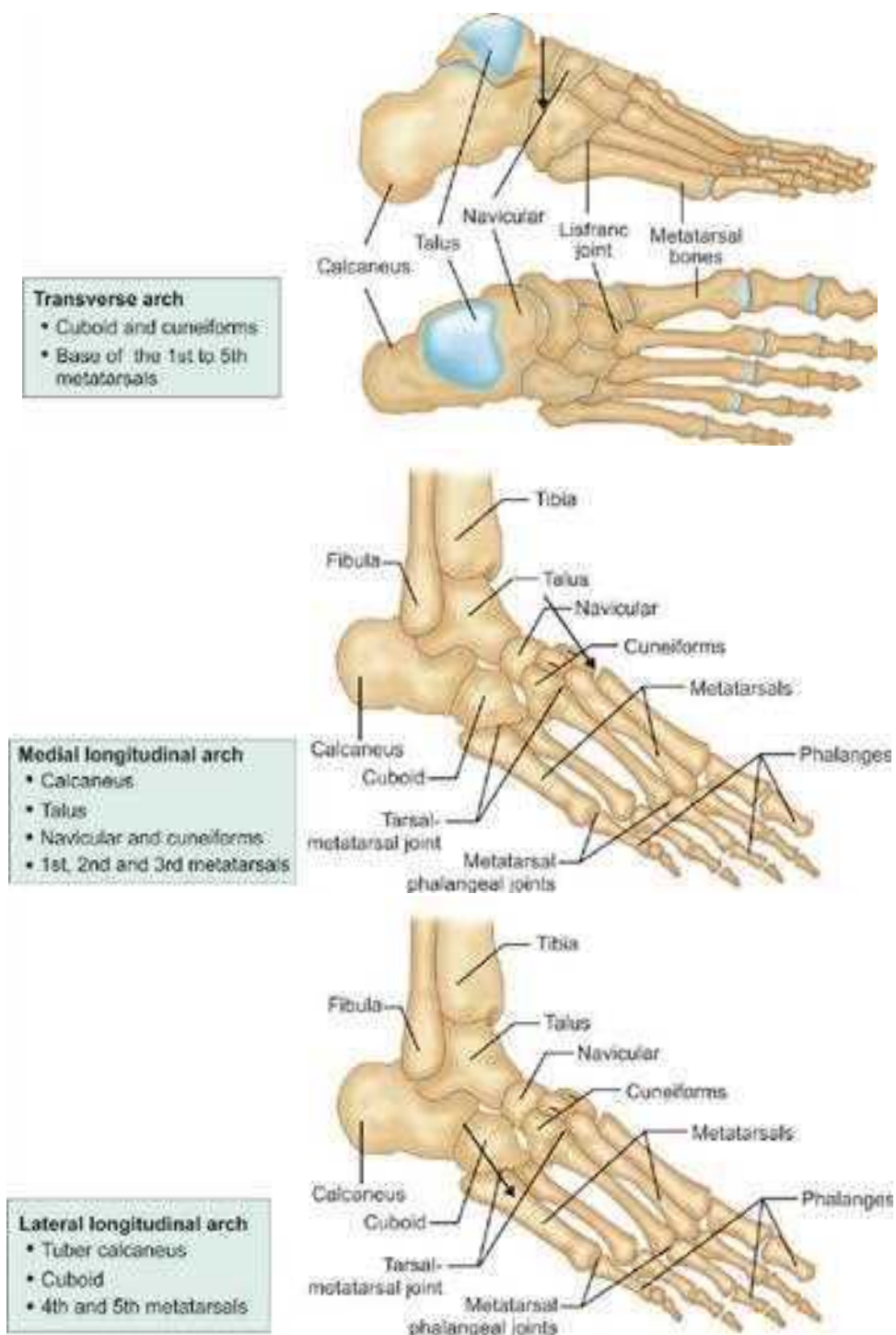


Fig. 11.8: Arches of the foot.



Fig. 11.9: Anatomical classification of neuroarthropathy.

Pattern 4 (Fig. 11.10B) involves the classical neuroarthropathy with descent of the talonavicular joint.

Loss of joint position and joint position sensation leads to friction between bones and joints. This leads to atrophy or sclerosis of bones. The picture (Fig. 11.10C) shows pattern 1 neuroarthropathy with atrophy of the distal bones of the feet.

The X-rays (Fig. 11.10D) show pattern 3 and 4 disease with sclerosis (predominantly hypertrophic) to diagnose early pattern 4 disease, a standing lateral X-ray may be taken to identify early collapse of the arch of the foot. Two angles may be measured to identify early collapse.

In the X-ray (Fig. 11.11A), Meary's angle is measured. If greater than 90° , it is pathological.

In the X-ray (Fig. 11.11B), the calcaneal pitch is measured, if it is less than 17° , it is pathological. The X-ray below shows clear evidence of a collapse of the longitudinal arch.

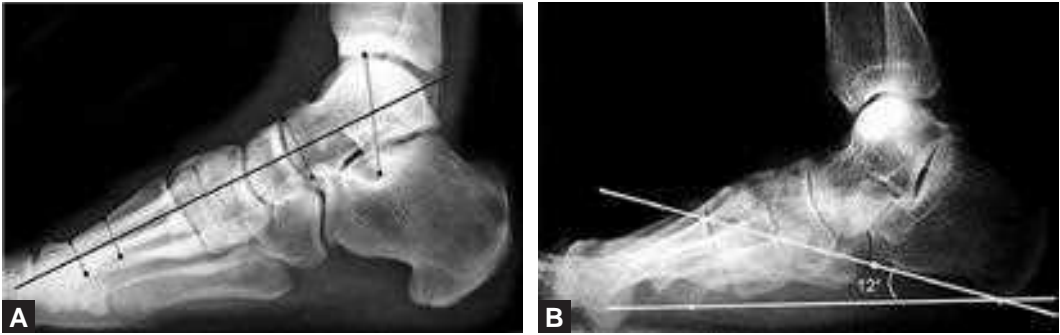
The X-ray (Fig. 11.12) shows advanced disease with a "rocker-bottom" foot deformity. There is collapse of the arch and gross descent of the talus.

There is also significant pattern 2 and 3 disease.

Mearys angle (Mearys line): It is also known as lateral talo-first metatarsal angel. This angle is formed between the long axis of the talus and first metatarsal on a weight-bearing lateral view. This is measurement is used to determine collapse in the longitudinal arch of the foot. The collapse can occur at talonavicular joint, naviculo-cuneiform, or cuneiform-metatarsal joints. In the normal weight-bearing foot, the midline axis of the talus intersects with midline axis of the first metatarsal. Normally Mearys angle is 0° . If the Meary's angle is greater than 90° , it is considered pathological.



Figs. 11.10A to D: (A) Neuroarthropathy pattern 2 Lisfranc's dislocation; (B) Neuroarthropathy pattern 4; (C) Neuroarthropathy predominantly atrophic; (D) Neuroarthropathy predominantly hypertrophic.



Figs. 11.11A and B: (A) Measurement of Meary's angle; (B) Measurement of calcaneal pitch.



Fig. 11.12: "Rocker-bottom" foot deformity.

The Calcaneal pitch: It is an angle drawn between two lines. The first line is drawn from the plantar-most surface of the calcaneus to the inferior border of the distal articular surface and second is a transverse plane and the line is drawn from the plantar surface of the calcaneus to the inferior surface of the 5th metatarsal head. The normal range of calcaneal pitch is 18–20°. The calcaneal pitch of less than 17 is considered pathological.

Bone Scan (Fig. 11.13)

- It is used to differentiate between Charcot joint and osteomyelitis. But the results are frequently ambiguous
- Indium-111 white blood cell (WBC) scan is used because it is more specific than the technetium-99 for detecting osteomyelitis. The technetium-99 scan can show positivity even in the presence of Charcot's arthropathy
- Does not differentiate septic inflammation
- Bilateral disease favors neuropathic disease
- The WBC scan is a triple-phase bone scan often used to help confirm diagnosis of osteomyelitis (positive in all phases).



Fig. 11.13: Technetium-99 bone scan.

Early and accurate diagnosis of osteomyelitis from Charcot foot is the key to successful management. If the radiographs are normal but the clinical suspicion of osteomyelitis is strong, bone scan and or magnetic resonance imaging (MRI) is recommended. Two most preferred are triple phase nuclear imaging scan are MDP bone scan and Indium-111 WBC scan. Indium-111 WBC scan preferred over ^{99m}Tc -MDP scan to exclude osteomyelitis in the setting of neuroarthropathy. In triple phase imaging images are obtained at three different time period after injection of 740–925 MBq (20–25 mCi) of ^{99m}Tc -labeled diphosphonates tracer. First phase (flow phase) images are taken within seconds, in Second phase (blood pool phase) images are taken 3–5 minutes and in third phase (bone metabolism phase) images taken after 3–4 hours after injection of tracer. Sometimes static images are taken after 24 hours. In osteomyelitis focal increased in the tracer seen in all three phases. In both cases of osteomyelitis and Charcot's foot abnormality in images are seen in all three phases and often looks similar. The WBC scan done with Indium-111 labeled leukocyte. In-vitro labeled leucocytes is use for such type of imaging, patient blood drawn initially and tagged with radionuclide in-vitro and subsequently injected into the patients. Following injection labeled WBC migrates to the area of infection. Images are obtained at 1, 2–4 hours and as well as at 24 hours. The main advantages of WBC scan more specific than bone scan. The main disadvantages of WBC scan are meticulous labeling of leukocytes, handling of blood products, potential spread of infection, long half-life, prolonged imaging times and more radiation burden.

MRI (Good Sensitivity and Specificity)

- Allows for anatomical imaging of the area
- May help distinguish between osteomyelitis and Charcot joint.

MRI is more sensitive and specific than X-ray and computed tomography (CT) scan. Equivocal bone scans are also an indication for MR imaging to establish the diagnosis (Fig. 11.14). The advantages of MRI over other modalities because of it better anatomical



Fig. 11.14: Charcot's arthropathy—computed tomography (CT).

delineation quality and better soft tissue contrast. MRI features of focal alternation of marrow signal abnormality due to marrow edema are more sensitive for diagnosis of osteomyelitis. The marrow edema in osteomyelitis is attributed to replacement of fat marrow by hyperemia, ischemia and exudates. MRI can help in differentiation between osteomyelitis and Charcot's foot in early stage. MRI is not essential in late stages when Charcot's features are quite evident.

Portable Infrared Dermal Thermometry

- Used for skin temperature assessment
- Can be used to monitor active inflammation
- A 3–5° difference generally seen in the acute stage.

Joint Aspiration

It is used to help rule out a septic joint.

Synovial Biopsy

Small fragments of bone and cartilage debris are embedded in the synovium due to joint destruction.

Treatment

Nonsurgical Therapy

Treatment of Charcot arthropathy is primarily nonoperative and consists of two phases:

1. An acute phase and
2. A postacute phase.

The cornerstone of management of Charcot's foot is offloading and immobilization.

Acute phase: Management of the acute phase includes—immobilization, reduction of stress and medical management.

- *Immobilization* usually is accomplished by casting. Total contact casts have been shown to allow patients to ambulate while preventing the progression of deformity. Casts must be checked weekly to evaluate for proper fit, and they should be replaced every 1–2 weeks.
- *Reduction of stress* is accomplished by decreasing the amount of weight bearing on the affected extremity, either by total non-weight bearing (NWB) or partial weight bearing (PWB) with assistive devices (e.g. crutches, walkers).
- *Medical management:* Pharmacological treatment with bisphosphonates (BPPs) acts by inhibiting osteoclastic inhibitions. It also may have direct anti-inflammatory properties. These drugs also can inhibit bone destruction by increasing apoptotic death of macrophages. The efficacy of BPPs can vary depends upon type of BPPs and duration of therapy. Pitocco et al. (2005) used alendronate 70 mg once weekly for 6 months among 20 patients with Charcot foot and showed improvement in the pain score, local temperatures and reduction in the bone markers (CTP). Similarly Pakarinen et al. (2011) used zoledronate 4 mg once month for duration of 12 months. Still data supporting BPPs as standard of care for acute Charcot foot is limited. The long-term efficacy of such drugs in preventing foot deformity and ulceration is still unknown.

Postacute phase: Management following removal of the cast includes life-long protection of the involved extremity. Patient education and professional foot care on a regular basis are integral aspects of life-long foot protection. After cast removal, patients should wear a brace to protect the foot. Many types of braces may be used, including a patellar tendon-bearing brace, accommodative footwear with a modified ankle foot orthosis (AFO), a Charcot restraint orthotic walker (CROW) and a double metal upright AFO.

Custom footwear includes extra depth shoes with rigid soles and a plastic or metal shank. If ulcers are present, a rocker-bottom sole can be used. Also, Plastazote inserts can be used for insensate feet. This regime may be eliminated after 6–24 months, based upon clinical and radiographic findings. Continued use of custom footwear in the postacute phase for foot protection and support is essential.

The total process of healing typically takes 1–2 years. Preventing further injury, noting temperature changes, checking feet every day, reporting trauma, and receiving professional foot care are also important steps of treatment.

Surgical Therapy

Surgery is warranted in less than 15% of cases and is generally a preventive measure. Surgery is performed when a deformity places the extremity at risk for ulceration and when the



Fig. 11.15: Feet with peripheral artery occlusive disease (PAD).

extremity cannot be protected safely in accommodative footwear. The goal of reconstruction is to create a stable plantigrade foot that can be protected appropriately in accommodative footwear and that can support ambulation. Surgery is indicated for malaligned, unstable, or nonreducible fractures or dislocations, as well as when nonsurgical means fail.

Medical Therapy

Reduction of inflammation and osteoporosis may be achieved by use of oral alendronate 70 mg once a week or intravenous pamidronate 60 mg once in 3 months.

PERIPHERAL ARTERY OCCLUSIVE DISEASE

Prevalence of diabetic peripheral artery occlusive disease (PAD) in India varies between 6% and 16%. PAD is four times more prevalent in diabetics than in nondiabetics with early large vessel involvement coupled with distal symmetrical neuropathy (Fig. 11.15). The arterial occlusion typically involves the infrapopliteal arteries but spares the dorsalis pedis artery. Smoking, hypertension and hyperlipidemia commonly contribute to the increased prevalence of peripheral arterial occlusive disease in diabetics. For every 1% increase in hemoglobin A1C there is a corresponding 26% increased risk of PAD.

Every 30 minutes, a person loses a limb related to injuries in land mines, and every 30 seconds, there is a limb loss somewhere in the world due to diabetic foot infection.

The presence of lower extremity ischemia is suggested by a combination of clinical signs and symptoms plus abnormal results on noninvasive vascular tests. Signs and symptoms may include claudication, pain occurring in the arch or forefoot at rest or during the night, absent popliteal or posterior tibial pulses, thinned or shiny skin, and absence of hair on the lower leg and foot, thickened nails, redness of the affected area when the legs are dependent (Figs. 11.16A and B). The need for a major amputation is 5–10 times higher in diabetics than nondiabetics.



Figs. 11.16A and B: A 52-year-old male, chronic smoker, known to have diabetes for past 5 years presented with rest pain and blackening of right foot for past 3 months. On examination, bilateral lower limb pulses were absent. Ankle-brachial index: Right 0, Left 0.2. The angiography showed juxta-renal aortic occlusion; (B) A 60-year-old male, chronic smoker, known to have diabetes for past 10 years presented with non-healing ulcer left second web space for past 3 months. Ankle brachial index: Right 0.5, Left 0.32. The angiography showed occlusion of common femoral artery.

Osteomyelitis increases the risk for the need of amputation by 23 folds as compared to soft-tissue infection.

Noninvasive vascular tests include:

- Transcutaneous oxygen measurement
- Ankle-brachial index (ABI)
- Absolute toe systolic pressure.



Fig. 11.17: Ankle brachial index is a noninvasive test that can be performed easily using a handheld Doppler device.

The ABI is a noninvasive test that can be performed easily using a handheld Doppler device (Fig. 11.17). A blood pressure cuff is placed on the upper arm and inflated until the Doppler device detects no brachial pulse. The cuff is then slowly deflated until a Doppler-detected pulse returns (the systolic pressure). This maneuver is repeated on the leg, with the cuff wrapped around the distal calf and the Doppler device placed over the dorsalis pedis or posterior tibial artery.

$$\text{ABI} = \frac{\text{Higher of the anklesystolic pressures - posterior tibial or dorsalis pedis}}{\text{Higher of the arm systolic pressures - left or right arm}}$$

Optimal ulcer healing requires adequate tissue perfusion. Thus, arterial insufficiency should be suspected if an ulcer fails to heal. Vascular surgery consultation and possible revascularization should be considered when clinical signs of ischemia and the results of noninvasive vascular tests or imaging studies suggest that the patient has peripheral arterial occlusive disease.

Proper control of concomitant hypertension or hyperlipidemia can help to reduce the risk of peripheral arterial occlusive disease. Smoking cessation is essential for preventing the progression of occlusive disease.

Recommendations by the Diabetic Foot Society of India (DFSI) for vascular evaluation and treatment are:

- All diabetics should undergo complete clinical vascular evaluation every 6 months.
- ABI should be done as a part of the initial examination to differentiate arterial claudication from neurogenic or venous claudication.
- All patients with PAD should have baseline laboratory studies which include lipid profile, electrocardiogram (ECG) and lipid profile. The abnormalities should be addressed and treated.

- Duplex scan (Doppler ultrasound) is recommended as the first imaging modality in patients with claudication, ulcer or gangrene. The scan should be performed by an experienced sonologist as it is operator-dependent.
- Angiogram [digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA)] should be done only after a judicious clinical evaluation.
- All patients with intermittent claudication should be placed on a (supervised) exercise program, lifestyle modification, control of risk factors and appropriate pharmacotherapy.
- Patients, who after adequate medical therapy develop disabling claudication or rest pain, need to be treated early and aggressively by a vascular surgeon. This includes patients with ABI less than 0.5 and/or toe pressure and/or transcutaneous oxygen measurement (TcPO₂) less than 40.
- The “watch and wait” policy in India after debridement of an ischemic lesion often results in increased morbidity, mortality and cost to the patient.
- Do not amputate—if you can help it.

Diabetes Maintenance Therapy for Vascular Disease Prevention

Blood Glucose Control

- Target hemoglobin A1C < 7%
- Monitor blood glucose and target premeal values of 80–120 mg/dL and bedtime values of 100–140 mg/dL.

Blood Pressure Control

- Angiotensin-converting enzyme inhibitor is the preferred antihypertensive for all adults with diabetes or if microalbuminuria is present
- Target level < 130/80 mm Hg.

Blood Lipid Control

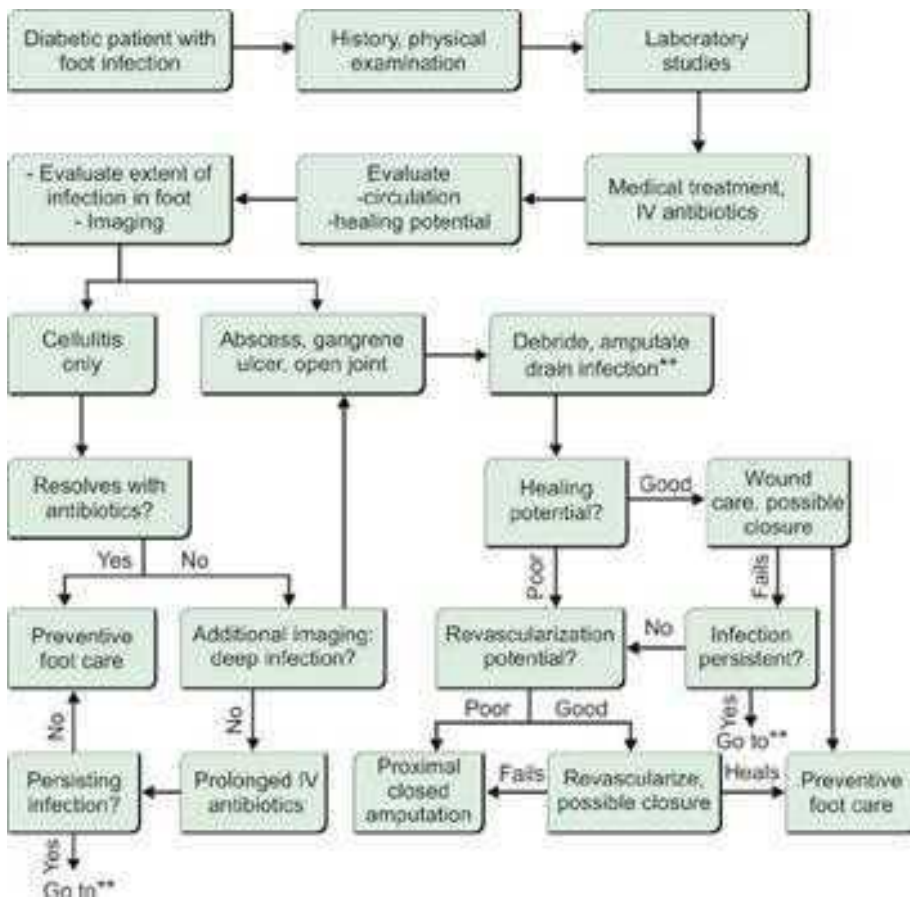
- Target low-density lipoprotein level < 100 mg/dL
- Target triglyceride level < 150 mg/dL.

Antiplatelet Therapy

- Aspirin for primary prevention if age more than 50 years in men or more than 60 years in women who have at least one additional major risk factor
- Clopidogrel
- Ticlopidine (associated with thrombotic thrombocytopenic purpura)
- Platelet IIb/IIIa inhibitor.

Miscellaneous Treatment

- Smoking cessation
- Foot care program.

Flowchart 11.1: Algorithm for the management of diabetic foot.

Source: Towne JB. Diabetic foot infection. In: Cronenwett JL, Rutherford RB (Eds). Decision making in vascular surgery. Philadelphia, PA: WB Saunders; 2001. pp. 212-7.

To summarize an algorithm to follow in a patient with diabetes foot is given in Flowchart 11.1.

SELF-ASSESSMENT

1. Foot care at home is done by the patient with:

- (a) Pumice stone (b) An old razor blade
 (c) Nylon dishwashing brush (d) A and C
 (e) None of the above

2. The medications used for the treatment of neuropathy include all *except*:

- (a) Amitriptyline (b) Carbamazepine
 (c) Gabapentin (d) Amlodipine
 (e) Tramadol

- 3. The painless, swollen, deformed foot of a patient with diabetes with severe proliferative, diabetic retinopathy and nephropathy is suspected to have:**
- (a) Osteomyelitis
 - (b) Charcot's arthropathy
 - (c) Claw foot
 - (d) Septic arthritis
 - (e) None of the above
- 4. Management of Charcot's arthropathy include all of the following *except*:**
- (a) Immobilization
 - (b) Rocker bottom shoes
 - (c) Treadmill exercises
 - (d) Malignant unstable dislocations need a total contact cast
 - (e) Alendronate
- 5. Which of the following are unlikely to be a symptom of neuropathic foot disease?**
- (a) Numbness
 - (b) Paresthesias
 - (c) Deep seated pain
 - (d) Loss of sensation
 - (e) None of the above
- 6. Which statement is not true?**
- (a) The risk of cardiovascular disease is two to three times higher in persons with diabetes than in nondiabetic subjects
 - (b) The risk of vascular disease associated with diabetes is secondary to obesity, lipid disorders, and increased blood pressure, but not diabetes per se
 - (c) The increased prevalence of congestive heart failure in diabetic patients with coronary artery disease has been attributed to microvascular disease and autonomic dysfunction
 - (d) Large vessel disease in one area of the vascular tree predicts disease in other areas as well
 - (e) Many vascular lesions in persons with diabetes are asymptomatic
- 7. Which of the following statements is not true?**
- (a) The ABI is not a good screening tool for persons with diabetes
 - (b) Intervention studies in persons with diabetes have shown improvement in the ABI after 9 months of normoglycemia and exercise
 - (c) The prevalence of foot ulcers in diabetic patients with peripheral vascular disease is increased in part by problems with the microcirculation and neuropathy
 - (d) Glucose control, blood pressure, and duration of diabetes are all independent predictors of amputation
- 8. Which of the following probably contributes to vascular disease in hyperglycemic subjects?**
- (a) Glycation and advanced glycation end products
 - (b) Perturbations in the fluid phase of coagulation
 - (c) Increased reactivity of the platelet
 - (d) Endothelial cell dysfunction
 - (e) Increased oxidative stress
 - (f) Vascular volume shifts
 - (g) All of the above

9. Which of the following statements is most accurate regarding the indications for vascular reconstruction in a diabetic patient?

- (a) It should be performed primarily for limb salvage rather than claudication
- (b) It should be avoided in subjects with severe neuropathy
- (c) It should be performed less frequently because of poorer outcome statistics
- (d) It should be performed for the same indications in diabetic and nondiabetic patients

10. Strict blood glucose control with careful glucose monitoring before, during, and after surgery is important for which of the following reasons?

- (a) To minimize the risk of infection
- (b) To increase wound healing and strength
- (c) To avoid hypoglycemia
- (d) To minimize the risk of a prothrombotic state
- (e) All of the above

PART B: WOUND CARE IN PATIENTS WITH DIABETES

□ari □ri□hna □air

INTRODUCTION

Diabetes is becoming a pandemic currently. It is noted that 25% of all patients with diabetes mellitus will develop diabetic foot complications. Armstrong et al. (1998) found that 85% of diabetic foot problems can be prevented. Therefore, this is the only complication that can be prevented with good foot screening, foot care and proper footwear.

When patients with diabetes mellitus develop a wound, a comprehensive assessment is required.

WOUND ASSESSMENT

Wound assessment and Bed preparation are essential in the management of a diabetic wound (Figs. 11.18 and 11.19).



Fig. 11.18: Wound assessment.



Fig. 11.19: Wound bed preparation.

Source: Sibbald RG, Williamson D, Orsted HL, Campbell K, Keast D, Krasner D, et al. Preparing the wound bed—debridement, bacterial balance, and moisture balance. *Ostomy Wound Manage.* 2000;46(11):14-22.

Under the *Wound Bed Preparation* concept, the anagram TIME is most important component. TIME has been used since 2003 till now to assess the wound bed and plan a proper management of the wound.

- T—tissue
- I—infection or inflammation
- M—moisture imbalance
- E—epidermal margin.

Table 11.3 shows the TIME concept in a systematic way. The general assessment involves a systematic approach and the acronym HEIDI describes it properly.

- H—history
- E—examination
- I—intervention
- D—diagnosis
- I—investigations.

WOUND CLEANSING

Wound cleansing is defined as “the process of removing inflammatory contaminants from the wound surface”.

Then we have to clean the wound with a cleansing solutions.

Cleansing Solutions

- Normal saline
- Water for irrigation.

Nontoxic Wound Cleansers

- PHMB (polyhexamethylene biguanide) with betaine
- Superoxide solution
- Octenidine dihydrochloride.

Table 11.3: TIME: Principles of wound bed preparation (WBP).

<i>Clinical observations</i>	<i>Proposed Pathophysiology</i>	<i>WBP clinical actions</i>	<i>Effect of WBP actions</i>	<i>Clinical outcome</i>
Tissue non-viable or deficient	Defective matrix and cell debris impair healing	Debridement (episodic or continuous) <ul style="list-style-type: none"> Autolytic, sharp surgical enzymatic, mechanical or biological Biological agents 	Restoration of wound base and functional extracellular matrix proteins	Viable wound base
Infection or Inflammation	<i>High bacterial counts or prolonged inflammation</i> ↑ Inflammatory cytokines ↑ Protease activity ↓ Growth factor activity	<ul style="list-style-type: none"> Remove infected foci <i>Topical/systemic</i> Antimicrobials Anti-inflammatories Protease inhibition 	<i>Low bacterial counts or controlled inflammation:</i> ↓ Inflammatory cytokines ↓ Pprotease activity ↑ Growth factor activity	Bacterial balance and reduced inflammation
Moisture imbalance	Desiccation slows epithelial cell migration Excessive fluid causes maceration of wound margin	Apply moisture balancing dressings Compression, negative pressure or other methods of removing fluid	Restored epithelial cell migration, desiccation avoided Edema, excessive fluid controlled, maceration avoided	Moisture balance
Epidermal Margin—non-advancing or Undermined	Non-migrating keratinocytes Non-responsive wound cells and abnormalities in protease activity	Re-assess cause or consider corrective therapies <ul style="list-style-type: none"> Debridement Skin grafts Biological agents Adjunctive therapies 	Migrating keratinocytes and responsive wound cells Restoration of appropriate protease profile	Advancing epidermal margin

However, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* can grow in normal saline solution.

Then we need to debride the dead, devitalized tissue and eschar as well as the slough.

DEBRIDEMENT

- “The removal of foreign matter or devitalized, injured and infected tissue from a wound.” [Whiteside MCR and Moorehead RJ (1998)]
- “To remove devitalized tissue when appropriate for the patient’s condition and when consistent with the patient’s goals.” [EPUAP Review (1999)]
- “Surgical debridement is the gold standard of care, once ischemia is excluded.” (Wagner 1984, Knowles 1997, Laing 1994)

Types of Debridement

- *Mechanical*: Using wet to dry gauze , low-pressure irrigation, whirlpool
- *Surgical*: Using a scalpel blade
- *Ultrasonic*: Using an ultrasonic debrider
- *Hydrostatic*: Using a handpiece with water to debride
- *Biological*: Using the Maggot Debridement Therapy utilizing *Lucilia cuprina*
- *Autolytic*: Using hydrogels
- *Enzymatic*: Using honey, clostridiopeptidase A, collagenase.

Choice of Dressings

There has been a lot of new dressing material being introduced in the world and we need to choose the correct advanced environmental moisture retentive dressings with the proper indications to obtain the best end outcome with minimal or no complications. Table 11.4 describes the dressing categories and their indications.

Other available dressings are:

- Silver dressings to manage bacterial bioburden
- Cadexomer iodine
- Polymeric membrane dressings
- Medical grade honey
- Collagen dressings
- Matrix, regenerative dressings

Table 11.4: Dressing categories with their advantages and disadvantages.

Dressings	Purpose	Advantages	Disadvantages
Films	Protect against contamination and friction	Adherent	Fluid collection
	Maintain moist surface	Transparent with measurement grid	Possibility of stripping away newly formed epithelium on removal
	Prevent evaporation	Bacterial barrier	
	Facilitate assessment	Water proof	
		Breathable	
Hydrogel	Rehydrate, debride and deslough wound	Comfortable	
	Promote moist healing	Provide moist environment and reduces pain	Need secondary dressing
	Cavity filling	Rehydrate eschar	Maceration around wound
		Desloughing agent	
		Promote granulation	

Contd...

Contd...

<i>Dressings</i>	<i>Purpose</i>	<i>Advantages</i>	<i>Disadvantages</i>
Hydrocolloids	Provide moist environment	Cleans and debrides by autolysis	Unpleasant odor
	Absorb exudate	Easy to use	Forms a yellow liquid gel
	Bacterial Barrier	Cost effective	Difficult to use in cavities
		Promote granulation tissue	Adhesive action damages fragile skin
		Effective for low to moderate exuding wounds	
Calcium alginate	Absorb wound exudate and maintain moisture	Economical and easy to apply	Not helpful for dry wounds
		Biodegradable	Need secondary dressing
		Hemostatic properties	
Hydrofiber	Manage heavy exuding wounds	Longer wear time	Cost
	Maintains moist healing environment	Comfortable	Not helpful for dry wounds
	Autolytic debridement	Non-traumatic	Needs secondary dressings
		Upon removal	
		Reduce risk of maceration	
Foams	Absorbent	Conforms to body contours	Can adhere to wounds if exudate dries
	Cushioning	Designed for cavity wounds	
		Highly absorbent	
		Provides protection	
		Bacterial and water proof	
Charcoal	Odor absorbent	Reduces odor	Needs secondary dressing

- TLC (technology lipido-colloid) + NOSF (nano-oligosaccharide factor): Urgostat®.
Following the dressings, we have to offload the patients' diabetic foot by using:
- Foam or felt
- Orthosis
- Custom made shoes, e.g. rocker bottom shoes

- Total contact cast
- Walkers, crutchers, etc.

SUGGESTED READING

1. Rezende Neta DS, Silva AR, Silva GR. Adherence to foot self-care in diabetes mellitus patients. *Rev Bras Enferm.* 2015;68(1):111-6.
2. Viswanathan V, Thomas N, Tandon N, et al. Profile of diabetic foot complications and its associated complications—a multicentric study from India. *J Assoc Physicians India.* 2005;53:933-6.

SELF-ASSESSMENT

1. **Which is true regarding the TIME concept *except* ?**
 - (a) TIME is a part of the Wound Bed Preparation
 - (b) T stands for tissue
 - (c) I stands for infection
 - (d) M stands for moisture imbalance
 - (e) E stands for eschar
2. **These are types of cleansing solutions suggested to be used in a diabetic foot wound *except*:**
 - (a) Octenidine dihydrochloride
 - (b) Water for irrigation
 - (c) PHMB with Betaine
 - (d) Super OXIDE solution
 - (e) Flavine
3. **These are the methods of debridement *except*:**
 - (a) Mechanical
 - (b) Enzymatic
 - (c) Autolytic
 - (d) Biological
 - (e) Electromagnetic
4. **Which of these statements are true?**
 - (a) *Lucilia cuprina* can be used to debride the dead tissues
 - (b) Mechanical debridement involves using the blade
 - (c) Honey is used to cleanse the wound
 - (d) Ultrasonic debridement uses pulse lavage
 - (e) Collagenase can be used for autolytic debridement.
5. **These statements are true regarding dressing materials *except*:**
 - (a) Foam can be used as a secondary dressing
 - (b) Hydrofiber can be used to manage exudates
 - (c) Charcoal can be used to manage the odor
 - (d) Film can absorb exudate
 - (e) Hydrocolloid produces a liquid on the surface of the wound
6. **These are types of offloading *except*:**
 - (a) Total contact cast
 - (b) Walker
 - (c) Insoles
 - (d) Film
 - (e) Shoes

7. These are true *except*:

- (a) 85% of diabetic foot ulcers can be prevented
- (b) Sugars must be controlled
- (c) 25% of patients with diabetes will develop diabetic foot complications
- (d) Customized shoes can offload the foot and alleviate pressures
- (e) Silver dressings are for granulation

8. Choose the correct statement:

- (a) Amputation is a failure of treatment
- (b) MRSA can grow in distilled water
- (c) Hydrogel can be used to debride the wound mechanically
- (d) HEIDI is used to describe the wound
- (e) Cleansing solution like Povidone Iodine should be used

9. All are advantages of using a dressing, *except*:

- (a) Conform to body contours
- (b) Highly absorbent
- (c) Provides protection
- (d) Hemostatic properties

10. Non toxic wound cleansers include all *except*:

- (a) PHMB
- (b) Superoxide solution
- (c) Hydrogen peroxide
- (d) Octenidine dihydrochloride

CHAPTER

12

Therapeutic Footwear

Judy Ann John, Bobeena Rachel Chandy, Rajan P, Premkumar R

*Wear shoes not hard or soft-make sure they're shore is right,
Stop walking without footwear-make sure they're not too tight,
If feet are badly deformed and sometimes tend to swell,
There are special shapes and sizes which could help you out quite well.*

Diabetic foot ulcers are the most common nontraumatic causes for lower extremity amputations. Research and clinical evidence have shown that proper footwear and therapeutic foot orthotics could help in preventing such amputations. These devices protect the insensitive foot from unnoticed trauma and excessive plantar pressures that occur during walking. Therefore, the objective of this chapter is to provide an understanding of the principles behind prescribing different footwear.

Selection of proper footwear is determined mainly by the loss of protective sensation, decreased intrinsic muscle strength of the feet, history of ulceration including callus and corn formation, weight bearing areas and foot deformities. During the visits of diabetic patients to the clinics it is important to examine the feet as well as the footwear.

INTRODUCTION

Mechanical factors play an important role in the etiology of the majority of foot ulcers. A strong relationship has been established between abnormal foot pressure and incidence of foot ulceration. Dr Paul Brand (1954) said that there is hope of saving the neuropathic foot only when it is recognized that the real problem is due to biomechanical abnormalities. Mechanical problems require mechanical solutions; likewise, problems of the foot require therapeutic footwear management, which acts in the following ways:

- It protects the skin from external trauma, extreme temperature and contamination
- If adapted to the altered biomechanics and deformities footwear therapy could
 - Reduce the incidence of ulceration by evenly distributing plantar pressure;
 - Relieve pressure from vulnerable sites in cases of recurrent ulcers.

FOOT INJURY MECHANISM DUE TO SENSORY NEUROPATHY

Ulcers can develop in a foot with diabetic neuropathy due to abnormal pressures in the following ways:

Prolonged low pressure: Patients with anesthetic limbs exert continuous low pressure in the foot, shoe/ground interface during many common activities such as standing, walking, sitting cross-legged and on wearing tight footwear for long periods of time. The pressure exerted in these ways results in tissues being deprived of blood supply for a prolonged time leading to ischemia in the tissues and subsequent ulceration.

High pressure: Overwhelming force greater than 80 kg/cm² causes high pressure that is sufficient to injure the skin. Such trauma can occur if a patient ambulate bare foot and stamps on a sharp object.

Shear stress: Shear stress is two forces acting in opposite directions. While walking this type of stress commonly occurs at the metatarsal heads due to backward and forward movement of the skin against the bone. Shearing stress is increased when walking faster or by taking long strides. Loose fitting footwear can also cause friction between upper straps and dorsum of the foot leading to break in the skin integrity.

Repetitive stress: Repetitive trauma can occur over prolonged periods of time at a pace that outstrips the tissue's ability to heal itself due to the absence of protective sensation in feet with sensory neuropathy.

FOOT INJURY MECHANISM DUE TO MOTOR AND SENSORY NEUROPATHY

Motor neuropathy can cause intrinsic muscle paralysis. This paralysis leads to muscular imbalance and to clawing of toes (Fig. 12.1A). This results in distal migration of the plantar fat pad, which leaves the metatarsophalangeal (MTP) joints without cushioning. In such instances, due to excessive pressure and friction, each step taken by the patient will lead to stress in the tissue over the metatarsal heads resulting in callus formation (Fig. 12.1B). Callus is an avascular, multilayered epithelial tissue, which gets hardened in course of time. Such calluses could also form in the healed ulcer sites. This in turn leads to constant localized high pressure to the inner soft tissues during walking and subsequently to subcutaneous hemorrhage and ulceration (Fig. 12.1C).



Figs. 12.1A to C: (A) Clawing of toes; (B) Callus built-up due to increased pressure, which results in subcutaneous hemorrhage; (C) Skin breakdown.

FOOT EXAMINATION FOR SELECTING APPROPRIATE FOOT ORTHOTICS

Examination begins with inspection of the patient's feet for swelling, warmth, percentage of scars in weight-bearing areas, ulcers, deformities, calluses and corns. Inspection of the footwear for signs of excessive wearing will also provide information regarding localized increase in plantar pressure. The following specialized tests need to be done after this inspection.

For convenience of describing the area of problem in the foot, it has been divided into the forefoot (metatarsal heads and toes), the midfoot (proximal to the metatarsal head to the subtalar joint) and the hindfoot (heel to the subtalar joint) (Fig. 12.2).

Test for Protective Sensation

Lack of protective sensation and weakness of the foot intrinsic muscles predispose a diabetic to an increased risk of developing foot ulceration. The clinical tests done for assessment of peripheral neuropathy are—

The Semmes-Weinstein monofilament test: As described in Chapter 10.

Intrinsic Muscle Strength

Intrinsic muscle paralysis is one of the important factors in selecting proper footwear. Loss/weakness of the intrinsic muscles of the feet results in the footwear slipping off the feet resulting in foot injuries/falls. The paper grip test is a good screening test to detect this (Figs. 12.3 and 12.4). During the test, footwear and socks are to be removed and the patient sits up straight with hips, knees in 90 degree flexion and ankles in neutral. The examiner ensures that the patients stay in the same position and keeps their heels on the floor during the test. The examiner puts a slip of paper under the phalanx of the big toe, just distal to the MTP joints. The



Fig. 12.2: Parts of foot.



Fig. 12.3: The paper grip test.



Fig. 12.4: A poor patient with neuropathy who had frequent slipping of sandals from feet with a cord tied around it as a back strap.

patients have to look at their feet, because they may not feel the paper due to their anesthetic feet. The examiner pulls the paper in a horizontal direction while the patient offers resistance to it. If the patient has normal intrinsic muscle strength they will be able to grip the paper at least one out of three times. Inability to grip the paper even once in three tries indicates intrinsic foot muscle paralysis.

Plantar Pressure Assessment

This assessment will specifically identify the areas of localized high pressure in the foot and also check the usefulness of both commercial and therapeutic footwear in relieving the high pressure. At present two assessments are available; one is using the Harris mat foot pressure measurement and the second is a computerized assessment.

1. *Harris mat assessment:* This is a semiquantitative and fairly reliable, inexpensive assessment widely used in the field of leprosy in India for the last half a century. The Harris mat is a rubber mat, which has ridges of graduated heights, forming squares of varying size. The rubber mat is evenly inked over with printer's ink on a rubber roller to spread the ink uniformly. The inked mat is then laid carefully faceup on a white sheet of paper. Ask the patient to walk over the mat to leave an impression of his foot on the paper (Fig. 12.5). Figure 12.6 depicts the quantification of plantar pressure using this mat. The Harris mat is available for sale from Diabetic Foot Care, India at Chennai. www.diabetikfootcareindia.com
2. *Computer assessments:* Plantar pressure assessment is now possible with at least six well-known computer software programs and pressure appreciating sensors that are commercially available. This is a quantitative assessment. In our experience, it is of more use in research than day-to-day clinical practice. There are two types of sensors; one is where the sensor is placed inside the footwear and the second is a sensor mat on which the patient is asked to walk barefoot (Fig. 12.7A). The results are presented as a two-dimensional figure in different colors, indicating the different levels of pressure. Three-dimensional figures are also obtainable with colors and "peaks" as shown in Figure 12.7B.



Fig. 12.5: The paper peeled off the inked Harris mat.



Fig. 12.6: Harris mat footprints. Left shows hard insole. Right is with microcellular rubber Interpretation of it as per Prem kumar et al. 1985 is as follows: Very dark blotch = High pressure ($> 1250 \text{ g/cm}^2$) Print large squares = Medium pressure ($500 \text{ g} - 1249 \text{ g/cm}^2$) Thin widely spread lines = Light pressure ($499 \text{ g} - 76 \text{ g/cm}^2$) Unmarked = No pressure ($< 75 \text{ g/cm}^2$).



A



B

Figs. 12.7A and B: (A) This shows a patient walking with the sensors placed inside his shoes on a marked platform. The sensors are attached to the cuff units at lower legs, which transfers the information to the receiver unit attached at waist and this is connected to the computer; (B) Three-dimension view of the foot pressure distribution. Left depicts foot pressure distribution with a hard flat insole and the right with a moulded hard insole. Interpretation is as follows: Peaks = High pressure; Blunt curves = Moderate pressure; Flat = No pressure.



Fig. 12.8: Parts of footwear.

SELECTION OF FOOTWEAR

The most important aspect of diabetic foot care is selection of an appropriate footwear. It is important to know the various parts of the footwear to be able to prescribe specific modifications as required for individual patients (Fig. 12.8).

Footwear is meant for protection and comfort. When prescribing footwear in a diabetic, the following characteristics must be specified:

- Both feet need to be measured when standing and preferably at the end of the day. Usually one foot is larger than the other so the fit should be for the larger of the two. The other footwear can be modified, with a soft insole liner, to prevent excessive movement within the footwear (Table 12.1).
- The insole should be able to redistribute the plantar pressures evenly and reduce shock and shear forces
- To accommodate, stabilize and support deformities
- Wide toe box with a finger width between the longest toes and the end of the shoe
- The depth of the toe box should be adequate to allow room for the toes to extend and flex minimally without any pressure (Table 12.2)
- A rigid outsole for protection from sharp objects, an appropriate insole with a shore value between "8 and 15"
- Back strap or heel counter for support
- Slip on footwear without heel counter or back strap are to be avoided as they are likely to cause the tips of toes to rub on the shoe, leading to corns and calluses. T-straps are also to be avoided as they can cause ulceration in the first web space due to pressure or constant friction.

Table 12.1: Choosing correct shoe size: Length.








<p>Too loose!</p> 	<p>Shoes are too long → shearing stress on the skin where it comes into contact with the straps → blistering</p>
<p>Too tight!</p> 	<p>Shoes are too short → injury to the toes and nails</p>
<p>Just right!!</p> 	<p>Ideal shoes/sandals-should be at least 1.25 cm longer than the longest toe while standing. This allows toes to move freely while walking.</p>

Table 12.2: Choosing correct toe space.

<p>A.</p> 	<p>Thin space for the toes in narrow fitting shoes → corns on the tops or in between the toes</p> <p>Shallow toe space → corns and callus on the pressed areas of the toes</p>	
<p>B.</p> 	<p>Sufficient space for the toes in proper width shoes allow the toes to rest flat inside the shoes without being cramped.</p> <p>Deep enough in the toe area, to avoid the upper parts of the toes being pressed against the leather.</p>	

The footwear needs of diabetic patients could be divided depending on the following categories: (1) low, (2) moderate, and (3) high risks to developing foot ulceration. This categorization is based on sensory, motor and autonomous neuropathy, vascular involvements, any pressure related lesions, previous history of ulcers and foot deformities.

The Low-risk Foot Patients (~ 85%)

- Normal sensation
- Normal muscle strength
- Palpable pulse
- Structurally normal foot—no deformity or skin changes
- No high pressure
- No current foot problems.

Footwear prescription: Properly fitting footwear of any type. A good shoe should have the following characteristics:

Correct length, width and depth

Proper fastening

Tight shoes → prolonged low pressure }
Loose shoes → shear stress } foot ulceration

Design: Sandals or shoes of the fastening types (with laces, buckles or velcro) could be slightly larger in size in order to accommodate swelling.

Checking proper fit: Footwear education is important in this group of patients. When they purchase new footwear, tell them to wear it for 30 minutes on the first day to ensure that there are no pressure signs such as red areas and localized warmth. They should gradually increase the wearing time of the footwear.

Footwear material: The footwear prescribed should be able to redistribute the plantar forces equally along the feet. Hence the ideal material should be durable and mouldable. The various materials used for insoles include rubbers, closed cell foam (plastazote), polyethylene foam, polyvinyl foam, polyurethane foam, cork rubber, silicone (Fig. 12.9) and leather. Microcellular rubber (MCR) is the most common material used to relieve plantar pressure.

The insole hardness is measured by an instrument called “durometer” (Figs. 12.10A and B) which gives the shore value. A value between 8 and 15 is desirable for diabetic footwear. A shore value of less than eight is too soft and unlikely to give protection, whereas a value above 15 is too hard leading to areas of callosities due to pressure.

Microcellular Rubber

More than 40 years of our experience have shown that 15° shore MCR gives satisfactory results in both preventing ulcers and ulcer recurrence in majority of patients with anesthetic feet. MCR

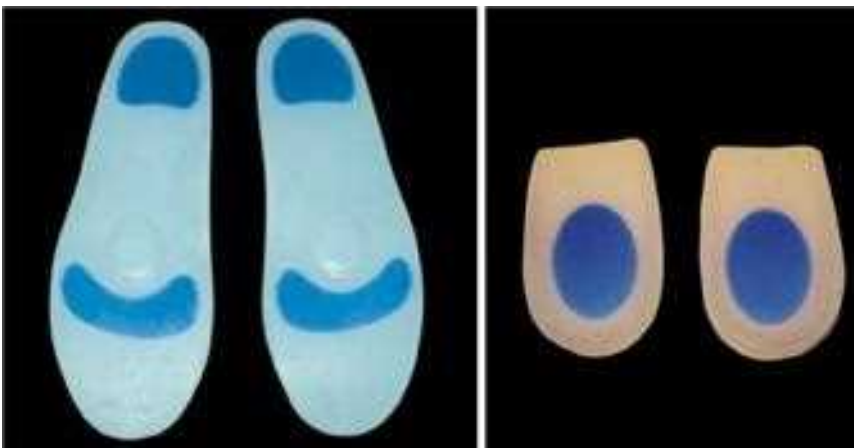


Fig. 12.9: Silicone insole and heel pad. This is to be used inside shoes for weight distribution and protection.



Figs. 12.10A and B: (A) Durometer; (B) Checking the shore value of the footwear.



Fig. 12.11: Microcellular rubber footwear with all the characteristics of a diabetic footwear.

is a specially processed rubber material with 15 chemicals, where bubbles of air are introduced into the rubber, creating millions of “micro cells” containing air. These micro-sized closed cells resemble fat filled cells under the sole of the foot. MCR is available for sale at Karigiri, Tamil Nadu, India.

Microcellular rubber is a self-molding material, which increases the area of contact and distributes weight evenly as illustrated in Figure 12.11. It is also an excellent replacement for fat pad loss and small muscle atrophy in the sole, which results in thinning of plantar padding due to nerve damage. Generally a pair of good MCR sandals will last for 18 to 24 months. It has the following qualities: (1) MCR withstands friction while walking and still maintains its thickness, (2) Its property of elastic recoiling molds the foot instantly to its shape; thus the area of the foot weight-bearing is increased. (Compression of the rubber indicates that the air spaces in the MCR are weak and it is not able to recoil), (3) Good rubber will not tear if it is hand stitched or cut to insert straps.



Fig. 12.12: Pinch test.

It is important to check the above three qualities of MCR and there are two ways to do it. One is a simple manual pinch test by pinching a piece of rubber between the finger and thumb. A firm pinch of average strength should be able to squeeze the rubber to half its resting thickness as shown in Figure 12.12. Flattening more than this indicates that the MCR is too soft; less than this, it is too firm. Second is by using an instrument called “durometer” which measures the degree of hardness of MCR in shores. 15 degree shore is the softness, footwear requires. MCR is manufactured in two thicknesses–10 mm thickness used in manufacturing open sandals, and 3 mm used inside closed shoes.

The Moderate-risk Foot Patients (~ 15%)

- Peripheral neuropathy and/or vasculopathy
- Mobile foot deformities such as high and low arches
- Pressure lesions such as callus, corns, minimal healed ulcers.

Footwear Prescription

Assessment in a foot clinic provides an opportunity for the physician to communicate with the fabricator regarding appropriate footwear with required features for pressure relief. Modifications can be made in the insole, on the outsole as well as in the shoe’s upper portion in order to relieve pressure in the regions at risk for ulceration (Figs. 12.13 and 12.14). Therapeutic footwear, including a custom molded insole in a shoe with adequate depth is the preferred intervention for the primary and secondary prevention of ulcers. The adjustable strap in the front can be adjusted in the presence of an ulcer on the dorsal aspect of foot.



Fig. 12.13: Microcellular rubber “Y” strap sandal.



Figs. 12.14A and B: (A) Partially scooped insole; (B) Surgical shoes.

Microcellular Rubber Sandal

Straps: Leather is good for the upper straps as it conforms well to the shape of the foot and allows minimal stretching of the straps.

Adjustments for areas of high pressure: A small localized high pressure area of the foot can be relieved by partially scooping-out material from the under surface of the MCR insole approximately 0.5 cm larger than the pressure lesions after accurately marking it on the insole. A back strap or heel counter is essential to keep high-pressure area right under the scooped surface.

Footwear Management for Ulcers and Deformities

As mentioned earlier in the chapter, the foot is divided into the forefoot, midfoot and hindfoot for easier description of the anatomical location of the ulcers (*see* Fig. 12.2) and subsequent planning for modifications. There are two common mobile deformities found in diabetic feet, namely, supination and pronation of the foot due to altered biomechanics and architecture of the foot resulting in excessive pressures in the medial or lateral aspects of the foot. As per the area of pressure, the footwear management will differ. Examination of the patient's footwear is as important as the foot. The management of these foot types is discussed below.

Addons to the footwear—forefoot ulcers/deformities: The forefoot may present with a wide range of deformities and ulcers as the pressures over the metatarsal heads and the big toe are highest during the toe-off of the gait cycle.

Hammer toe, mallet toe and claw toe: These result due to intrinsic muscle weakness, subsequent muscle imbalance and improper footwear.

Hammer toe is when there is hyperextension of the MTP joint with flexion at the proximal interphalangeal (PIP) joint. Due to this deformity, the toe is susceptible to injury over the dorsum of the PIP joint as well as the MTP joint. Mallet toe occurs when there is flexion deformity of the distal interphalangeal (DIP) joint. Claw toe is seen with flexion deformities of the PIP and the DIP joints (Figs. 12.15A to C).

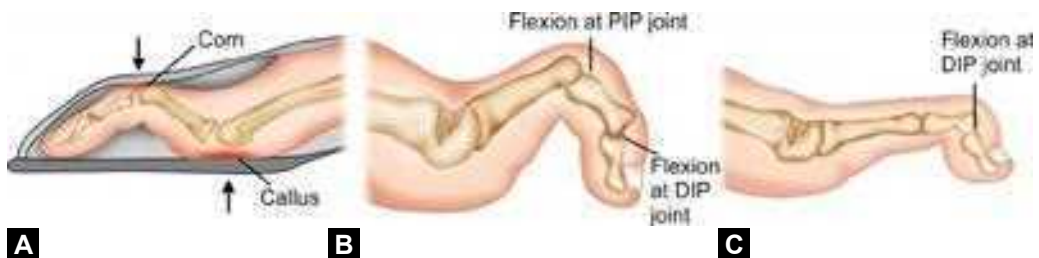
The addons that may be given for the above are:

- Silicone toe caps or toe sleeve (Fig. 12.16) for protection of the PIP joint
- Silicone toe prop or elevator which reduces contact of the pulp of the toes with the footwear
- A metatarsal pad (Fig. 12.17A) can be given to take pressure off the metatarsal heads
- Alternatively a metatarsal bar (Fig. 12.17B) in the footwear, placed just proximal to the metatarsal head reduces the forefoot pressure by decreasing the time taken in toe-off during the gait cycle.

Addons to the sole of the footwear

Rocker bottom sole: This is an add-on (Fig. 12.18), given for forefoot problems like superficial ulcers, and callosities. It helps in reducing the forefoot pressure by almost 50%.

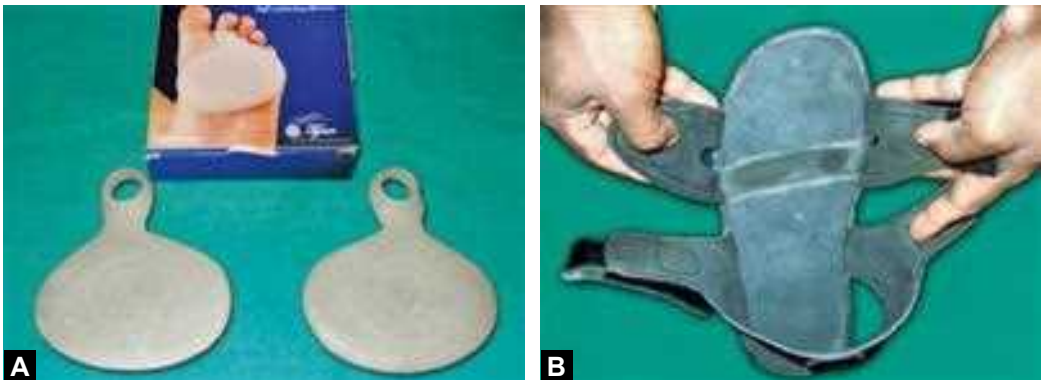
Hallux valgus: In this there is medial migration of the first metatarsal along with rotation and lateral deviation of the hallux (Fig. 12.19A). There is an enlargement of the bursa leading to bunion formation which often ulcerates due to increase in pressure.



Figs. 12.15A to C: (A) Hammer toe; (B) Claw toe; (C) Mallet toe.



Fig. 12.16: Toe cap and toe sleeve for hammer toe, claw toes and mallet toes.



Figs. 12.17A and B: (A) Metatarsal pad for relieving forefoot pressure; (B) Metatarsal bar for forefoot problems. The microcellular rubber bar is placed just proximal to the metatarsal heads.



Fig. 12.18: Rocker bottom sole.



Figs. 12.19A and B: (A) Hallux valgus; (B) Toe separator.

Bunion caps or shields are used to protect ulceration of the area. To prevent worsening of the valgus deformity, toe separators (Fig. 12.19B) are used in the first web space to maintain the anatomy of the big toe.

Ulcers in the forefoot: Ulcers are commonly seen over the first or the fifth metatarsal head. Ulcers may also be present in the plantar surface of the big toe due to injury from a sharp object or more often a rat bite. The footwear can be modified to a clog with relief in the ulcer area. This allows for the patient to be mobile and at the same time takes off the pressure over the ulcerated area even though contact is maintained. The opposite footwear is given a mild height correction to compensate for the clog.

Wedge on the outsole of the shoe to take off pressure from the region of the callus/ulcer.

Addons to the footwear—midfoot abnormalities Abnormal arches of the foot

Pes cavus: A filler pad (Fig. 12.20) made of MCR is fixed on a similar rubber insole of the patient's footwear. Such footwear should have a backstrap so that the foot does not move away from the pad. This pad fills the empty space between the high arch area and the insole of the footwear, thereby enlarging the weight-bearing area of the foot and reducing the pressure on metatarsal heads and heel.

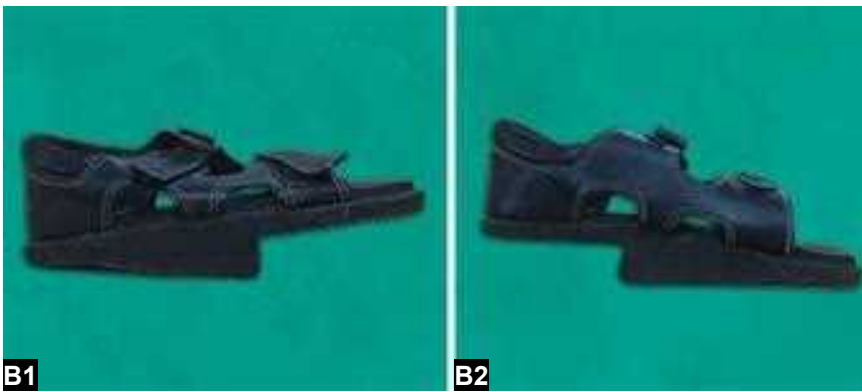
Pes planus: For people with flat feet, an MCR or silicone medial arch support can be given (Figs. 12.21 and 12.22). This helps in supporting and protecting the soft tissue in the medial aspect of the foot and also helps in prevention of plantar fasciitis and metatarsalgia by redistribution of weight.

Midfoot ulcers: Midfoot ulcers especially the medial aspect are generally a result of injury from a sharp object (Fig. 12.23).

Scooping out the insole is done in case of a superficial ulcer or callosity (see Fig. 12.14). In case of deep ulcers, management is preferable with total contact casting or with the use of a Bohler iron orthosis (Fig. 12.24). Alternatively, a clog (Fig. 12.20A) or a wedge (Fig. 12.20B) can be given on the outsole in the area of the ulcer for pressure relief. Addons to the footwear—hind foot ulcers.



Fig. 12.20A: CLOGs are modifications in the outsole given for ulcers in the forefoot, midfoot or hindfoot.



Figs. 12.20B (B1 and B2): Wedge on the outsole of the shoe to take off pressure from the region of the callus/ulcer.



Fig. 12.21: A high arch foot (left) and a tarsal platform fixed below the metatarsal heads and above the heel (middle). The last illustration shows what the microcellular rubber filler pad looks like.



Fig. 12.22: Medial arch support.



Fig. 12.23: Midfoot ulcers.



Fig. 12.24: Patellar tendon bearing boehler iron orthosis - given for complete off loading of the foot for ulcers or amputation wounds in the weight bearing areas.

Hindfoot Ulcers

These ulcers are generally a result of excessive pressure in the heel due to the biomechanical abnormalities. When protective footwear is not used, injury due to sharp objects can also lead to these injuries. One of the more frequent causes of hindfoot ulcers is poor care of the heels (Fig. 12.25). Poor hygiene and contamination can lead to local infection, abscess formation and subsequent ulceration.

Other than footwear modifications in the form of a clog or wedge (Figs. 12.20A and B), the Bohler iron orthosis (*see* Fig. 12.24) and aircast walker (Fig. 12.26A) are more effective in offloading the foot for ulcer healing.

Addons to the sole of the footwear

Heel wedges: This could be given for both the supinated and pronated foot. A heel wedge reduces the stress at the subtalar joint and improves stability by resisting abnormal foot function (Fig. 12.27).



Fig. 12.25: Hindfoot ulcer due to inappropriate footwear (absence of back straps, insole deformed due to abnormal pressures).



Fig. 12.26A: Aircast walker.

Source: Available from www.djoglobal.com/content/aircast-airselect [accessed 10 January 2015]



Fig. 12.26B: Patellar tendon bearing ankle foot orthosis—given for off loading the foot in Charcot's foot.



Fig. 12.27: Both the above illustrations are of right shoes. Medial heel wedge shown in the right illustration correct the excessive pronation; while the lateral heel wedge in the same shoe in the left illustration corrects the excessive supination.

The High-Risk Foot Patients

Patients with this foot will have gross deformities such as extensive scarring, rocker-bottom foot, gangrene and amputation. Besides, they may have ischemic pain and absence of foot pulses in their legs. Generally for this group of patients, special shoes are given. In some instances these shoes are attached to a brace that extends from the ankle to the knee level. Details are as follows:

Molded Shoes (Fig. 12.28): This is prescribed for those who have stable foot and ankle but have extensive scarring in the sole of the foot. Such affected plantar skin is generally incapable of withstanding even the stresses of normal walking and an ulcer may quickly form. The deciding factor for the use of a molded shoe is, if the patient has less than 50% of normal weight-bearing surface. Molded shoes consist of two parts. (1) molded insole and (2) rigid rocker outer sole. The function of the molded insole is to conform to the shape of the foot, enabling the entire plantar surface of the foot to participate in the weight-bearing process. This wider distribution of weight-bearing reduces the risk of high-pressure lesions at vulnerable sites.



Fig. 12.28: The three steps involved in the manufacturing moulded insole. The first procedure is making a negative cast (extreme left). This is done by applying Plaster of Paris (PoP) bandage to the patient's foot in a semi-weight bearing position with knee and ankle at 90° angles. Next step is producing a positive cast (middle) by filling the negative cast with PoP paste. This cast is used as a base to make a moulded insole either with leather and cork (middle and right top) or ethylene vinyl acetate (right bottom).



Fig. 12.29: The foot shown in the left picture has more than 50 percent of plantar skin damage. Such foot may require rigid rocker sandals (middle) or shoes (right) with moulded insole. The “rocker” should be placed proximal to any area for which pressure relief is desired. In the shoe (right), the patient required offloading of pressure in his metatarsal heads; therefore, the “rocker” was placed directly behind the metatarsal heads. In the sandal (middle) the “rocker” at forefoot relieves the pressure at that site by shifting the peak pressure areas posteriorly, to midfoot area.

The rocker sole provides a smooth rocking motion from heel to toe, without requiring either the footwear or the foot itself to bend (Figs. 12.18 and 12.29). This results in very little movement at the MTP joints and subsequently reduces motion at the ankle, subtalar, talonavicular, calcaneocuboid and tarsometatarsal joints. Studies have shown that the rigid rocker sole can reduce 30% of forefoot pressure during the push-off phase of gait by preventing toe hyperextension.

Ankle-Foot Orthosis (Fig. 12.30): Ankle-foot orthosis (AFO) is also known as fixed ankle brace (FAB). It helps to completely immobilize the foot and ankle in cases of instability at the



Fig. 12.30: The foot in the extreme left has swelling due to neuroarthropathic changes at subtalar and ankle joints. This foot needs AFO/FAB till the calf level. Three different types of AFOs/FABs are depicted in the subsequent pictures on the right side. The first picture is a conventional orthosis. The second is made of mouldable plastic sheets; the last picture is made of a resin material, which is bi-valved at calf level. AFO/FAB comprises of orthosis, which extends from the heel to calf level, moulded insole with rigid rocker outer-sole. Conventional orthosis is made of leather, metal strip and cork and also has a closed shoe. Therefore it is much heavier compared to the other two devices.

subtalar or ankle joints. It is prescribed after surgically stabilizing the above instabilities and also after resolution of an acute Charcot's foot (*see Fig. 12.26B*), to protect these joints. It functions by restricting all the joint movements in such feet, thereby reducing stress and protecting the joints. A molded insole can be given to support the deformity and equalize the plantar pressures. Alternatively an aircast walker (*see Fig. 12.26A*) can be used as a pneumatic brace. The air cells in this brace can be adjusted by the patient for a custom fit within the strong plastic shell.

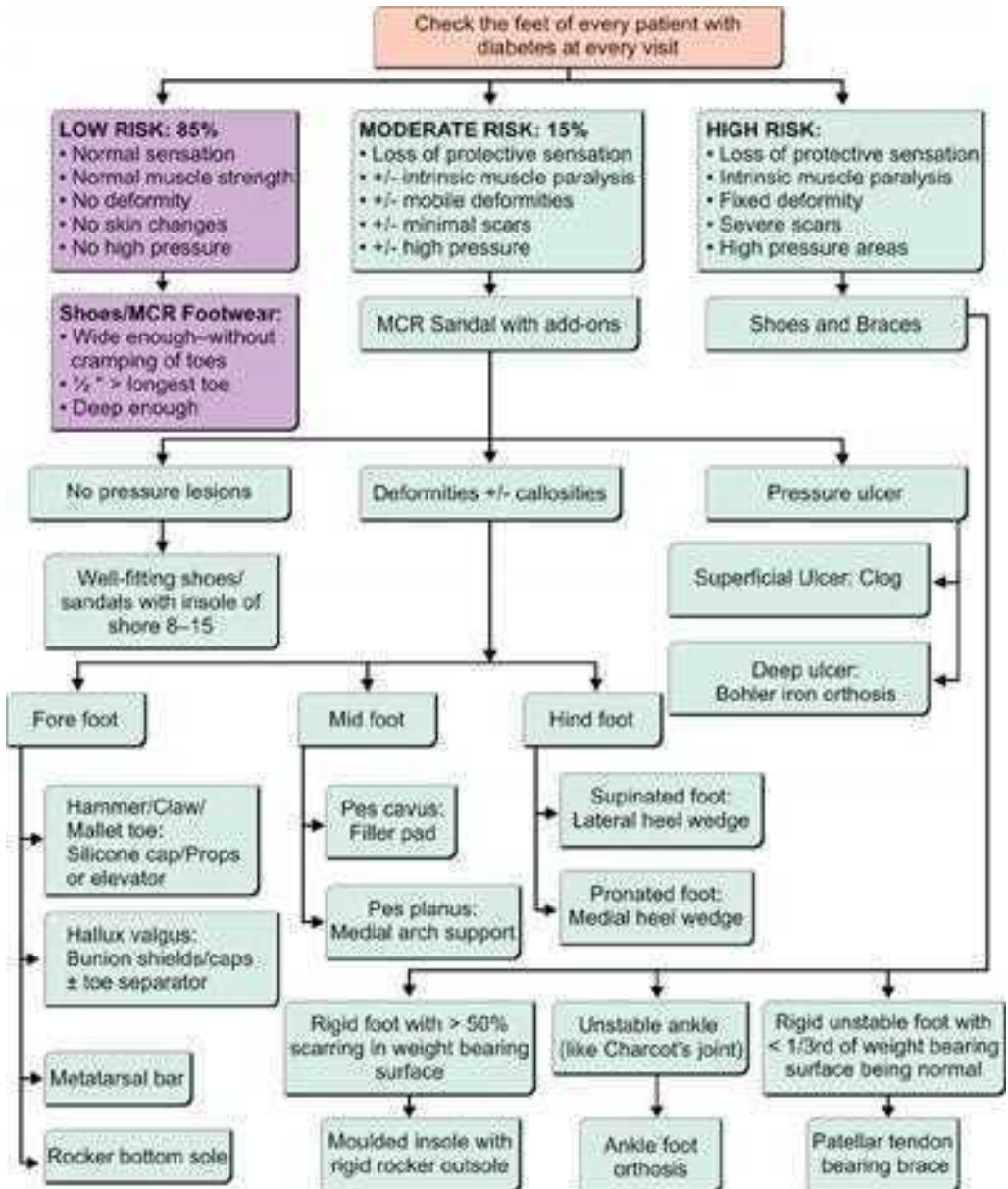
Patellar Tendon Bearing Orthosis (see Fig. 12.23): When there is permanent destruction of joints in the foot, extensive scarring of the plantar surface and a shortened foot becomes insufficient to support the body weight during standing and walking. Such feet require a patella tendon bearing orthosis. This is similar to the AFO/FAB, explained above, the only difference being that the AFO/FAB comes to the level of the calf, whereas in the PTB it extends all the way up to the knee joint. A shelf is made below the patella tendon to bear most of the body weight while the foot bears minimal weight. This is used generally in patients with Charcot's foot who need off-loading and need to continue ambulation.

SUMMARY

Majority of the injuries to the diabetic feet are due to repetitive mechanical stress on the soft tissue with inability of the person to recognize it due to neuropathy. Dorsal ulcers are usually related to footwear and this can be avoided by using a shoe/sandal of the appropriate size/depth. Elevated plantar pressures affect microcirculation, lymph flow and interstitial transport resulting in ischemia in the tissues. The primary goal of the footwear is to redistribute these

forces acting at the foot sole interface equally. Modifications in the footwear are made in the presence of biomechanical abnormalities causing focal pressure areas with a goal of off-loading these areas prone to injury. Shoes with appropriate insoles (shore of 8 to 15) and a curved or rockered outsole are effective in relieving plantar pressures. An excellent footwear

Flowchart 12.1: Algorithm for choosing footwear and braces.



(MCR: Microcellular rubber)

intervention can be a failure if the patient is not compliant with its use. Hence, education and regular follow-up to assess its use and effectiveness are the key factors in the success of any footwear prescribed.

An algorithm for choosing footwear and braces is described in Flowchart 12.1.

ACKNOWLEDGMENT

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SELF-ASSESSMENT

1. **Which of the following is not the mechanism of injury resulting in a plantar ulceration?**
 - (a) Low pressure over a short period of time
 - (b) High pressure over a short period of time
 - (c) Moderate repetitive pressure
 - (d) Low pressure over a long period of time
2. **A 45-year-old lady, with type 2 diabetes presented with a callus on the 5th metatarsal heads bilaterally. She has a history of recurrent ulceration on these sites. Foot examination reveals bilateral motor and sensory neuropathy and high arch foot type. What footwear will you prescribe to off-load 5th metatarsal heads?**
 - (a) Microcellular rubber sandals with medical arch support
 - (b) Microcellular rubber sandals with an insole filler pad and clog/wedge in the outsole for pressure relief
 - (c) Microcellular rubber sandals with filler metatarsal bar
 - (d) All of the above

- 3. A 50-year-old man, with type 2 diabetes presented with a rocker foot deformity. Radiographic investigation shows neuroarthropathic changes in the subtalar and ankle joint. Which foot appliance will you prescribe?**
- (a) Microcellular rubber sandals
 - (b) Fixed ankle brace
 - (c) Patella tendon bearing orthosis
 - (d) None of the above
- 4. Microcellular rubber insole in a sandal:**
- (a) Will not change the total amount of weight borne by the foot
 - (b) Will decrease the amount of weight borne by the foot
 - (c) Will shift body weight from the heels to the ball of the foot
 - (d) None of the above
- 5. What happens to forefoot pressures with an increase in heel height when standing?**
- (a) Nothing
 - (b) It decreases
 - (c) It increases
 - (d) It fluctuates
- 6. The purpose of the rocker bottom sole is to relieve the pressure on the**
- (a) Hindfoot
 - (b) Midfoot
 - (c) Entire forefoot
 - (d) All of the above
- 7. A 48-year-old male, with type 2 diabetes presented with healed scar under the 3rd metatarsal head. Foot examination reveals glove and stocking anesthesia and low arch foot type. What footwear will you prescribe to offload the 3rd metatarsal head?**
- (a) Microcellular rubber sandal with heel wedge
 - (b) Microcellular rubber sandal with combined pad (Medial arch support with metatarsal bar)
 - (c) Microcellular rubber sandal with combined pad (Filler pad with metatarsal bar)
 - (d) Microcellular rubber footwear with back strap
- 8. A 56-year-old male, with type 1 diabetes has no history of foot ulcers or pressure lesion but has stocking anesthesia. What footwear will you prescribe?**
- (a) Microcellular rubber sandal
 - (b) Microcellular rubber sandal with medial arch support.
 - (c) Microcellular rubber sandal with filler pad
 - (d) Microcellular rubber sandal with scooping
- 9. Match the following:**
- 1. Shear stress (a) Measure softness of microcellular rubber
 - 2. Paper grip test (b) Loose fitting footwear
 - 3. Harris mat (c) Detects plantar intrinsic foot muscle paralysis
 - 4. Microcellular rubber (d) Measure foot pressure
 - 5. Durometer (e) A substitute for fatty pad tissue

10. Match the following:

- | | |
|--|--|
| 1. Commercial footwear | (a) Loss of protective sensation with/
without intrinsic muscle paralysis |
| 2. Microcellular rubber sandal with
back strap | (b) Low risk foot |
| 3. Microcellular rubber sandal with
medial arch support | (c) Very badly scarred feet (> two thirds
of weight bearing surface) |
| 4. Patellar tendon bearing brace | (d) Unstable ankle and subtalar joint |
| 5. Fixed ankle brace | (e) Neuropathy with no pressure lesion
in mobile flat feet |

CHAPTER

13

Hypertension

Sudeep K, Jubbin Jagan Jacob

*“When kidneys are involved in the early phase,
The tendency’ is for the pressure to raise,
ACE, ARBs are the drugs which work,
But thiazides surely, we wouldn’t shirk.”*

Cardiovascular diseases are the most common macrovascular complications and the leading cause of death in diabetes. Hypertension is an independent risk factor for vascular diseases and a leading contributor for cardiovascular (CVS) mortality. When hypertension coexists with diabetes, there is a 7-fold increase in mortality. Both diabetes and hypertension synergistically damage the vascular tree resulting in acceleration of retinal, renal, cerebral and coronary vascular diseases.

DEFINITIONS

Hypertension in general population is defined as a blood pressure (BP) above or equal to 140/90 mm Hg. BP is classified as normal, “prehypertension”, stage 1 and stage 2 hypertension (Table 13.1) depending on the systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. The JNC 6 committee recommended that the BP should be below 130/80 mm Hg in patients with diabetes which was endorsed by the JNC 7 committee. The American Diabetic Association also recommended a BP of below or equal to 130/80 mm Hg as the target BP for patients with diabetes. The JNC 8 committee (2014) has recommended a BP of below 140/90 mm Hg as a reasonable target irrespective of the presence or absence of diabetes. It states that in the population aged 18 years or older and with diabetes, pharmacologic treatment has to be initiated and modified to maintain a goal of SBP below or equal to 140 mm Hg and DBP below or equal to 90 mm Hg.

HYPERTENSION AND AGE

In type 1 diabetes, hypertension occurs at the onset of nephropathy. The incidence of hypertension in type 1 diabetes rises from 5% at 10 years to 33% at 20 years and 70% at 40 years

Table 13.1: General classification of hypertension (JNC-7).

BP classification	SBP mm Hg*	DBP mm Hg*	Suggested interventions in DM
Normal	below 120	below 80	Recheck BP at least annually
Prehypertensive (Not a disease category)	120–139	80–89	Try lifestyle modifications only for 3 months before starting drug treatment
Stage 1 hypertension	140–159	90–99	Confirm BP reading and start lifestyle modifications + single drug treatment
Stage 2 hypertension	above or equal to 160	above or equal to 100	Confirm BP reading and start lifestyle modifications + combination drug treatment

*If systolic BP and diastolic BP fall into different categories the higher value should be taken for classification.

(BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; DM: Diabetes mellitus).

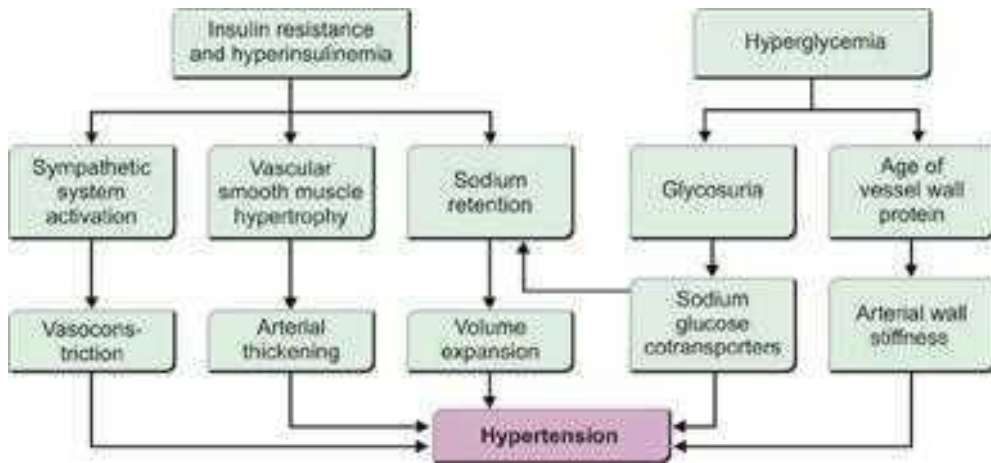
which is closely related to the onset of microalbuminuria and increases progressively as the renal disease progresses. In type 2 diabetes, more than 50% of patients have hypertension even at the time of diagnosis of diabetes. While DBP rises till age 50 and plateaus, SBP progresses with advancing age. In children, the incidence of type 2 diabetes is progressively increasing with increase in the incidence of obesity. Many of these obese children have features of metabolic syndrome. Essential hypertension which was considered uncommon in children is now the most common cause of hypertension in adolescents. In type 1 diabetes, the prevalence of essential hypertension is not different from the general population.

HYPERTENSION AND THE VASCULAR SYSTEM

In hypertension, reduction in elasticity of blood vessels and endothelial damage allows lipids to deposit in the form of atheromas, which in turn leads to thrombus/emboli formation and ischemia. In the heart, concentric left ventricular hypertrophy (LVH) is caused by pressure overload which results in diastolic dysfunction, i.e. compromised relaxation and filling. LVH is an independent risk factor for sudden death as myocardial hypoxia due to increased muscle mass accentuates ischemia and heart failure. Cardiac failure may commence as diastolic dysfunction and eventually progresses to overt systolic failure. Strokes result from thrombosis, thromboembolism or intracranial hemorrhage. There is progressive glomerular injury to the kidneys with progressive albuminuria and subsequent glomerulosclerosis.

PATHOPHYSIOLOGY

A common pathophysiological mechanism contributes to the occurrence/exacerbation of diabetes and hypertension since both are major components of metabolic syndrome (Flowchart 13.1). The underlying insulin resistance and the resultant hyperinsulinemia affect the nitric oxide pathway, sympathetic drive, smooth muscles cells multiplication and sodium fluid status, all contributing to the pathogenesis of hypertension (Table 13.2). Hyperglycemia also has a direct effect on the renin-angiotensin-aldosterone system (RAAS).

Flowchart 13.1: Mechanisms of hypertension in diabetes.

SECONDARY HYPERTENSION

About 5–10% subjects with hypertension have a potentially correctable secondary cause for hypertension. In the presence of clinical or laboratory abnormalities (Table 13.3), evaluation for secondary hypertension is indicated. Even when asymptomatic, preadolescent-onset hypertension, resistant hypertension, hypertension in type 1 diabetes mellitus (DM) without nephropathy, rapid onset hypertension all requires evaluation for a secondary cause. Drugs like nasal decongestants, glucocorticoids, tricyclic antidepressants, sibutramine, amphetamine, cocaine, oral contraceptives, etc. can increase the BP. Endocrine causes like hyperthyroidism and hypothyroidism, Cushing's syndrome, acromegaly, pheochromocytoma and primary hyperaldosteronism (PA) are associated with hypertension and hyperglycemia.

Renovascular Hypertension

About 6% of the populations aged above 65 years, 33% of elderly patients with atherosclerotic coronary artery disease and 50% of patients with diffuse atherosclerotic disease have significant renovascular atherosclerosis. It is an independent risk factor for aggravation of CVS disease, renal failure and activation of RAAS. It should be suspected in high risk groups (Table 13.4). The two most common primary diseases are atherosclerotic renal artery stenosis (ARAS) and fibromuscular dysplasia (FMD). ARAS accounts for 90% of all cases while FMD is the most common cause of RAS in young adults. Significant ARAS is defined as a reduction in the lumen diameter by at least 60%. However, recent studies have failed to show significant progression in ARAS which may be due to the increased awareness for BP control and widespread statin use. Renal revascularization is considered in situations such as resistant hypertension, progressive renal insufficiency in the presence of salvageable kidneys and refractory congestive cardiac failure (CCF) in the presence of bilateral renal artery stenosis. Due to lack of concrete evidences to show that revascularization is beneficial, indiscriminate revascularization ARAS is no longer advisable.

Table 13.2: Pathophysiological mechanism of hypertension in diabetes.

<i>Pathophysiological pathways</i>	<i>Mechanisms involved</i>
Insulin resistance	Receptor specific resistance prevents the favorable effects of insulin on the vascular and fat cells, while the unfavorable effects of insulin are unhindered. The phosphatidylinositol-3-kinase signaling pathway mediated glucose utilization, lipid metabolism and endothelium-dependent vasodilatation (nitric oxide pathway) are defective. On the other hand the extracellular signal-regulated kinase-dependent sodium retention, activation of the sympathetic nervous system, vascular smooth muscle cell (VSMC) proliferation, increase in VSMC cytosolic calcium, induction of endothelin secretion and enhancement of vascular lipid deposition all progress under the influence of hyperinsulinemia.
Sympathetic nervous system	An increase in the sympathetic activity and circulating norepinephrine has been observed in people with insulin resistance and obesity.
Sodium and water retention	Insulin promotes renal tubular reabsorption of sodium via the direct stimulation of the Na/H antiport system or the Na, K-ATPase in the renal tubule.
Renin-angiotensin-aldosterone system (RAAS)	Activation of the RAAS results in unregulated angiotensinogen II activity through its AT1 receptor leading to the formation of reactive oxygen species (ROS). Increase in the activity of the local tissue renin-angiotensin system (especially vascular renin with local generation of angiotensin II) and enhanced arterial sensitivity to angiotensin II is a possible explanation for the progression of nephropathy in spite of the systemic hyporeninemia and hypoaldosteronism.
Sodium-lithium (Na/Li) counter transport	RBC Na/Li counter transport, which represents sodium reabsorption in the proximal tubule, has been found to be overactive in those with diabetes and hypertension. First degree relatives of patients with diabetic nephropathy also display increased activity of Na/Li counter transport.
Genetic factors	Missense mutation of the β_3 -adrenergic receptor gene (<i>ADRB3</i>) is associated with low resting metabolic rate, weight gain, early onset of type 2 diabetes and hypertension. Polymorphisms of the glucocorticoid receptor gene-enhanced activity of enzyme 11 β -hydroxysteroid dehydrogenase type 1 leading to increased fat tissue-specific cortisol production and reduced inactivation of cortisol by altered 11 β -hydroxysteroid dehydrogenase type 2 in fat cells.
Hyperglycemia	Glucose activates the nuclear transcription factor (NF κ B) through a PKC-dependent pathway and upregulates PAI-1 expression and angiotensin II-mediated action. Glycosuria stimulates fluid and sodium reabsorption through the proximal tubule sodium-glucose cotransporters. Hyperglycemia associated protein glycation can lead to arterial stiffness.

(PAI-1: Plasminogen activator inhibitor-1; PKC: Protein kinase C)

Table 13.3: Clinical and laboratory abnormalities in secondary hypertension.

<i>Clinical situations</i>	<i>Etiology to be considered</i>
Headache, flushing, sweating	Pheochromocytoma
Central obesity, uncontrolled hypertension and hyperglycemia, proximal myopathy and skin changes	Cushing's syndrome
Weight gain, edema, goiter, lethargy, diastolic hypertension and bradycardia	Hypothyroidism
Weight loss, goiter, hyperactivity, eye signs, systolic hypertension and tachycardia	Hyperthyroidism
Brachial to femoral systolic blood pressure difference of above or equal to 20 mm Hg	Coarctation of aorta
Resistant hypertension, renal artery bruit, renal impairment, flash pulmonary edema, and/or atherosclerosis in other vascular territories. Worsening creatinine on ACE inhibitors or ARBs	Renal artery stenosis
Apneic spells	Obstructive sleep apnea
Spontaneous or diuretic induced hypokalemia, alkalosis	Hyperaldosteronism
Multiple drug intake (including over the counter drugs)	Drug-induced hypertension

(ACE: Angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker).

Table 13.4: Evaluation for renovascular hypertension.

<i>Patients with the following features should be screened for renal artery stenosis with an ultrasound Doppler of the renal arteries</i>
<ul style="list-style-type: none"> • Resistant hypertension • Deterioration in renal functions on adding ARB or ACE inhibitor • Unexplained renal failure with no urine sediments • Patients with episodes of flash pulmonary edema with normal left ventricular functions • Patients presenting with malignant hypertension.
<i>Patients with following features should be screened for PA with a morning plasma aldosterone-renin ratio</i>
<ul style="list-style-type: none"> • Resistant/ severe hypertension (when not controlled in spite of three antihypertensive drugs) • Spontaneous or diuretic induced hypokalemia • Young patients with cerebrovascular disease (< 40 years) • Patients with adrenal incidentalomas • In all hypertensive first-degree relatives of patients with PA

(ACE: Angiotensin-converting-enzyme; PA: Primary hyperaldosteronism).

Primary Hyperaldosteronism

Primary hyperaldosteronism is characterized by autonomous production of aldosterone by an adrenal adenoma or by unilateral or bilateral adrenal hyperplasia resulting in low-renin hypertension, sodium retention and hypokalemia. It is associated with a higher CVS morbidity and mortality when compared to essential hypertension. More than 10% of hypertensive patients are likely to have PA. Screening is recommended in high risk groups (Table 13.4).

Some experts propose screening for PA in those patients with diabetes who do not meet their BP goals in spite of treatment with more than three antihypertensive drugs. DM is more prevalent in patients with PA than in hypertensive controls (23 vs 10%). The mechanisms for impairment in glucose and lipid metabolism include the diabetogenic effect of hypokalemia (impaired insulin release) and effects of aldosterone on the insulin receptor and adipose tissues. As most antihypertensive agents interfere with renin activity (angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB) and diuretics increase while β -blockers decrease), plasma aldosterone-renin ratio (ARR) in the morning sample is used as the screening test. The diagnosis is confirmed with suppression tests (either by saline loading or by using fludrocortisone) which are followed by adrenal imaging using a CT scan.

MANAGEMENT OF HYPERTENSION

Screening and Initial Evaluation

- Seat the patient quietly for about 5 minutes with both feet flat on the floor
- They should be stress-free and should have refrained from smoking, exercise, alcohol or caffeine at least 30 minutes prior to BP measurement
- The bare arm supported at the level of the heart should be used
- An appropriate sized cuff that covers 80% of the arm should be used. The apparatus should have been properly maintained and validated
- Take at least two measurements, especially if the first measurement is high
- Orthostatic measurement should be performed.



Blood pressure readings are considered accurate when an average of two or more proper measurements on each of two or more office visits is taken. BP should be measured at every routine visit for diabetes and a SBP of above or equal to 140 mm Hg or a DBP of above or equal to 90 mm Hg should be confirmed on a separate day. On diagnosis, patient should be evaluated for CVS disease, CVS risk factors and diabetes related complications. The initial laboratory assessment includes renal function tests, hemogram, serum electrolytes, urine albumin, urine microscopic examination, electrocardiogram and lipid profile. Based on the investigation reports and clinical features, additional investigations to assess for end-organ damage and tests to rule out secondary hypertension should be ordered.

Target Blood Pressure

Similar to glycemic control, control of hypertension is important in all subjects with diabetes. The United Kingdom Prospective Diabetic Study (UKPDS) group had shown a significant reduction in stroke; CVS morbidity and diabetes-related mortality after achieving tight BP control (mean BP 144/82 mm Hg). Each 10 mm Hg of SBP reduction was associated with a 12% reduction in any complication related to diabetes, 15% reduction in the deaths due to diabetes,

11% reduction in myocardial infarction and 13% reduction in microvascular complications. Also the benefits reaped (DBP, 87 mm Hg vs 82 mm Hg) were better than those of intensive glucose control (mean HbA_{1c} level 7.9% vs 7.0%), with a 2–5 fold absolute risk reduction and much lower numbers needed to treat. A DBP of below 80 mm Hg was associated with 50% lesser morbidity than those who had a higher DBP in the hypertension optimum trial (HOT) study. Hence in the presence of coexisting diabetes or chronic kidney disease, a target BP of below or equal to 130/80 mm Hg was recommended by the JNC 7 committee. Therapy was recommended in prehypertension if lifestyle modification failed to bring the BP to below or equal to 130/80 mm Hg. Even though there is no defined lower limit, reducing the DBP to below 60 mm Hg has an adverse CVS outcome and carries the burden of excess cost.

JNC 8 report: The committee considered that the evidences available to recommend a BP below 130/80 mm Hg in adults with diabetes and hypertension are insufficient and has pointed out that none of the randomized control trials (RCTs) have addressed the question of whether treatment to an SBP goal of lower than 140 mm Hg improves health outcomes. Except for the reduction in total stroke events, there were no differences in the primary outcome, a composite of CVS death, nonfatal myocardial infarction and nonfatal stroke in action to control cardiovascular risk in diabetes-blood pressure (ACCORD-BP) trial. Hence a target BP of below or equal to 140/90 mm Hg has been recommended for all hypertensive groups irrespective of their age, diabetic status and renal function. However, it has to be noted that the target BP proposed by JNC 8 is grade E recommendation (expert opinion based on insufficient evidence). Even in well-designed RCT such as the HOT trial where there was intensive volunteer follow-up, only about 50% of the subjects could achieve the target BP. Hence the BP targets need to be individualized so as to prevent worsening of renal and CVS function.

Nonpharmacologic Therapy of Hypertension

Initiation of lifestyle modifications like dietary changes, cessation of smoking and moderation of alcohol consumption even at the prehypertensive stage are very important for successful hypertension management. The dietary approach to stop hypertension (DASH) diet plan with low sodium, low calorie, high potassium and high fiber in the diet has been proven to be beneficial (Table 13.5). A decrease in the daily total salt intake from 4.5 g to 2.3 g can reduce SBP by 5 mm Hg and DBP by 3 mm Hg. Simple physical activities like walking (30–45 minutes for at least 5 days a week), jogging, cycling and swimming help in reducing body weight, sympathetic pressor tone, insulin resistance, lipid levels and impart physical and social well-being. Weight reduction has been shown to lower the need for medications (one kg weight loss accounts to 1 mm Hg fall in BP).

Pharmacotherapy of Hypertension

If lifestyle modification fails to control BP to below 140/90 mm Hg, pharmacotherapy has to be initiated (Table 13.6). There is limited data from trials comparing different classes of antihypertensive drugs in diabetes and the choice is based on their ability to prevent adverse CVS events and progression of renal disease. Even though certain groups have been shown

Table 13.5: Lifestyle modifications for hypertensive subjects.

Lifestyle components	Modifications advised
Physical activity	Moderate-intensity activity 30–45 minutes a day, at least 5 days a week
Smoking	Complete abstinence
Alcohol	Two drinks per day for men and one drink per day for women
Sodium	To less than 2.4 g per day
DASH diet	6–8 servings of whole grains; 4–5 servings of fruits, vegetables; saturated fat 6% of total calories; total cholesterol intake to less than 150 mg/day. Adequate potassium and magnesium in diet
Weight loss	To maintain BMI less than 25 kg/m ²

(BMI: Body mass index; DASH: Dietary approach to stop hypertension).

Table 13.6: Antihypertensive drug classes.

Class	Drugs and dosage	Side effects	Practical considerations
Diuretics reduce plasma volume, cardiac output and peripheral resistance	1) Thiazides hydrochlorothiazide 12.5/25/50 mg Indapamide 1.25/2.5 mg 2) Loop diuretic frusemide—10/20 mg 3) Potassium sparing spironolactone 25/50/200 mg	Hypokalemia, hypomagnesemia, erectile dysfunction <i>Thiazides:</i> hypercalcemia, hyperuricemia, hypergly- cemia, hyponatremia K ⁺ sparing diuretic: hyperkalemia	Cheaper, effective in elderly, volume over-load states and in systolic hypertension; have morbidity and mortality reduction benefit; loop diuretics used when GFR is below or equal to 50 mL/minutes/m ² and resistant BP
Angiotensin converting enzyme inhibitors (ACEI) Reduce aldosterone increase bradykinin and prostacyclin	Captopril 6.25/12.5/25 mg Ramipril 2.5/10/20 mg Enalapril 5/10/20 mg Lisinopril 5/10/20 mg Perindopril 2/4/8 mg	Cough, postural hypotension, skin rashes, angioedema, renal failure, hyperkalemia, teratogenicity; contraindicated in bilateral renal artery stenosis;	Reduce all-cause and CVS mortality; renal protection; favorable metabolic profile; contraindicated in pregnancy;
Aldosterone receptor blocker (ARB) Block aldosterone I and II receptors	Losartan 25/50/100 mg Irbesartan 150/300 mg Valsartan 40/80/320 mg Telmisartan 20/ 40/80 mg Olmesartan 20/40 mg	Similar to ACE inhibitors; but no cough	First alternative for ACE inhibitors intolerance; renal protection proven; studied more in type 2 DM; costlier.
Beta-blockers Decrease in cardiac output and decreased peripheral resistance	Cardio selective Atenolol 25/50/100 mg Metoprolol 25/50/150 mg Bisoprolol 5/10/20 mg $\alpha + \beta$ blocker Labetalol 100/200/400 mg Carvedilol 12.5/25/50 mg	Should not be discontinued abruptly; bronchoconstriction, bradycardia, vasospasm, erectile dysfunction, dyslipidemia	Cardio protective; Reduced CV mortality; mainly in diabetics with CAD and supraventricular tachycardia

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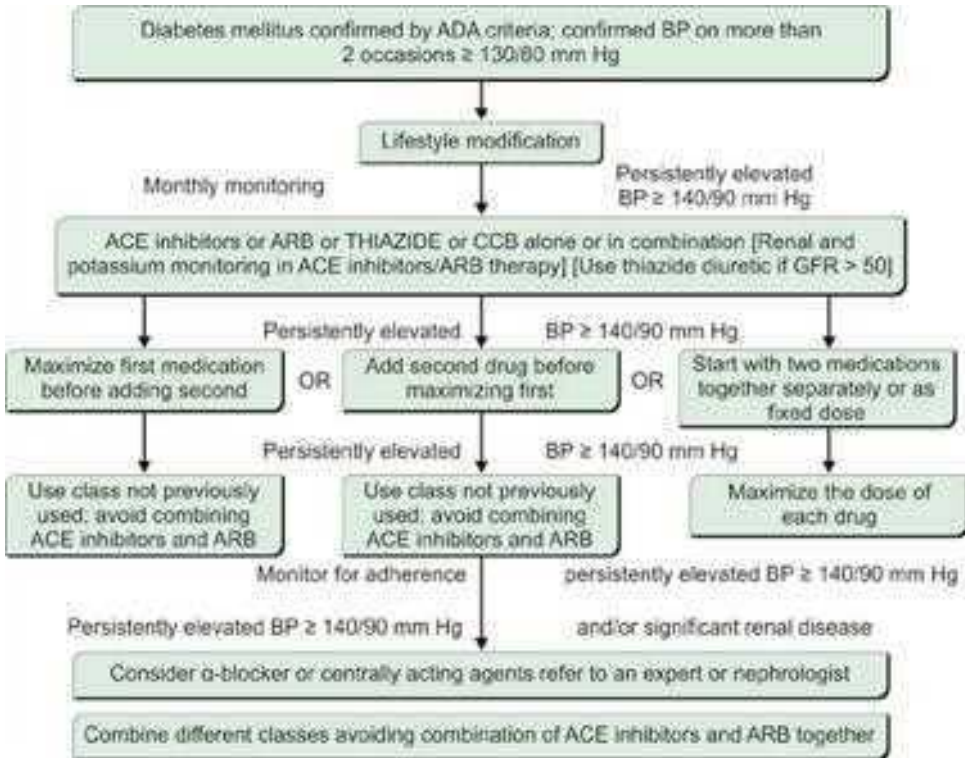
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Class	Drugs and dosage	Side effects	Practical considerations
Calcium-channel blockers Vasodilators; increase renal blood flow;	DCCB Nifedipine 30/60/120 mg Amlodipine 5/10 mg Nisoldipine 10/20/60 mg Cilnidipine 5/10/20 mg Non-DCCB Verapamil 40/80/240 mg Diltiazem 30/60/120 mg	Flushing, headache, pedal edema, heart failure and heart block	No metabolic or sexual disturbances; antianginal; useful in elderly and Raynaud's phenomenon
α -1 adrenergic receptor blockers	Prazosin 2.5/5/10/20 mg Doxacin 1/2/4 mg	Postural hypotension, cardiac failure tachycardia, edema	Improve insulin sensitivity, are lipid neutral; useful in BPH
Central sympatholytics	Methyldopa 250/500/1,000/2,000 mg	Sedation, hepatotoxicity, hemolytic anemia	Can be used in pregnancy; increases renal blood flow.
Central α -2 agonists	Clonidine 0.1/0.2/0/6 mg	Dry mouth, sedation, erectile dysfunction; rebound high BP	Clonidine can bring down BP rapidly
Peripherally acting adrenergic antagonists	Reserpine 0.1/0.25 mg	Depression, lethargy, weight loss, peptic ulcer, diarrhea, erectile dysfunction	Neutral metabolic effect; cheaper
Imidazoline receptor agonists central action at brain stem; reduce sympathetic activity	Moxonidine 0.2/0.4 mg Rilmenidine 1.0/2.0 mg	Supraphysiological doses produced heart failure; contraindicated in angioedema; can produce bradycardia; should be avoided while on β blocker	Improve insulin sensitivity, are lipid neutral; can promote sodium excretion

(CVS: Cardiovascular; CAD: Coronary artery disease; DCCB: Dihydropyridine calcium-channel blockers; BP: Blood pressure; GFR: Glomerular filtration rate; BPH: Benign prostatic hypertrophy; DM: Diabetes mellitus).

to have advantage, it is the degree of BP reduction rather than the drug class that should be considered primarily. Majority of the studies have used ACE inhibitors, ARB and diuretics as the first line of therapy. ACE inhibitors/ARB in hypertensive diabetic patients with albuminuria have been shown to improve CVS mortality and reduce the decline in glomerular filtration rate (GFR).

The JNC 8 report: It recommends (grade B) thiazides, calcium-channel blockers (CCB), ACE inhibitors or ARB as the initial agent for nonblack subjects. For black subjects it recommends (grade C) thiazides and CCBs over ACE inhibitors as first line drugs. The group found convincing evidence for thiazides to be more effective than ACE inhibitors in improving cerebrovascular, heart failure and combined CVS outcomes in blacks. Except for heart failure outcomes, CCBs were found to be similar to thiazides. The panel has recommended CCBs over ACE inhibitors due to superior stroke prevention and more effective BP control.

Flowchart 13.2: Treatment approach to a patient with diabetes and hypertension.

Note: 1. In case of established coronary artery disease, β -blocker can be considered.

2. If GFR more than equal to 50 mL/minutes, loop diuretics should be used instead of thiazides (ADA: American diabetes association; ACE: Angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker; CCB: Calcium-channel blockers; GFR: Glomerular filtration rate).

Combination of drugs: Majority of patients require two or more drugs to achieve satisfactory BP control. Once a patient requires more than one drug, a second drug with an alternative mechanism of action has to be utilized (Flowchart 13.2). Fixed dose combinations can be used if it suits the individual. Adverse effects like dyslipidemia, hyperglycemia, dyselectrolytemia, worsening renal function, edema, cardiac failure, peripheral vasoconstriction, sexual dysfunction and bronchoconstriction are a matter of concern with some antihypertensive drugs. Dual RAAS inhibition with ACE inhibitors plus ARBs or ACE inhibitors plus direct renin inhibitors (DRIs) has not consistently shown to improve CVS or renal outcomes and is associated with serious adverse events. It is not advocated at present.

ANTIHYPERTENSIVE DRUGS (SEE TABLE 13.6)

Thiazides: Most commonly used as antihypertensive diuretics and are effective when the GFR is above or equal to 50 mL/minute/m². They effectively reduce volume expansion and are

complimentary to ACE inhibitors/ARB. They are associated with lower risk of heart failure, stroke, combined CVS events, all-cause mortality and have been found to be as effective as ACE inhibitors (Lisinopril) in reducing all-cause mortality. Metabolic side effects are a matter of concern with higher doses.

Angiotensin-converting-enzyme inhibitors and angiotensin receptor blocker: Angiotensin-converting-enzyme inhibitors have favorable effects on renal and CVS outcomes, as demonstrated in the micro-HOPE study. This effect may be independent of BP reduction. The recent ONTARGET study demonstrated similar benefits with telmisartan indicating that ARBs are equivalent to ACE inhibitors. Recent studies have shown reduction in CVS morbidity and mortality in subjects with LVH. They are lipid neutral, lower plasma glucose and reduce albuminuria. Hyperkalemia, dry cough and worsening renal functions need monitoring. Following the initiation of ACE inhibitors, an elevation in serum creatinine occurs temporarily along with a transient fall in GFR both of which may improve subsequently. If the serum creatinine rises by less than 30% or if there is hyperkalemia, then ACE inhibitors/ARBs should be stopped.

Calcium-channel blockers: Non-dihydropyridine CCBs (e.g. diltiazem, verapamil) have antialbuminuric effect and no adverse metabolic effects. But their renoprotective effect is lesser than ACE inhibitors. Some smaller studies have shown an excess of cardiac events in patients treated with dihydropyridine calcium channel blockers (DCCBs) compared with ACE inhibitors. However when DCCBs were combined with ACE inhibitors, β -blockers and diuretics as in the HOT study and the systolic hypertension in Europe (Syst-Eur) trial, they did not appear to be associated with increased CVS morbidity. Cilnidipine (N-type and L-type calcium-channel inhibitor) which inhibits excessive release of norepinephrine from the sympathetic nerve ending is supposed to have a more favorable effect on glucose and lipid metabolism and renal functions when compared to amlodipine (L-type calcium-channel inhibitor).

Beta-blockers: They are particularly important in patients with diabetes who have coronary artery disease and unstable angina. They reduce postmyocardial infarction mortality. Combined nonselective β -blockers like carvedilol have the advantage over drugs like metoprolol and atenolol in that worsening of glycemic control is absent and antialbuminuric effect has been documented. However they are not used as the primary agent for hypertension. Masking of hypoglycemia and worsening of peripheral vascular disease has been a concern with nonselective β -blockers.

Other drugs: There is very little information on the benefits of other group of antihypertensive drugs (α -blockers, loop diuretics and central agents) in diabetic population. An increased incidence of new onset heart failure was seen in the ALLHAT study when they were on α -blockers. Hence they can be best used as an alternative when other agents are not tolerated or if there are coexisting problems like benign prostatic hyperplasia. Antihypertensive drugs known to be effective and safe in pregnancy include methyl dopa, labetalol, diltiazem, clonidine and prazosin. Moxonidine is a centrally acting imidazoline receptor type 1 (found in the ventromedial and venterolateral pressor areas of brain stem) agonist. They reduce the sympathetic nerve activity, promote sodium excretion; improve insulin resistance and glucose tolerance.

PRINCIPLES IN MANAGEMENT OF HYPERTENSION (SEE FLOWCHART 13.2)

- All patients with diabetes and hypertension should maintain their BP below 140/90 mm Hg. Drug therapy should be initiated in addition to lifestyle modification. The target may be lowered to below 130/80 in those with proteinuria without producing adverse effects.
- When a preferred group of antihypertensive drug is not tolerated or is contraindicated an alternative agent should be initiated to achieve the target BP. In case of postural fall in BP, salt and fluids intake and medication dose should be titrated carefully.
- In the presence of albuminuria and nephropathy the first line drug is ACE inhibitors/ARB unless there is a contraindication. In patients with type 1 diabetes with any degree of proteinuria, ACE inhibitors have been shown to delay the progression. If ACE inhibitors are not tolerated, ARBs may be used. In type 2 diabetes with macroalbuminuria (> 300 mg/24 hours), ARBs should be strongly considered. If ACE inhibitors/ARBs are used, monitor renal function and serum potassium levels. In situations where such monitoring is not possible, ACE inhibitors/ARB should be avoided and thiazide/CCBs should be initiated.
- In those without albuminuria initial drug can be ACE inhibitors/ARB/thiazide/CCB
- Beta-blockers are particularly effective in coronary artery disease especially in postmyocardial infarction.
- Those patients who are not achieving the target BP in spite of three drugs including a diuretic and those with renal impairment should be referred to an expert. Urine analysis for active sediments and renal artery Doppler should be ordered in appropriate situation.
- Home BP monitoring and ambulatory BP monitoring: It helps to unmask previously undiagnosed hypertension and “white-coat hypertension”. A more practical approach to assess the above problems and is particularly useful in assessing BP in smokers as smoking acutely increases BP. It helps in identifying apparent drug resistance (office resistance), hypotensive symptoms with drugs, episodic hypertension and in autonomic dysfunction.

SUGGESTED READING

1. Cheung BM. The hypertension-diabetes continuum. J Cardiovasc Pharmacol. 2010;55(4):333-9. Review

SELF-ASSESSMENT

1. **The target blood pressure (BP) goal in a patient with diabetes is according to JNC 8 recommendations is:**
 - (a) 130/85 mm Hg
 - (b) 140/90 mm Hg
 - (c) 130/80 mm Hg
 - (d) 125/80 mm Hg
 - (e) 135/85 mm Hg
2. **Following is true about angiotensin-converting-enzyme (ACE) inhibitors *except*:**
 - (a) Favorable renal and cardiovascular outcome
 - (b) First-line drug in the management of macroalbuminuria in diabetes
 - (c) Contraindicated in bilateral renal artery stenosis

- (d) Serum potassium levels need to be monitored
- (e) Can be used safely in pregnancy

3. Which is the false statement?

- (a) β -blockers are favored in patients with ischemic heart disease (IHD)
- (b) Calcium-channel blockers (CCBs) can reduce coronary events and albuminuria
- (c) Thiazides are preferred in end-stage renal failure
- (d) Beta-blockers should be preferably avoided in patients with peripheral vascular disease
- (e) Angiotensin receptor blocker (ARBs) have renoprotective effect

4. The following are true about *except*:

- (a) Moxonidine decreases sympathetic activity
- (b) Imidazoline group of drugs act on the brainstem and have a favorable metabolic profile
- (c) α -methyldopa is safe in pregnancy
- (d) Cilnidipine belongs to centrally acting group of drugs
- (e) α -1 receptor antagonists have a risk of precipitating cardiac failure

5. Pick up the correct statement about renal artery stenosis:

- (a) Atherosclerosis is the commonest cause for renal artery stenosis
- (b) It should be suspected in uncontrolled severe hypertension and acute pulmonary edema
- (c) Progression of stenosis has been shown to be slow with medical therapy
- (d) To be called as significant stenosis, the lumen diameter should be compromised by at least 60%
- (e) Once diagnosed angioplasty or bypass surgery should be done in all patients

6. Which of the following micronutrients do not have an inverse relationship with blood pressure?

- (a) Sodium
- (b) Calcium
- (c) Potassium
- (d) Magnesium

7. Which of the following antihypertensive of choice for a 65-year-old gentleman with type 2 diabetes and left ventricular dysfunction?

- (a) α methyldopa
- (b) Diuretics
- (c) Beta-blockers
- (d) Calcium-channel blockers (CCB)
- (e) α -blockers

8. One kilogram of weight loss results in lowering of the mean arterial pressure by:

- (a) 3 mm Hg
- (b) 2 mm Hg
- (c) 4 mm Hg
- (d) 1 mm Hg
- (e) 5 mm Hg

9. Twenty-five-year-old with type 1 diabetes has bilateral nonproliferative retinopathy. Which of the following drugs has maximum impact on renal function?

- (a) Diltiazem
- (b) Lisinopril
- (c) Atenolol
- (d) Moxonidine
- (e) Amlodipine

10. Moderate salt restriction results in a lowering of diastolic blood pressure of:

- (a) 1-2 mm Hg
- (b) 5-6 mm Hg
- (c) No improvement in diastolic blood pressure (DBP)
- (d) 4-5 mm Hg
- (e) 2-3 mm Hg

CHAPTER

14

Nephropathy

Santosh Varghese, Suceena Alexander

*“Hey man! How’s your GFR?
Take ACE inhibitors and you’ll get far,
With ARBs they may be the next,
Avoid NSAIDs and you won’t be vexed”*

Diabetes has become the most common cause of chronic kidney disease (CKD) in most countries. This is due to the fact that diabetes, particularly type 2, is increasing in prevalence and these patients now live longer. Patients with diabetic CKD are now accepted for renal replacement therapy (RRT) programs where formerly they had been excluded. About 20–30% of all patients with type 1 or type 2 diabetes develop evidence of nephropathy. The onset and course of diabetic nephropathy can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if instituted at a point very early in the course of the development of this complication. Once CKD develops, therapy must be geared toward slowing the progression and prevention of complications and where that fails, preparation for RRT.

INTRODUCTION

With increases in the prevalence of type 2 diabetes, aging population and obesity, diabetic nephropathy is vast assuming alarming proportions as many of them develop CKD. In fact, nearly the world over, diabetes has become the most common cause of CKD in adults. Detection of proteinuria is the hallmark of diabetic nephropathy. Domenico Cotugno was perhaps the earliest to detect and describe proteinuria in patients with diabetes in his *De Ischiade Nervosa Commentarius* in 1765. Knowledge of the natural history of diabetic nephropathy, its clinical presentation, progression and treatment options is crucial for all physicians who care for patients with diabetes.

The incidence of nephropathy differs between type 1 and 2 diabetes. In type 1 diabetes, overt nephropathy occurs after 15–20 years of diagnosis and is seen in about 25–40% of patients. The number seems to have decreased possibly due to better glycemic control and earlier initiation of therapy targeted at preventing microvascular complications. In type 2 diabetes, however, although the cumulative incidence is 25% after 20 years of diagnosis, in about 5–10%, diabetic nephropathy will be present at the time of diagnosis itself. The latter again

is a feature underscoring the need for early diagnosis of diabetes mellitus through screening programs, etc. Though unlikely to be causally related, mortality is higher in those who have proteinuria with the risk being higher for those with markedly increased albuminuria (formerly known as macroalbuminuria) as compared to those with moderately increased albuminuria (formerly known as microalbuminuria).

DEFINITIONS

Diabetic nephropathy: Clinical syndrome characterized by persistent albuminuria (>300 mg/24 hours or >200 μ g/minute) on at least two occasions separated by 3–6 months. (Albuminuria >300 mg/24 hours is equivalent to a total proteinuria >500 mg/24 hours). This is also called severely increased albuminuria (formerly macroalbuminuria).

Moderately increased albuminuria (formerly microalbuminuria): Urine albumin excretion of 30–300 mg/24 hours or 20–200 μ g/minute.

RISK FACTORS

The most important risk factor for the development of diabetic nephropathy is poor glycemic control. In patients with poor glycemic control, uncontrolled hypertension may predispose them further as was noted by studies that showed that those with HbA1c more than 12% and uncontrolled hypertension were at a higher risk for developing nephropathy when followed up for 20 years. Risk factors like hyperglycemia induced glomerular hyperfiltration, obesity, smoking, dyslipidemia, degree of proteinuria at diagnosis and dietary factors, including amount and type of ingested protein and fat have also been suggested as possible contributing factors. Individuals who develop type 2 diabetes after the age of 50 years are considered more prone to nephropathy. Family history of hypertension and cardiovascular events in the first degree relatives may act as a sentinel to warn of impending development of nephropathy. Intrauterine exposure to high blood sugars may also increase the risk of developing nephropathy.

However, it has also been observed that in a group of patients with prolonged periods of uncontrolled blood sugars, only 40% actually develop nephropathy. This has led to the speculation that some have inherent susceptibility to diabetic nephropathy. The reasons for this are incompletely understood. Familial clustering of diabetic nephropathy, like diabetes itself has been described. Polymorphisms in angiotensin-converting enzyme, angiotensin 2 receptor, aldose reductase genes and others are implicated as the candidate genes. In both type 1 and 2 diabetes mellitus, males are more prone to develop nephropathy. Certain ethnic populations (Blacks, Mexican Americans, Pima Indians and South Asians) are at greater risk for developing nephropathy.

CLASSIFICATION

Carl Erik Mogensen's classical description in 1983 of the five stages of diabetic nephropathy was for type 1 diabetes mellitus. However, the general pattern remains the same for type 2 diabetes as well. These are briefly detailed below with emphasis on the clinical correlation (Fig. 14.1).

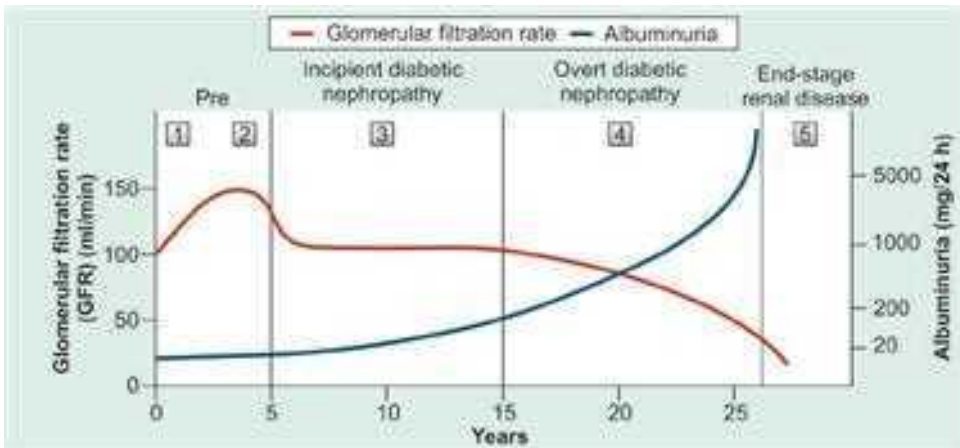


Fig. 14.1: Stages of diabetic nephropathy.

Stage 1: Stage of renal hypertrophy and glomerular hyperfiltration: In this stage, there is renal hypertrophy, glomerular hyperfiltration and increase in glomerular filtration rate (GFR). This sets in when the blood sugars are uncontrolled and both glomerular hyperfiltration and increased GFR return to baseline with institution of good control of blood sugars.

Stage 2: Stage of apparent normalcy: This stage is clinically silent and lasts for 5–15 years. Glomerular hyperfiltration continues during this period and is related to the degree of hyperglycemia. If the blood sugars are above 250 mg/dL, there will be a reduction of GFR, which is otherwise not a regular characteristic of this stage.

Stage 3: Stage of moderately increased albuminuria (formerly microalbuminuria) or incipient nephropathy: This stage typically occurs after 6–15 years after the diagnosis of diabetes and occurs in about 20–30% of patients with type 1 diabetes. The albumin excretion in the urine is in the range of 30–300 mg/24 hours. There are two more important characteristics of this stage. There is a small increase in the blood pressure and a loss of the normal “dipping” of the nocturnal blood pressure. The GFR usually remains almost stable in this stage. To avoid false positives (e.g. following strenuous exercise, excessive protein intake, fluid overload, urinary tract infections and pregnancy), the test should be repeated within three months. Other associations reported with moderately increased albuminuria are dyslipidemia, retinopathy, amputation and increased cardiovascular disease. Moderately increased albuminuria also predicts increased cardiovascular mortality. Hence, the patient may die before uremia sets in. The impact of nephropathy on survival is discussed below.

This stage is arguably the most important; since, although diabetic nephropathy has set in, it is potentially reversible. This degree of albuminuria may remain stable or regress with blood sugar and blood pressure control and fortunately, less than 50% progress to the next stage, i.e. overt nephropathy.

Stage 4: Stage of overt (or established) nephropathy: This stage sets in typically after 15–18 years after a diagnosis of diabetes is made and occurs in 25–45% of patients. Unlike the previous stage, this stage is irreversible and all attempts are aimed at preventing patients from reaching

this stage. With good glycemic control (HbA1c <7.0) the number may be as low as 8.9%. In this stage, proteinuria increases and nephrotic syndrome is common. Most patients will have hypertension now and the GFR declines in the majority and at a rate as high as 10 mL/minute/year. The progression of disease is usually unremitting in type 1 and many patients progress to stage 5. In type 2, however, the progression to stage 5 is not invariable and in many, the proteinuria may actually regress to lower levels. This stage is also associated with dyslipidemia and asymptomatic myocardial ischemia.

The risk for renal failure doubles when baseline protein value doubles, whereas halving of proteinuria decreases the risk of renal failure by half.

Isolated microscopic hematuria may occur in up to 66% of patients with overt diabetic nephropathy and by itself, does not imply a proliferative glomerular disease as was previously thought. However, red blood cells (RBC) casts are uncommon and may suggest the presence of the latter, especially when accompanied by rapid worsening of renal function.

Stage 5: End stage renal disease: The terminal stage of diabetic nephropathy typically occurs about 25 years or more after the initial diagnosis of diabetes and after a median of 7 years after the stage of overt nephropathy. In those with poor glycemic diagnosis of diabetes, the incidence is less than 2%, once again underscoring the importance of blood sugar control.

By comparison, the rate of decline of GFR in type 2 diabetes with overt nephropathy can range from 1 mL/minute/year to 20 mL/minute/year, though usually it is 5–10 mL/minute/year. The rate of decline of GFR is generally predictable in a patient unless another illness superimposes causing a steep decline in the GFR.

Those who progress rapidly are characterized by poorer glycemic control, higher blood pressures, initial high urine albumin excretion rates (AER), hypercholesterolemia and smoking.

SURVIVAL IN PATIENTS WITH DIABETIC NEPHROPATHY

In both type 1 and type 2 diabetes, diabetic nephropathy increases mortality risk. While diabetes itself increases the risk of death about 2-fold, this risk reaches 20–200-fold in those with nephropathy. The increased risk of dying starts from the upper normal range of microalbuminuria itself and hence, the need for prevention of nephropathy by glycemic control. Albuminuria is a reflector of endothelial cell dysfunction and is associated with increased atherosclerosis, hypertension, dyslipidemia, increased inflammatory markers, platelet aggregation, cardiovascular risk and autonomic neuropathy. The latter may predispose to arrhythmias and risk of death.

PATHOGENESIS OF NEPHROPATHY

The primary insult to the kidneys in a patient with diabetes is hyperglycemia. In the patient who develops nephropathy, hypertension and proteinuria add insult to the injury. It is postulated that an increase in the intracellular glucose leads to its oxidation and oxygen free radical generation. This step results in activation of four pathways that finally result in the development of nephropathy. These are the protein kinase c pathway, polyol pathway, hexosamine pathway and formation of advanced glycation end products. The end result is overproduction of cytokines like transforming growth factor beta (TGF- β 1), connective

tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), AT1, prorenin, etc. which induce fibrosis and increase vascular permeability. Systemic and intraglomerular hypertension exert mechanical stress over the extracellular matrix and mesangial cells and induce expression of similar cytokines. The intraglomerular hypertension in diabetic kidneys is due to a selective vasodilatation of the afferent arterioles. Once proteinuria starts, it further damages the kidney because accumulation of protein in the tubular cells initiates epithelial mesenchymal cell transformation, leading to formation of fibroblasts, matrix formation and chronic tubular injury. Chronic tubular hypoxia is another mechanism of direct damage to tubules in diabetic nephropathy, both for initiation and progression of disease. Despite the description of the possible pathogenetic mechanisms, there is no single clinically useful agent or drug available that has been shown to consistently interrupt the development of nephropathy.

PATHOLOGY

There are three main changes that are seen in diabetic nephropathy. In the glomeruli, there is expansion of the mesangium that is a direct result of hyperglycemia, by increased production of matrix or by their glycosylation. These may result in a nodular appearance called Kimmelstiel-Wilson nodules and is seen in nearly half of those who develop overt nephropathy. The second change seen is thickening of glomerular basement membrane. The third pattern of injury is glomerular sclerosis caused by intraglomerular hypertension (due to dilatation of the afferent renal artery or ischemic injury due to narrowing of vessels supplying the glomeruli). The prognostic significance of these different histological patterns is similar. The Renal Pathology Society introduced a pathological classification of diabetic nephropathy in 2010. These are useful for prognostication where available but are not used in daily practice. The usual indications for renal biopsy in diabetic with renal dysfunction are discussed below.

Screening

For early detection of nephropathy, it is recommended that all type I diabetes, 5 years after diagnosis and over 12 years of age should have urine screened for moderate increase in albumin excretion (formerly microalbumin) yearly. All type II diabetics should have their urine screened at diagnosis and thereafter yearly. Those who have moderately increased albuminuria (formerly microalbuminuria) should have their urine tested on two more occasions with overnight urine collections. Those who have elevated urine albumin should be screened every 6 months.

Screening can be done by three methods:

1. Random (preferably early morning) urine sample: Albumin to creatinine ratio
2. Twenty-four hours' urine protein collection
3. Timed urine collection.

The initial screening may be done using a standard urine dipstick which is specific for albumin. If negative, moderate increase in albuminuria (formerly microalbuminuria) must be excluded by an albumin to creatinine ratio. Estimation of this ratio is based on

the presumption that the average excretion of albumin is less than 30 mg/day and that of creatinine is about 1 g/day, resulting in a normal ratio of less than 0.03. Understandably, the ratio is lower in muscular individuals who excrete more creatinine and higher in those with low muscle mass. Twenty-four hours estimations are cumbersome but are the best to estimate proteinuria once it reaches levels corresponding to severely increased albuminuria (formerly macroalbuminuria). Care must be taken to avoid screening when there is any associated condition that may increase albumin excretion, e.g. fever, uncontrolled hypertension, congestive heart failure, urinary tract infection and following vigorous exercise.

Concomitant estimation of GFR (discussed later) should also be done at screening and thereafter yearly.

Clinical Presentation

Early in the course of illness (especially when picked up during screening), diabetic nephropathy is asymptomatic. If there is established nephropathy, there may be history of fatigue, foamy urine and pedal edema secondary to hypoalbuminemia (especially if the proteinuria is in the nephrotic range). There may be associated diabetic retinopathy, peripheral vascular disease, hypertension or coronary artery disease.

DIFFERENTIATING FROM OTHER CAUSES OF KIDNEY DISEASES

In general, the etiology of nephropathy in a diabetic is diabetic nephropathy but there are important exceptions to watch out for.

Decline of Glomerular Filtration Rate without Proteinuria

This can indicate interstitial nephritis (acute or chronic, including pyelonephritis), hypertension (including renovascular hypertension), etc. If this decline occurs very rapidly, it may indicate a crescentic glomerulonephritis.

Absence of Retinopathy

Retinopathy and nephropathy have a concordance rate of 85–99% in type I and 63% in type 2 diabetes. Therefore, the absence of retinopathy is a strong indicator toward consideration of another glomerular disease.

Sudden and Rapid Onset of Proteinuria

Sudden onset and rapid progression of proteinuria, development of nephrotic syndrome without the stage of microalbuminuria, especially occurring with known disease duration of less than 5 years may indicate an alternative glomerular pathology.

Macroscopic Hematuria and/or Red Blood Cells Casts in Urine

Macroscopic hematuria and RBC casts are unusual in diabetic nephropathy and suggest a proliferative glomerulonephritis.

Presence of Systemic Symptoms

Presence of skin rash, arthritis, fever and other constitutional symptoms suggest an autoimmune disorder like systemic lupus erythematosus as an alternative etiology.

All the above instances warrant immediate referral to a nephrologist. A renal biopsy may be indicated and especially in a case of crescentic glomerulonephritis, urgent intervention may help in salvaging kidney function.

MANAGEMENT

Prevention is Better than Cure!

Early initiation of strict glycemic control (HbA1c < 7%) has been proven to reduce the risk of reaching the stage of moderately increased albuminuria (formerly microalbuminuria) or incipient nephropathy, slow the progression to overt nephropathy and reduction in GFR. The Diabetes Control and Complications Trial (DCCT) (in patients with type 1 diabetes) showed a 39% reduction in the risk of developing moderately increased albuminuria and a 54% reduction in the occurrence of overt nephropathy in the intensively treated group. Further follow-up of the DCCT cohort showed that strict glycemic control reduced impaired GFR or death by 37%. Similarly the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes showed a 25% risk reduction in microvascular complications in the intensively treated group. At 12 years, this group had a lower proportion that had doubling of creatinine (0.91 vs 3.52%, $P = 0.0028$).

Once overt nephropathy has set in, it is controversial if strict control is beneficial and indeed, may lead to increased risk of hypoglycemic episodes. Indeed, several patients are discovered to have nephropathy when they develop recurrent hypoglycemia. Glycemic control at this point may stabilize or decrease the protein excretion but the benefit becomes apparent only after maintaining relative normoglycemia for at least 2 years. One must not forget that other complications, e.g. severe nonproliferative diabetic retinopathy may be also present and that coincident tight control may be required to prevent these complications from becoming worse.

Primary prevention: Prevent kidney disease from occurring at all by modifying, removing or avoiding risk factors that predispose to renal disease.

Secondary prevention: Identifying factors that aid or hasten progression of kidney disease and/or accelerate loss of kidney function, and preventing or removing such factors.

Tertiary prevention: Proper early management of CKD.

Management plan for the different stages of diabetic nephropathy is shown in the Figure 14.2.

Renin-Angiotensin-Aldosterone System Blockade

Renin-angiotensin-aldosterone system (RAAS) blockade has several benefits in the management of patients with diabetic nephropathy. Drugs that block RAAS have been shown to be useful at all levels—primary, secondary and tertiary prevention with one important difference between type 1 and 2 diabetes. Studies have failed in demonstrating any benefit of



Fig. 14.2: Management plan for the different stages of diabetic nephropathy. (CKD: Chronic kidney disease; GFR: Glomerular filtration rate).

giving either an angiotensin-converting-enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) in preventing the onset of the stage of moderately increased albuminuria in type 1 diabetes. However, in patients with type 2 diabetes and hypertension, both ACE inhibitors and ARBs are efficacious in preventing the onset of the stage of moderately increased albuminuria, i.e. primary prevention of diabetic nephropathy. The role in those who are normotensive is less clear though some studies do show some benefit. Once moderately increased albuminuria sets in, either an ACE inhibitor or ARB can be used in effecting a decrease in proteinuria and rate of decline of renal function in both type 1 and type 2 diabetic nephropathy. However, patients who have advanced CKD are likely to continue to progress despite RAAS blockade, although more slowly. Adding an aldosterone antagonist like spironolactone has been shown to reduce proteinuria and the degree of reduction in proteinuria is more in combination with either an ACE inhibitor or an ARB. However, two important points need to be borne in mind. Addition of an aldosterone antagonist may worsen the risk of hyperkalemia in these patients. Also, its effect in retarding the decline of renal function is still unknown. For these two important reasons, routine administration of aldosterone antagonists in diabetic nephropathy is not common practice. The combination of ACE inhibitor and an ARB has also become controversial in recent times. In patients with type 1 and 2 diabetes, combination of an ACE inhibitor with an ARB is superior to either given alone in reduction of proteinuria. However, a large trial (ONTARGET) found that combination therapy was more likely to be associated with hypotension, syncope, hyperkalemia and worsening of renal function. There was also an increased risk of death in the group receiving combination therapy. A meta-analysis of four studies (17337 patients) using combination therapy for left ventricular dysfunction also showed a similar increased risks of hypotension, hyperkalemia and worsening of renal function. In the light of this new data, combination therapy is now used less commonly.

In practice, we could start either an ACE inhibitor or an ARB. If there is intolerance to one class, the other may be substituted. There is some evidence to suggest that higher the dose the greater the benefit in reduction of proteinuria and, therefore, prescribing the highest tolerated dose would be prudent. Both ACE inhibitors and ARBs are contraindicated in pregnancy and, therefore, should be used with caution in women in the reproductive age-group and must be stopped before pregnancy is planned.

Control of Hypertension

Hypertension is common in patients with diabetes. It usually occurs in stage 4 or late in stage 3 of nephropathy in type 1 but may be present at or shortly after diagnosis in type 2 diabetes. Apart from diabetic nephropathy per se (the most common etiology in type 1), hypertension occurs because of insulin resistance and consequential hyperinsulinemia, vessel wall thickness, activation of the RAAS, direct sympathetic activation, salt retention and volume expansion. Even in those who are apparently normotensive, the response to exercise is exaggerated. Vascular changes causing an increased systolic and diminished diastolic pressure and isolated systolic hypertension is common in type 2 diabetes. The lower diastolic pressure increases risk of acute coronary events as perfusion to the coronary arteries occurs only during diastole. Antihypertensive therapy (nonpharmacologic followed by drugs) must be started at a blood pressure (BP) of 130/85 mm Hg with a goal of 125/75 mm Hg in proteinuric patients to reduce progression of diabetic nephropathy. In the absence of proteinuria, the BP goal is 130/80 mm Hg. Appropriate antihypertensive intervention can significantly reduce mortality from 94 % to 45% and a reduction in the need for dialysis and transplantation from 73% to 31% 16 years after the development of overt nephropathy. From the UKPDS data, it was seen that when a lower systolic blood pressure was maintained, in addition to a lower incidence of renal failure, other medical complications like myocardial infarction (MI), sudden death, stroke, heart failure, etc. were also reduced. In patients with isolated systolic hypertension with a systolic pressure of 180 mm Hg, the initial goal of treatment is to gradually lower the systolic blood pressure in stages. If initial goals are met and well tolerated, further lowering may be indicated. The hypertension optimal treatment trial showed that in patients with diabetes, reducing diastolic blood pressure from 85 mm Hg to 81 mm Hg reduced the risk of cardiovascular events by 50%. For reasons discussed in the previous section, an ACE inhibitor or an ARB is the drug of initial choice. As suggested above, these drugs should be used at the highest tolerated doses for maximal efficacy of proteinuria reduction. Addition of a low dose of a thiazide diuretic potentiates the antihypertensive effect of ACE inhibitors and ARBs. However, a dihydropyridine calcium-channel blocker like amlodipine may provide better cardiovascular protection in combination with an ACE inhibitor than a diuretic. Nondihydropyridine calcium-channel blockers like diltiazem or verapamil may reduce proteinuria and addition to an ARB may be better than either alone. Beta-blockers and alpha-blockers also may be used in the treatment of hypertension in diabetic nephropathy, though with the former there are concerns of worsening peripheral vascular disease and masking of hypoglycemic symptoms.

Dietary Restriction

Obviously calorie restriction is necessary for all patients with diabetes. High salt intake blunts the antiproteinuric effects of ACE inhibitors. Also seen is that salt restriction to less than equal to 70 mEq/day enhances the antiproteinuric effects of ARBs. Hence, salt restriction is advised to patients with diabetic nephropathy. Salt restriction also reduces the edema in patients with advanced nephropathy. Simultaneous administration of a diuretic will also help by natriuresis. It is unclear whether dietary protein restriction reduces the decline

in GFR in diabetic nephropathy. But once there is evidence of CKD, protein restriction to 0.8 g/kg/day and potassium restriction to 0.9 mEq/kg/day is to be enforced while continuing salt restriction. This is best prescribed by a dietician; however, the rule of thumb in dietary prescription would be avoidance of salty food, no added salt to the diet and avoidance of potassium-rich food (fruits, juices, tender coconut water, etc.). Fruits that are permitted are papayas, guavas, apples and pineapples.

Lifestyle Modification

Obese patients with diabetic nephropathy should be encouraged to lose weight as it is associated with marked decrease in proteinuria. Exercise and avoidance of smoking is also beneficial.

Lipid Lowering

Dyslipidemia is an important risk factor for progression of CKD and patients with diabetic nephropathy and CKD with may need medical therapy with statins in addition to dietary restrictions and weight reduction. The Kidney Disease Improving Global Outcome (KDIGO) clinical practice guideline for lipid management in CKD 2013 completely abandons the Adult Treatment Panel III (ATP III) guidelines hitherto followed. All patients with CKD are to be screened for dyslipidemia upon initial diagnosis of CKD for diagnosis of secondary dyslipidemia, not for assessment of coronary artery disease risk. Thereafter, serial monitoring of lipids is no longer necessary. In all patients with diabetes mellitus and CKD, the rate of coronary death or nonfatal MI is estimated to be above 10 per 1000 patient-years and are to receive lipid lowering therapy with statins or statin/ezetimibe combination, irrespective of age. The choice of statin and dose will depend on the route of drug elimination. Atorvastatin has only minimal renal elimination while rosuvastatin and simvastatin have 10% and 13% urinary excretion respectively and hence require lower doses to be administered. Statins are to be continued indefinitely and also during the stages of dialysis and transplantation. Fenofibrate by its action of decreasing inflammation and production of type I collagen in mesangial cells may prevent the onset of increased urinary albumin excretion. The dose of fenofibrate needs to be halved when the estimated glomerular filtration rate (eGFR) drops below 60 mL/minute/1.73 m² and further reduction to 25% when the eGFR drops below 30 mL/minute/1.73 m² and below 15 mL/minute/1.73 m², it is contraindicated.

WHAT SHOULD BE DONE WHEN THE GFR HAS BEGUN TO DECLINE?

Once the GFR begins to decline, there is no reversal possible. What we attempt aims at slowing the progression of disease and this must be discussed with the patient.

Proven benefits to slow the progression are:

- Diet (as discussed above)
- Strict blood pressure control

- Angiotensin-converting-enzyme inhibitor/Angiotensin receptor blocker therapy: Use of ACE inhibitors or ARBs may exacerbate hyperkalemia in patients with advanced renal insufficiency and/or hyporeninemic hypoaldosteronism. In older patients with bilateral renal artery stenosis and in patients with advanced renal disease even without renal artery stenosis, ACE inhibitors may cause a rapid decline in renal function. Potassium restriction in diet and addition of a thiazide diuretic may permit continuation of these drugs.

The GFR must be estimated monthly to assess the rate of decline of renal function. This can be done by measuring serum creatinine and using the GFR estimation formulae. The abbreviated modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI) formulae are more accurate but need computer software for calculation. The Cockcroft and Gault equation is easily calculated and is ideal for the bed side.

$$\text{Creatinine clearance} = [(140 - \text{age}) \times \text{Wt}] / [\text{serum creatinine} \times 72]$$

This value is multiplied by 0.85 to estimate the GFR and by a further 0.85 in women.

The estimation of GFR enables us to categorize (or stage) CKD. A patient is said to have CKD when kidney damage (e.g. AER ≥ 30 mg/day or decreased kidney function (GFR < 60 mL/minute/1.73 m²) is present for more than equal to 3 months. This staging is not unique to diabetic nephropathy but is applicable to all causes of CKD. Staging allows risk stratification and guides management. The stages are given in Figure 14.3. Stage G5 is called the stage of

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
G5	Kidney failure	<15				

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk

Fig. 14.3: Revised KDIGO CKD classification based on GFR and albuminuria and risk stratification. (CKD: Chronic kidney disease; GFR: Glomerular filtration rate; KDIGO: The kidney disease improving global outcome).

kidney failure and 5D (or end stage renal disease) is the stage after initiation of RRT. Efforts are made to prevent the patient from reaching this stage. If the GFR is near or less than 15 mL/minute/1.73 m², the patient must be prepared for RRT (detailed below).

AVOIDANCE OF FURTHER INJURY

Another important precaution to observe is to avoid additional insults. This commonly occurs due to commonly prescribed drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides (Inj. gentamicin, amikacin, etc.). Coronary artery disease may be present in some diabetics and the contrast agents used for coronary angiography may cause contrast-induced nephropathy. Here, when the benefits outweigh the risk, the procedure must be done explaining the possible risk of deterioration of renal function to the patient. Another potential danger in our country is the widespread use of alternative remedies. Though, unproven some of the alternate medicines may have a deleterious effect on the kidney and it may be prudent to exercise caution in indiscriminate use of these drugs. If during the course of follow-up, the patient develops hypovolemia due to some reason, ACE inhibitors, ARBs and diuretics may need to be temporarily withheld to prevent acute worsening of kidney function. Flowchart 14.1 shows the management of patients with moderately or severely increased albuminuria.

SUPPORTIVE TREATMENT FOR THE CHRONIC KIDNEY DISEASE PATIENT

Lifestyle Modifications

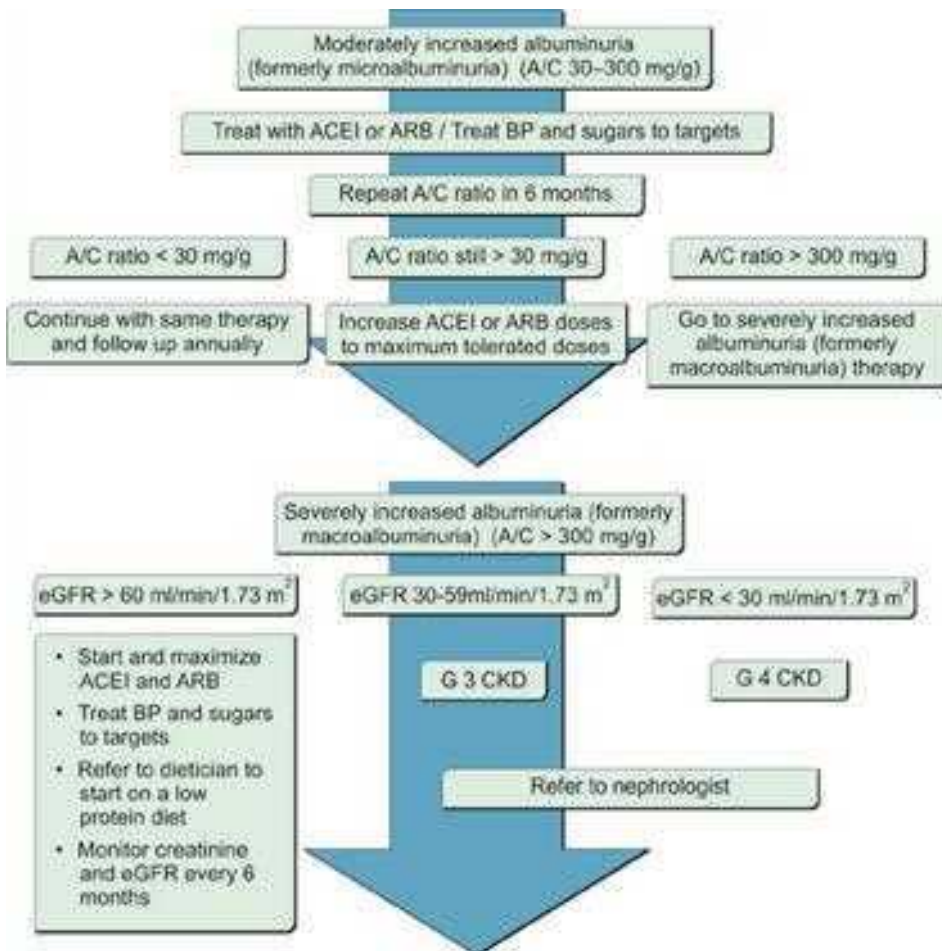
Lifestyle modifications are continued including weight reduction (if necessary) to target BMI less than 25 kg/m², avoidance of tobacco and regular aerobic exercises for at least 30 minutes/day.

Control of Dyslipidemia

A combination of diet, exercise and statins are necessary as discussed above. If not already on statins, new addition of statins once the patient has been started on dialysis is probably not useful.

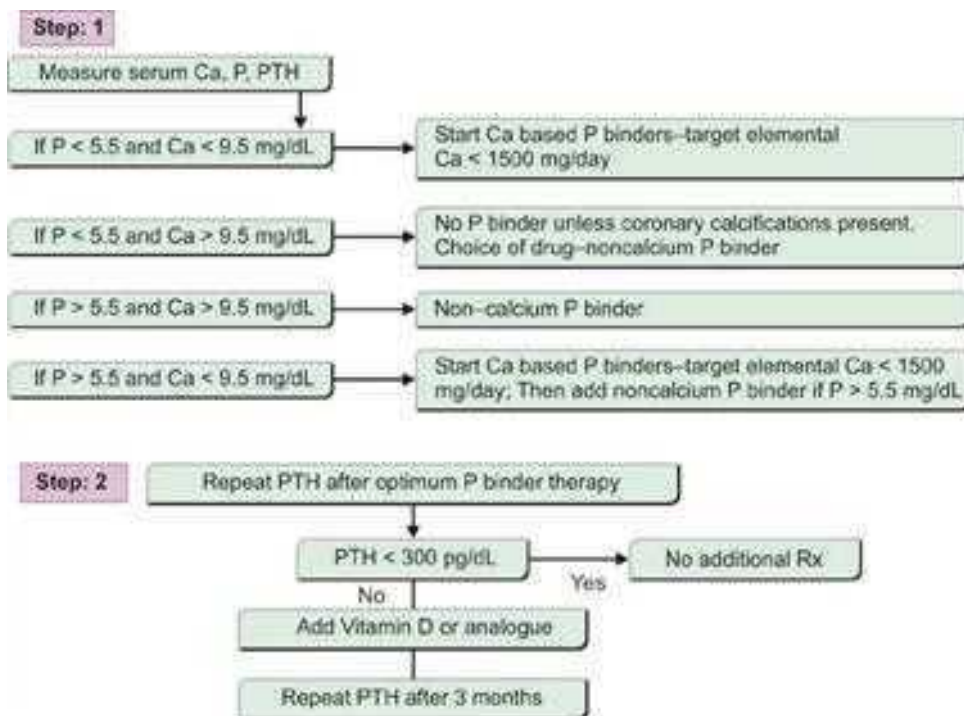
Phosphate Binders and Vitamin D Analogs

Once the GFR declines to less than 60 mL/minute, there is retention of phosphate by the failing kidney and phosphate binders are often needed to prevent secondary hyperparathyroidism. The most common phosphate binders used are calcium-based preparation (acetate or carbonate) given after each meal. However, these have the potential adverse effect of hypercalcemia and coronary vascular calcification. The noncalcium-based phosphate binders (sevelamer carbonate and lanthanum carbonate) are less likely to cause these adverse

Flowchart 14.1: Algorithm for management of patients with moderately or severely increased albuminuria.

(ACE: Angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker; A/C: Albumin/creatinine; eGFR: Estimated glomerular filtration rate; BP: Blood pressure).

effects but are much more expensive. The survival benefit of noncalcium-based phosphate binders is yet unproven. The serum calcium and phosphate must be checked monthly especially as CKD advances and serum phosphate kept within target range. The target calcium is at the low normal range. Vitamin D is given in the dose of 0.25 µg of calcitriol on alternate days (starting dose). This usually suppresses the parathyroid hormone (PTH), which is checked three-monthly. Vitamin D analogs may be preferred as these are less prone to cause hypercalcemia and coronary calcification. Vitamin D may also increase the hyperphosphatemia by increasing intestinal phosphate absorption. The limiting factors for vitamin D analogs are cost and availability. Phosphate binders like aluminum hydroxide, magnesium hydroxide and calcium citrate are avoided in CKD. The phosphate binding ability of these binders is limited and effective only if there is adherence to phosphate restriction in the diet (Flowchart 14.2).

Flowchart 14.2: Algorithm for phosphate binders and vitamin D/analogues in advanced CKD.

(CKD: Chronic kidney disease; PTH: Parathyroid hormone).

Treatment of Anemia

Among patients with CKD and anemia, an extensive evaluation should be done to exclude causes of anemia other than erythropoietin (EPO) deficiency prior to initiating therapy with erythropoiesis-stimulating agents (ESAs). The first approved ESA was recombinant human erythropoietin (rhEPO). It is usually started in the dose 50–150 units/kg/week. The commonly prescribed starting dose is 2,000 units administered subcutaneously (or intravenously) twice a week. Alternatives to EPO are continuous erythropoietin receptor activator (CERA) and darbepoetin, both of which have the advantage of two-weekly or monthly administration. Darbepoetin alfa has a higher potency and a longer half-life than rhEPO. The recommended starting dose in EPO naive patients is 0.45 $\mu\text{g}/\text{kg}$ administered once weekly. Less frequent dosing (i.e. monthly dosing) is also useful in many patients. Darbepoetin alfa can also be given either intravenously or subcutaneously. The dose can then be titrated to achieve the target Hb levels between 10 g/dL and 11.5 g/dL. There is increasing evidence that there is little benefit, and even potential risk, associated with targeting and maintaining Hb levels greater than 12 g/dL in predialysis patients. Major adverse consequences reported with normal or near-normal Hb levels include increased mortality, cerebrovascular events, arteriovenous access thrombosis and hypertension. The most recent boxed warning on ESAs recommends that the benefit to risk ratio of ESAs should be carefully considered before

recommending ESAs. The insert states that the dosage should be individualized and the lowest dose of ESA sufficient to reduce the need for transfusion should be used. ESAs should be considered only when the Hb is less than 10 g/dL. Concomitant iron deficiency must be looked for and if present, intravenous iron sucrose 100–200 mg in 100 mL normal saline can be given once or twice weekly for a total of 10 doses.

Avoidance of Fluid Overload, Hyperkalemia and Metabolic Acidosis

Intravascular volume balance is usually well compensated until late CKD G4 or G5, unless there is concomitant hypoalbuminemia. Salt and fluid restriction is to be initiated initially and loop diuretics may be added thereafter. Hyperkalemia is avoided by strict adherence to diet. ACE inhibitors or ARBs may require to be stopped as well. Retention of H⁺ ions in CKD leads to metabolic acidosis (serum bicarbonate between 12 mEq/L and 20 mEq/L). Bicarbonate therapy in CKD has done a volte-face in recent times with evidence of bicarbonate therapy having the ability to slow down the progression of CKD. Correction of acidosis can reduce the bone buffering of H⁺ ions, thus decreasing the damage due to impaired bone and mineral metabolism in CKD. Also, acidosis may cause skeletal muscle break down and diminish albumin synthesis. Bicarbonate therapy has been shown to increase lean body mass and serum albumin. Hence, sodium bicarbonate (or citrate, if intolerant to bicarbonate) at a dose of 0.5–1 mEq/kg/day is given to maintain the serum bicarbonate above 23 mEq/L. Typically, in CKD G4 and G5, electrolytes are tested monthly.

INVESTIGATIONS

Investigations for the different stages of diabetic nephropathy and CKD are given in Table 14.1.

RENAL REPLACEMENT THERAPY

Despite all efforts, if the GFR continues to steadily decline and reaches about 20 mL/minute, it is prudent to start planning for RRT. The patient and the family must be psychologically supported at this time and they must be helped to make an informed decision about the feasibility of RRT. In our country where the majority have to bear the expenses of RRT, options and their costs must be frankly dealt with. Initiation of RRT must never be an emotional decision rather a deliberate one as expenses for the same will have to be borne throughout the lifetime of the patient. Timely construction of an arteriovenous fistula and vaccination

Table 14.1: Investigations to be done in the different stages of diabetic nephropathy and CKD.

	<i>Hemoglobin</i>		<i>Ca, P</i>		<i>PTH</i>	
	<i>Frequency</i>	<i>Target (g/dL)</i>	<i>Frequency</i>	<i>Target (P) mg/dL</i>	<i>Frequency</i>	<i>Target (pg/mL)</i>
CKD G3	Monthly	10.5–11.5	6 monthly	2.7–4.6	6 monthly	35–70
CKD G4	Monthly	10.5–11.5	3 monthly	2.7–4.6	3 monthly	70–110
CKD G5	Monthly	10.5–11.5	monthly	3.5–5.5	3 monthly	150–300

(CKD: Chronic kidney disease; PTH: Parathyroid hormone)

against hepatitis B (20 mcg IM on each deltoid monthly for 3 months and booster after 6 months) must be initiated. If the patient is planning peritoneal dialysis, catheter placement intraperitoneally must be done early enough for the catheter to be well fixed without reduced risk of pericatheter leak. Any modality of RRT (hemodialysis, peritoneal dialysis or transplantation) can be chosen with important exceptions. In patients with severe cardiac disease, hemodialysis may be difficult to accomplish and transplantation surgery may not be tolerated. Similarly, someone with multiple intra-abdominal surgeries with likelihood of intraperitoneal adhesions may not be a suitable candidate for peritoneal dialysis. Between hemodialysis and peritoneal dialysis, in those medically suitable for either, there is no survival advantage of one modality over another. Patients need to be educated about RRT modalities before an informed decision is made. Survival of patients with diabetes on maintenance dialysis is lower than those with CKD due to an alternate etiology and is about 30% at 5 years. Cardiovascular disease is the most common cause of death. The first hemodialysis in India was done at Christian Medical College, Vellore (CMC) in 1962. Transplantation is the RRT of choice in those who are medically eligible. The first successful kidney transplantation in India was done in 1971 at CMC, Vellore. Transplant of Human Organs Act (THOA) allows a parent, grandparent, spouse, sibling or child to be a voluntary kidney donor. The donor undergoes extensive investigation to ensure that he/she has near normal health and faces little or no long-term consequences of kidney donation. Even carefully chosen donors need follow-up of their blood pressures, urinary excretion of protein and renal function periodically. For those without a suitable living donor, deceased donor transplantation is an excellent option. The survival after deceased donor transplantation is between 67% and 77% at 5 years. Another option is an ABO incompatible transplantation in those who do not have a blood group compatible voluntary kidney donor. The first ABO incompatible transplantation without splenectomy in India was done at CMC in 2009. Prior to transplantation, ideally a coronary angiogram is required to exclude covert coronary artery disease followed by revascularization, if needed. However, opinion is varied on the absolute necessity of a cardiac catheterization in all patients and many centers opt for a stress test instead and proceed for angiogram. Post-transplant and glycemic control continues to be an important medical consideration. Recurrence of diabetic nephropathy takes about 6 years and histological features of diabetic nephropathy is nearly universal. Fortunately, graft loss due to diabetic nephropathy is rare.

Simultaneous pancreas-kidney transplantation is a feasible treatment and is being increasingly done worldwide. The first one in India was done at the All India Institute of Medical Sciences in 2005. This procedure has the potential to cure the patient of both the diabetes and renal failure.

NORMOALBUMINURIC CHRONIC KIDNEY DISEASE IN DIABETES

While moderately increased albuminuria (formerly microalbuminuria) is the earliest change seen in diabetic nephropathy, the assumption that all patients with long-standing diabetes who develop CKD go through the stages of albuminuria has been increasingly questioned in recent times. In the DCCT cohort of patients with type 1 diabetes, 20 of the 89 patients who

developed a sustained eGFR less than 60 mL/minute/1.73m² were persistently normo-albuminuric. This phenomenon seems to be more common among female patients with long-standing diabetes, hypertension and/or retinopathy. Higher proportions are reported in patients with type 2 diabetes. 30% of patients with type 2 diabetes in Third National Health and Nutrition Examination Survey (NHANES III); $n = 1,197$ had eGFR less than 60 mL/minute/1.73 m² without any albuminuria. While the renal biopsies in these patients do show features of classic diabetic nephropathy, nephropathy in this cohort is likely to be a consequence of premature senescence, interstitial fibrosis and vascular disease causing ischemia or cholesterol emboli rather than due to diabetic nephropathy per se. The natural history of CKD in these patients is more benign than those who develop proteinuria and most are unlikely to progress to CKD stage 5.

NEWER/EXPERIMENTAL THERAPY FOR DIABETIC NEPHROPATHY

Pentoxifylline has been shown to have some renoprotection in diabetic nephropathy. In the recently concluded open-label, prospective, randomized trial— PREDIAN study in Spanish patients, addition of pentoxifylline to RAAS blockade slowed the GFR decline by an additional 4.3 mL/minute/1.73 m². Further trials are necessary to confirm this finding.

Preliminary studies have shown that aldose reductase inhibitors (tolrestat, ponalrestat and epalrestat) may have short-term benefits in reversing glomerular hyperfiltration, lowering GFR and decreasing urinary AER of the early stages of diabetic nephropathy. However, the long-term benefits need further confirmation.

Protein kinase C inhibitor (ruboxistaurin) therapy was shown to stabilize the progression of nephropathy in patients with type 2 diabetes and ACR 200–2000 mg/g and serum creatinine less than equal to 1.7 mg/dL (women) and less than equal to 2.0 mg/dL (men) who were already on RAAS blockade but long-term beneficial effects were not seen.

Initial studies with sulodexide, a heterogeneous mixture of glycosaminoglycans showed reduction in proteinuria. However, the randomized, double-blind, placebo-controlled Sun-MACRO trial failed to show renoprotective effect of sulodexide in patients with type 2 diabetes, renal impairment, and significant proteinuria (>900 mg/day) already on maximal RAAS blockade.

Bardoxolone methyl, an oral antioxidant inflammation modulator, in the randomized placebo-controlled BEAM trial showed improvement in the GFR in patients with diabetic nephropathy. However, the subsequent trial (bardoxolone methyl evaluation in patients with CKD and type 2 diabetes mellitus, BEACON) had to be stopped for important safety issues and it is no longer recommended.

Other techniques like receptor for advanced glycation end-products deletion, prevention of advanced glycation end-products (AGE) accumulation, dietary AGE control await clinical confirmation of utility.

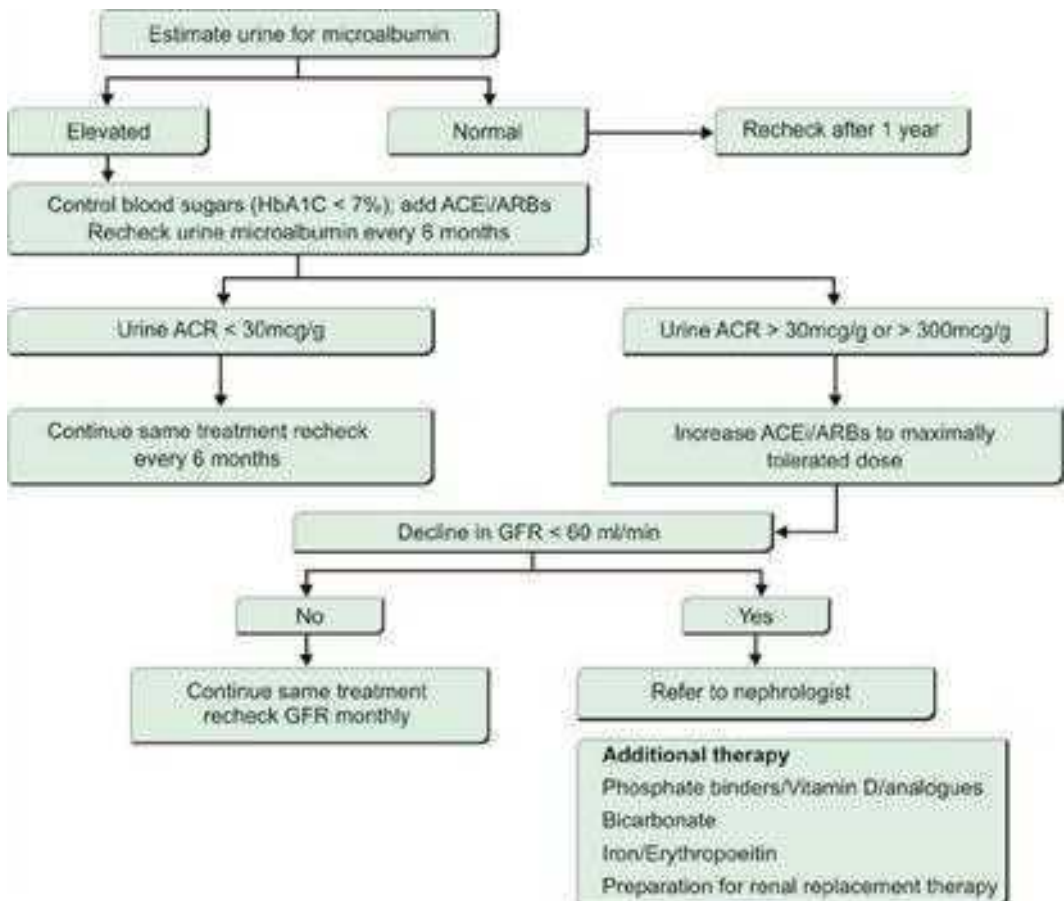
CONCLUSION

Diabetic nephropathy is the most common etiology of adult CKD today. Apart from anticipating, screening, detecting early and intervening appropriately, it is also important to refer the patient with diabetic nephropathy to a nephrologist in the following situations:

- Severely increased albuminuria (formerly macroalbuminuria) (proteinuria more than 1 g/day or ACR more than 300 mg/g with eGFR more than 60 mL/minute (CKD G3 to G5)
- Rapidly deteriorating kidney function; serum creatinine more than 1.7 to 2 mg/dL (150–180 $\mu\text{mol/L}$)
- Difficult to control hypertension
- Refractory anemia
- Development of hyperkalemia during treatment
- When nondiabetic nephropathy suspected
- Unexplained macroscopic or microscopic hematuria.

The appropriate management of the patient with diabetic nephropathy with CKD will go a long way in maintaining good health in these patients (Flowchart 14.3).

Flowchart 14.3: Algorithm for management of diabetic nephropathy.



(ACE: angiotensin-converting-enzyme; ARB: Angiotensin receptor blocker; ACR: Albumin-creatinine ratio; GFR: Glomerular filtration rate).

SUGGESTED READING

1. Blaslov K, Bulum T, Duvnjak L. Pathophysiological factors in the development of diabetic nephropathy—new insights. *Acta Med Croatica*. 2014;68(2):135-40.

SELF-ASSESSMENT

1. **The term moderately increased albuminuria refers to:**
 - (a) Microalbuminuria
 - (b) Macroalbuminuria
 - (c) Persistent albuminuria
 - (d) Overt albuminuria
2. **All of the following are risk factors for progression of diabetic nephropathy *except*:**
 - (a) Poor diabetic control
 - (b) Asian ethnicity
 - (c) Male gender
 - (d) Tight control of blood pressure
3. **All are true about incipient nephropathy, *except*:**
 - (a) Occurs within 1 to 5 years of onset of diabetes
 - (b) Occurs in about 20 to 30% of patients with type 1 diabetes
 - (c) Usually is associated with 30 to 300 milligram of protein in 24 hours
 - (d) Associated with loss of normal dipping of nocturnal blood pressure
4. **All of the following factors can prevent the progression of nephropathy, *except*:**
 - (a) Good blood pressure control
 - (b) Salt restriction
 - (c) Usage of ACE/ARB
 - (d) Usage of multivitamins and micronutrients
5. **All of the following are true about dyslipidemia in diabetic nephropathy, *except*:**
 - (a) Atorvastatin is excreted through the kidneys
 - (b) Fenofibrate dose reduction is required in patients with renal failure
 - (c) It is important to measure lipid profile in patients with diabetic nephropathy, mainly for assessing cardiovascular risk
 - (d) Dyslipidemia in nephropathy warrants aggressive treatment
6. **All of the following regarding measurement of hemoglobin are true in patients with diabetic nephropathy, *except*:**
 - (a) The target hemoglobin in these patients should be more than 12 gm%
 - (b) It should be monitored every month in patients with stage 3
 - (c) Iron deficiency should be treated prior to starting erythropoietin
 - (d) Darbepoetin has a longer half life than erythropoietin
7. **All of the following are true regarding monitoring PTH in patients with diabetic nephropathy, *except*:**
 - (a) It should be monitored every 3 months in patients with stage 4 and stage 5 diabetic nephropathy
 - (b) It should be monitored every 6 months in patients with stage 3 diabetic nephropathy
 - (c) Active Vitamin D should be started if the PTH is more than 300 pg/dL
 - (d) Vitamin D analogs are commonly used in patients with diabetic nephropathy

8. All of the following are true about Renal replacement therapy in patients with diabetic nephropathy, except:

- (a) Renal transplant is the treatment of choice in those who are medically eligible
- (b) Survival benefit in patients with diabetes, who receive hemodialysis is lower than in those with other aetiologies
- (c) ABO incompatible renal transplant is possible in patients with diabetes mellitus.
- (d) Graft loss due to diabetic nephropathy is common in practice

9. All of the following are implicated in the pathogenesis of diabetic nephropathy, except:

- (a) Protein kinase C pathway
- (b) Increase production of advanced glycosylated end products
- (c) Hexosamine pathway
- (d) Nitric oxide pathway

10. All of the following increase the suspicion of non-diabetic nephropathy, except:

- (a) Absence of proteinuria, despite decline in GFR
- (b) Presence of retinopathy
- (c) Presence of microscopic hematuria
- (d) Rapid onset of proteinuria

CHAPTER

15

Macrovascular Complications in Diabetes

PART A: CARDIOVASCULAR COMPLICATIONS AND DYSLIPIDEMIA

Subhrangshu Dey, Viji Samuel

*"In diabetes you'd think it insipid,
But why worry to treat the lipid,
HDL rise and LDL drop,
Ultimate effect is heart attack-stop."*

EPIDEMIOLOGY

Diabetes is among the most common chronic diseases in the world, affecting an estimated 285 million adults in 2010 (6.4% of the global adult population). The increase in the incidence and prevalence of type 2 diabetes can be attributed to the increase in population age. Furthermore, obesity and physical inactivity compound problem. It has been projected that diabetes will affect more than 430 million persons (7.7% of the global adult population) by 2030.

Cardiovascular disease remains the main comorbid condition and contributor to mortality in the setting of diabetes. This occurs most commonly in the form of coronary heart disease (CHD), but also in the incremental risk associated with diabetes for cerebrovascular disease, peripheral vascular disease, and heart failure (HF).

DIABETES MELLITUS AND CARDIOVASCULAR DISEASE

Compared with nondiabetic persons, patients with diabetes have a two- to fourfold increased risk for development of and death from CHD. Although older studies have suggested a diabetes associated CHD risk similar to that for nondiabetic patients with a previous myocardial

infarction (MI), more recent observations from clinical trials including patients with diabetes suggest a substantially lower CHD risk, most likely reflecting the effectiveness of contemporary therapeutic interventions.

Diabetes is associated with an increased risk for MI. Across the spectrum of acute coronary syndrome (ACS) events, in which diabetes may affect more than one in three patients, those with diabetes have worse CHD outcomes after ACS. Furthermore, the graded association of increased risk observed with diabetes in the setting of ACS extends to glucose values in the range well below the diabetes threshold.

Diabetes is independently associated with a two- to fivefold increased risk of HF over that in persons without diabetes, comprising both systolic and diastolic HF, and patients with diabetes have worse outcomes once HF has developed. In addition, diabetes is associated with an increased HF risk in the setting of ACS events. The multiple factors that increase HF risk in diabetes include ischemic, metabolic, and functional myocardial derangements.

Screening for Coronary Artery Disease in Diabetes

The goal of screening patients with diabetes for advanced asymptomatic coronary artery disease (CAD) is to identify patients with high cardiac risk, whose outcomes might be improved through more aggressive risk factor modification, medical surveillance, or revascularization of their CAD. Tests that detect inducible ischemia or assess atherosclerotic burden do not always identify those patients at risk for plaque rupture and thrombosis, which typically leads to acute coronary events. In the absence of symptomatic CAD, clinical features that help to identify the patient with increased risk for MI or cardiac death include evidence of other atherosclerotic vascular disease (peripheral vascular disease or carotid artery occlusive disease), renal disease, abnormal resting electrocardiogram (ECG), diabetic retinopathy, autonomic neuropathy, age (> 65 years), and traditional cardiac risk factors such as hypertension, dyslipidemia, inactivity, smoking, and abdominal obesity. Cardiac testing in asymptomatic individuals is a controversial issue.

Resting ECG

Findings on the resting ECG are normal in approximately half of patients with stable CAD, and even patients with severe CAD may have a normal ECG at rest. A normal resting ECG suggests the presence of normal resting left ventricular (LV) function and is an unusual finding in a patient with an extensive previous MI. In patients with known CAD, however, the occurrence of ST-T wave abnormalities on the resting ECG (particularly if obtained during an episode of angina) can correlate with the severity of the underlying heart disease. In contrast, a normal resting ECG is a more favorable long-term prognostic sign in patients with suspected or definite CAD.

Noninvasive Stress Testing

Noninvasive stress testing can provide useful information to establish the diagnosis and estimate the prognosis in patients with chronic stable angina. Noninvasive testing should be performed only if the information provided by a test is likely to alter the planned management strategy. The value of noninvasive stress testing is greatest when the pretest likelihood is

intermediate because the test result is likely to have the greatest effect on the post-test probability of CAD and hence on clinical decision making.

Exercise ECG

The exercise ECG is particularly helpful in patients with chest pain syndromes who are considered to have a moderate probability of CAD and in whom the resting ECG is normal, provided that they are capable of achieving an adequate workload. This test provides useful additional information about the degree of functional limitation in patients and about the severity of ischemia and prognosis in patients with a high pretest probability of CAD. Interpretation of the exercise test should include consideration of the patient's exercise capacity (duration and metabolic equivalents) and clinical, hemodynamic, and electrocardiographic responses.

Stress Myocardial Perfusion Imaging

Exercise myocardial perfusion imaging (MPI) with simultaneous ECG recording is generally considered to be superior to an exercise ECG alone in detecting CAD, in identifying multivessel CAD, in localizing diseased vessels, and in determining the magnitude of ischemic and infarcted myocardium. Exercise single photon emission computed tomography (SPECT) yields an average sensitivity and specificity of 88% and 72%, respectively, as opposed to 68% sensitivity and 77% specificity for exercise electrocardiography alone. Stress MPI is particularly helpful in the diagnosis of CAD in patients with abnormal resting ECGs and in those in whom ST-segment responses cannot be interpreted accurately, such as patients with repolarization abnormalities caused by LV hypertrophy, those with left bundle branch block, and those receiving digitalis. Because stress MPI is a relatively expensive test, stress MPI should not be used as a screening test in patients in whom the prevalence of CAD is low because most abnormal test findings will yield false-positive results, and a regular exercise ECG should always be considered first in patients with chest pain and a normal resting ECG for screening and detection of CAD.

Stress Echocardiography

Two-dimensional echocardiography is useful for the evaluation of patients with chronic CAD because it can be used to assess global and regional LV function under basal conditions and during ischemia, as well as to detect LV hypertrophy and associated valve disease. Stress echocardiography may be performed with exercise or pharmacologic stress and allows detection of regional ischemia by identifying new areas of wall motion disorders. Numerous studies have shown that exercise echocardiography can detect the presence of CAD with accuracy similar to that of stress MPI. Stress echocardiography is also valuable in localizing and quantifying ischemic myocardium. As with perfusion imaging, stress echocardiography also provides important prognostic information about patients with known or suspected CAD. Although less expensive than nuclear perfusion imaging, stress echocardiography is more expensive than and not as widely available as exercise electrocardiography.

Computed Tomography

Cardiac CT has made substantial advances as a noninvasive approach to imaging atherosclerosis and its consequences. It is a highly sensitive method for detecting coronary calcification, which is a good marker of the total coronary atherosclerotic burden. It can also provide angiography of the coronary arterial tree, assessment of myocardial perfusion, and quantification of ventricular function and myocardial viability. Although coronary calcification is a highly sensitive ($\approx 90\%$) finding in patients with CAD, its specificity for identifying patients with obstructive CAD is low ($\approx 50\%$). In view of this limitation, CT is currently not recommended as a routine approach to screen for obstructive CAD in individuals at low risk for ischemic heart disease (IHD). However, selective screening of individuals at intermediate risk for CAD events may be reasonable to consider because a high calcium score may reclassify an individual as being at higher risk and thereby lead to more intense risk factor modification. In patients with known CAD, exercise testing is preferable to CT in guiding decisions for coronary angiography.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMRI) is established as a valuable clinical tool for imaging the aorta and cerebral and peripheral arterial vasculature and is evolving as a versatile noninvasive cardiac imaging modality that has multiple applications in patients with CHD. Clinical use of CMR for assessment of myocardial viability has grown because of evidence demonstrating its ability to predict functional recovery after percutaneous or surgical revascularization and its very good correlation with PET.

Pharmacologic stress perfusion imaging with CMR compares favorably with SPECT and also offers accurate characterization of LV function, as well as delineation of patterns of myocardial disease. Because of its ability to visualize arteries in three dimensions and differentiate tissue constituents, CMR has received interest as a method to characterize arterial atheroma and assess vulnerability to rupture on the basis of compositional analysis.

Catheterization, Angiography, and Coronary Arteriography

Coronary angiography should be done early when indicated. Diabetics with CHD have an increased incidence of multivessel and more severe CAD. Advanced invasive imaging techniques such as intravascular ultrasonography (IVUS) provides a cross-sectional view of the coronary artery. Studies incorporating both coronary angiography and IVUS have demonstrated that the severity of CAD may be underestimated by angiography alone. Intravascular optical coherence tomography, angioscopy, and thermography are evolving as additional tools for more complete characterization of coronary atheroma.

Lifestyle Management

Weight Reduction

Structured programs that emphasize lifestyle changes such as reduced fat ($<30\%$ of daily energy) and total energy intake and increased regular physical activity, along with regular

participant contact, can produce long-term weight loss on the order of 5–7% of starting weight, with improvement in blood pressure (BP). For persons with elevated plasma triglycerides and reduced high-density lipoprotein (HDL) cholesterol, improved glycemic control, moderate weight loss (5–7% of initial weight), dietary saturated fat restriction, increased physical activity, and modest replacement of dietary carbohydrate (5–7%) by either monounsaturated or polyunsaturated fats may be beneficial.

Medical Nutrition Therapy

Saturated fats should be less than 7% of energy intake. Dietary cholesterol intake should be less than 200 mg/day. Intake of trans-unsaturated fatty acids should be less than 1% of energy intake. Total energy intake should be adjusted to achieve body weight goals. Total dietary fat intake should be moderated (25–35% of total calories) and should consist mainly of monounsaturated or polyunsaturated fat. Ample intake of dietary fiber (≥ 14 g/1,000 calories consumed) may be of benefit.

If individuals choose to drink alcohol, daily intake should be limited to one drink for adult women and two drinks for adult men. Individuals with elevated plasma triglyceride levels should limit intake of alcohol, because it may exacerbate hypertriglyceridemia.

In both normotensive and hypertensive persons, a reduction in sodium intake may lower blood pressure. The goal should be to reduce sodium intake to 1,200–2,300 mg/day, equivalent to 3,000–6,000 mg/day of sodium chloride.

Physical Activity

To improve glycemic control, assist with weight loss or maintenance, and reduce risk of CHD, at least 150 minutes of moderate-intensity aerobic physical activity or at least 90 minutes of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.

For long-term maintenance of major weight loss, a larger amount of exercise (7 hours of moderate or vigorous aerobic physical activity per week) may be helpful.

Blood Pressure

Blood pressure should be measured at every routine diabetes visit. Patients found to have systolic blood pressure (SBP) more than or equal to 130 mm Hg or diastolic blood pressure (DBP) more than or equal to 80 mm Hg should have blood pressure confirmed on a separate day. Patients with diabetes should be treated to achieve a SBP at least less than 140 mm Hg and a DBP less than 90 mm Hg, and for patients who can tolerate without adverse symptoms, can target as low as SBP less than 130 mm Hg and DBP less than 80 mm Hg.

Patients with a SBP of 130–139 mm Hg or a DBP of 80–89 mm Hg should initiate lifestyle modification alone (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products) for a maximum of 3 months. If, after these efforts, targets are not achieved, treatment with pharmacologic agents should be initiated.

Patients with hypertension should receive drug therapy in addition to lifestyle and behavioral therapy. All patients with diabetes and hypertension should be treated with a regimen that includes either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). If one class is not tolerated, the other should be substituted. Other drug classes demonstrated to reduce CHD events in patients with diabetes—beta blockers, thiazide diuretics, and calcium channel blockers—should be added as needed to achieve blood pressure targets. Multiple-drug therapy generally is required to achieve blood pressure targets. Patients not achieving target BP despite multiple-drug therapy should be referred to a physician specializing in the care of patients with hypertension.

If BP is stable, follow-up could occur every 6 months thereafter. In elderly hypertensive patients, BP should be lowered gradually to avoid complications.

Orthostatic measurement of BP should be performed in people with diabetes and hypertension when clinically indicated.

Tobacco

Every tobacco user should be advised to quit. The tobacco user's willingness to quit should be assessed. The patient can be assisted by counseling and by developing a plan to quit. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement either as gums or patches and bupropion) should be incorporated as needed. Bupropion is initiated as an oral tablet at 150 mg orally once a day for 3 days, increased to 150 mg orally twice a day. This is given for a duration of 7–12 weeks.

Antiplatelet Agents

Aspirin therapy (75–162 mg/day) should be recommended as a primary prevention strategy in those with diabetes at increased cardiovascular risk, including those who are older than 40 years of age or who have additional risk factors (family history of CHD, hypertension, smoking, dyslipidemia, or albuminuria). People with aspirin allergy, bleeding tendency, existing anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients with high risk. Aspirin therapy should not be recommended for patients younger than 21 years of age because of the increased risk of Reye syndrome associated with aspirin use in this population.

Glycemic Control

The glycated hemoglobin (HbA1C) goal for patients in general is less than 7%. The HbA1C goal for the individual patient is an A1C level as close to normal (<6%) as possible, without causing significant hypoglycemia.

Coronary Revascularization Considerations in Diabetes

Percutaneous Coronary Intervention

The optimal strategy of coronary revascularization in diabetics remains controversial. Although initial success rates in diabetic and nondiabetic patients are similar, diabetics exhibit

higher restenosis rates after percutaneous coronary intervention (PCI) and worse long-term outcomes. A variety of metabolic and anatomic abnormalities associated with diabetes and a greater degree of plaque burden may be responsible for this. Although drug-eluting stents (DES) have reduced the need for target lesion revascularization in these patients, these patients still experience more restenosis.

Coronary Artery Bypass Grafting

Most studies comparing outcomes in diabetic and nondiabetic patients undergoing coronary artery bypass grafting (CABG) show an increased risk of postoperative death and 30-day and long-term mortality and an increased need for subsequent reoperation in the diabetic population. Although diabetic patients have a worse risk profile, tend to be older, and have more extensive CAD and poorer LV function in comparison with nondiabetic patients, their higher long-term mortality does not depend entirely on these factors, and probably reflects accelerated disease progression in both bypassed and untreated coronary vessels.

CABG versus PCI

Randomized trials comparing PCI and CABG have reported similar outcomes. In patients with diabetes, however, CABG yields superior mortality outcomes compared with PCI. This emerged first from the *bypass angioplasty revascularization investigation (BARI) trial*, which compared balloon angioplasty with bypass surgery in patients with multivessel coronary disease. Patients with diabetes had a significantly lower mortality in the bypass arm than in those undergoing angioplasty (19% vs. 34%; $P < 0.003$), prompting a National Heart, Lung, and Blood Institute (NHLBI) clinical alert advocating CABG over angioplasty for all such diabetic patients. Subsequently, despite the widespread availability of DES and other advances in devices, techniques, and adjunctive pharmacotherapy, the mortality benefit of CABG over PCI remains, as most clearly demonstrated in the *future revascularization evaluation in patients with diabetes mellitus: optimal management of multivessel disease (FREEDOM)* randomized trial. In FREEDOM, 1,900 patients with type 2 diabetes and multivessel CAD were randomized to multivessel PCI using DES versus CABG. Over a median follow-up period of 3.8 years, CABG versus PCI was associated with a statistically significant reduction in a 5-year all-cause mortality, MI, and stroke (18.7% vs. 26.6%; $P = 0.005$). CABG was also associated with significantly lower risk for MI ($P = 0.001$) and death ($P = 0.049$), but with statistically increased risk for stroke (2.4 vs. 5.2%; $P = 0.03$). Therefore CABG continues to be recommended as the preferred mode of revascularization for patients with diabetes and multivessel coronary disease.

Revascularization versus Optimal Medical Therapy

The BARI 2D trial randomly assigned 2,368 patients with type 2 diabetes and CAD to receive prompt revascularization plus intensive medical therapy for CHD risk reduction, or to intensive medical therapy alone. During 5 years of study follow-up, the overall mortality rates between the two groups did not differ significantly. All cardiovascular outcomes were

statistically similar between the PCI and medical therapy groups, but CABG compared with medical therapy was associated with a significant reduction in major adverse cardiovascular events (22.4% vs. 30.5%; $P = 0.01$). These data provide support for an initial strategy of intensive medical therapy and additionally suggest the benefit of bypass surgery.

DIABETIC DYSLIPIDEMIA

A triad of high triglycerides, low HDL cholesterol and elevated small dense low-density lipoprotein (LDL) particles occurring in a patient with type 2 diabetes is referred to as atherogenic diabetic dyslipidemia (ADD). Insulin resistance at the level of adipocyte causing increased free fatty acid (FFA) efflux is thought to be central to the pathogenesis of ADD. This results in increased very LDL (VLDL) cholesterol from the liver facilitated by increased synthesis of apoprotein B. Subsequent actions mediated by cholesterol ester transferase protein in transferring triglycerides from VLDL particles to HDL and LDL result in increased Apo A1 containing small dense HDL and Apo B containing small dense LDL particles. The triglyceride-enriched HDL is subsequently hydrolyzed by hepatic lipase or lipoprotein lipase resulting in low HDL; Apo A-I dissociates from the reduced-size HDL, which is filtered by the renal glomeruli and degraded in renal tubular cells. Reducing LDL cholesterol using statins is a proven strategy for primary as well as secondary prevention of cardiovascular events. Hence, statin therapy is accepted as a first line in management of dyslipidemia, diabetic, or otherwise. But, despite statin therapy, a significant residual risk remains potentially attributable to increased triglyceride concentration and low HDL cholesterol, a characteristic hallmark of ADD. Omega 3 fatty acids, nicotinic acid, and fibrates are currently available drugs used to target such dyslipidemia.

Primary Prevention in Individuals with Diabetes

A high level of evidence supports the use of moderate-intensity statin therapy in persons with diabetes 40–75 years of age as this group is at substantially increased lifetime risk for atherosclerotic cardiovascular disease (ASCVD) events and death. Moreover, individuals with diabetes experience greater morbidity and worse survival following the onset of clinical ASCVD.

In persons with diabetes less than 40 or more than 75 years of age, statin therapy should be individualized based on considerations of ASCVD risk reduction benefits, the potential for adverse effects and drug-drug interactions, and patient preferences.

In adult patients, lipid levels should be measured at least annually and more often if needed to achieve goals. In adults younger than 40 years of age with low-risk lipid values (LDL cholesterol < 100 mg/dL, HDL cholesterol > 50 mg/dL, and triglycerides < 150 mg/dL), lipid assessments may be repeated every 2 years.

Lifestyle modification deserves primary emphasis in all diabetic individuals. In persons with diabetes who are older than 40 years of age, without overt CHD but with one or more major CHD risk factors, the primary goal is a LDL cholesterol level less than 100 mg/dL.

If LDL-lowering drugs are used, a reduction of at least 30–40% in LDL cholesterol levels should be obtained. If baseline LDL cholesterol is less than 100 mg/dL, statin therapy should be initiated based on risk factor assessment and clinical judgment. In people with diabetes who are younger than 40 years of age, without overt CHD, but who are estimated to be at increased risk for CHD either by clinical judgment or by risk calculator, the LDL cholesterol goal is less than 100 mg/dL, and LDL-lowering drugs should be considered if lifestyle changes do not achieve the goal.

The American Diabetes Association (ADA) and American Heart Association (AHA) suggest different approaches to the management of HDL- and triglyceride-associated CHD risk. The AHA suggests that in patients with triglyceride levels of 200–499 mg/dL, a non-HDL cholesterol (total cholesterol minus HDL cholesterol) goal of less than or equal to 130 mg/dL is a secondary target. If triglycerides are more than or equal to 500 mg/dL, therapeutic options include fibrate or niacin before LDL-lowering therapy and treatment of LDL cholesterol to goal after triglyceride-lowering therapy. A non-HDL cholesterol level less than or equal to 130 mg/dL should be achieved if possible. The ADA suggests lowering triglycerides to less than 150 mg/dL and raising HDL cholesterol to more than 40 mg/dL. In women, a HDL goal 10 mg/dL higher (>50 mg/dL) should be considered. Combination therapy with LDL-lowering drugs (e.g. statins) and fibrates or niacin may be necessary to achieve lipid targets, but this strategy has not been evaluated in outcomes studied for either CHD event reduction or safety.

Pharmacological Management of Dyslipidemia

Bile Acid-Binding Resins

Bile acid-binding resins interrupt the enterohepatic circulation of bile acids by inhibiting their reabsorption in the intestine. Currently, their main use is adjunctive therapy in patients with severe hypercholesterolemia secondary to increased LDL-cholesterol. Cholestyramine is used in 4 g unit doses as a powder, and colestipol is used in 5 g unit doses. Effective doses range from 2 to 6 unit doses/day, always taken with meals. The most important side effects are predominantly gastrointestinal: constipation, a sensation of fullness, and gastrointestinal discomfort. These drugs can cause hypertriglyceridemia.

Bile acid-binding resins can be used in combination with statins and/or cholesterol absorption inhibitors in cases of severe hypercholesterolemia. Colesevelam is a bioengineered bile acid-binding resin that has roughly twice the capacity to bind cholesterol as cholestyramine does. In doses of 3.8–4.5 g/day, it can be a useful third-line therapy for patients not meeting their LDL-cholesterol targets or in whom the side effects of statins preclude their optimal use. Colesevelam can also decrease HbA1C, thus making this drug a potentially useful adjunct in the treatment of complicated diabetic patients.

Statins (Hydroxymethylglutaryl-Coenzyme A Reductase Inhibitors)

Statins inhibit the enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase and prevent the formation of mevalonate, the rate-limiting step of sterol synthesis. To maintain cellular cholesterol homeostasis, expression of LDL-R increases and the rate of cholesteryl

ester formation declines. These homeostatic adjustments to HMG-CoA reductase inhibition increase clearance of LDL-cholesterol from plasma and decrease hepatic production of VLDL and LDL. In addition to blocking the synthesis of cholesterol, statins also interfere with the synthesis of lipid intermediates with important biologic effects. In studies using standard doses, statins have been found to lower LDL-cholesterol by 18% to 55%, depending on the specific statin being used.

Statins modestly increase the excess risk of type 2 diabetes in individuals with risk factors for diabetes. The potential for an ASCVD risk reduction benefit outweighs the excess risk of diabetes in all but the lowest risk individuals. Data from the Cholesterol Treatment Trialists (CTT), a meta-analysis of statin trials in subjects with diabetes showed a 21% reduction in CHD events and a 9% all-cause mortality benefit in favor of statins.

All individuals receiving statins should be counseled on healthy lifestyle habits. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines. Those who develop diabetes during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.

Statins are generally well tolerated; side effects include reversible elevation of transaminases and myositis, which necessitates discontinuation of use of the drug in less than 1% of patients. After initiation of statin therapy, the response should be checked within the first 3 months, along with transaminase and creatine kinase (CK) levels. Thereafter, clinical judgment should dictate the interval between follow-up visits.

Adverse side effects seen in up to 10% of statin users, to myositis, defined as diffuse muscle pain with evidence of muscle inflammation and elevated CK levels. Rarely, rhabdomyolysis can be associated with statin use.

Ezetimibe

The development of selective inhibitors of intestinal sterol absorption has added to the treatment of lipoprotein disorders. Ezetimibe is the first such compound. Ezetimibe limits selective uptake of cholesterol and other sterols by intestinal epithelial cells by interfering with NPC1L1. This agent has seen use in patients with LDL-cholesterol levels above target while receiving the maximally tolerated statin dose. Ezetimibe lowers LDL-cholesterol by about 18% and adds to the effect of statins. The dose of ezetimibe is 10 mg/day. The large scale study of ezetimibe in post-ACS patients called the IMPROVE IT study showed a modest benefit in reducing cardiovascular events when ezetimibe was added to simvastatin in this population.

Omega 3 Fatty Acids

They lower plasma triglycerides in low dosage. They can be used alone or as adjunctive therapy. They are abundant in fish oil.

Fibrates

The mechanism of action of fibrates involves interaction with the nuclear transcription factor PPAR- α , which regulates transcription of the LPL, apo C-II, and apo A-I genes. Side effects of fibrates include cutaneous manifestations, gastrointestinal effects (abdominal discomfort, increased bile lithogenicity), erectile dysfunction, elevated transaminase levels, interaction with oral anticoagulants, and elevated plasma homocysteine, (especially with fenofibrate). Because fibrates increase lipoprotein lipase (LPL) activity, LDL-C levels may rise in patients with hypertriglyceridemia treated with this class of medications. Fibrates, especially gemfibrozil, can inhibit the glucuronidation of statins and thus retard their elimination. For this reason, gemfibrozil combined with statins may increase the risk for myotoxicity; therefore such a combination is contraindicated. Subgroup analyses suggest a benefit of some fibrates in individuals with baseline high triglyceride levels, but no large endpoint study has tested this conjecture. Some advocate their use in very high-risk subjects such as diabetic patients with CHD and patients with renal failure.

Niacin

Niacin increases HDL-cholesterol and lowers triglyceride levels but has more modest effects on LDL levels. Niacin requires doses in the range of 2,000–3,000 mg/day in three separate doses to maximize effects on lipid levels. An escalating dose schedule to reach the full dose in 2–3 weeks rather than starting with the full dose can help manage the adverse effects of this agent. Slow-release forms of niacin decrease the side-effect profile of the drug. Daily aspirin intake can attenuate skin flushing, as does the prostaglandin D2 receptor (DP1) antagonist laropiprant. Niacin decreases the hepatic secretion of VLDL and reduces FFA mobilization in the periphery. Side effects of niacin include flushing, hyperuricemia, hyperglycemia, hepatotoxicity, acanthosis nigricans, and gastritis. Long-acting niacin has the advantage of a once- or twice-daily dosing schedule, but older preparations of slow-release niacin were potentially more hepatotoxic. Niacin effectively raises HDL-C levels and, in combination with a low-dose statin, can retard the angiographic progression of CAD and decrease the frequency of adverse cardiac events. The mechanism of action of niacin remains unsettled. However, HPS2-THRIVE study showed that niacin did not significantly reduce the risk of major vascular events in patients with vascular disease.

Cholesterylester Transfer Protein Inhibitors

Though cholesterylester transfer protein (CETP) inhibitors effectively and impressively raise HDL levels, they are yet to prove the clinical benefits of such an action. They also seem to reduce VLDL and LDL plasma levels. Torcetrapib and Dalcetrapib did not see further development. Anacetrapib and Evacetrapib are undergoing phase III trials.

PART B: STROKE AND DIABETES

Sanjith Aaron

*“Blood Vessels connect the brain,
Anticoagulants they may be in vain,
There is damage to grey matter,
It does not help if you are fatter”*

INTRODUCTION

The World Health Organization (WHO) has estimated that every year 15 million people worldwide can develop a stroke and out of this one-third will die and one-third will be left with permanent disability.

Strokes can be caused by a sudden occlusion of an intracranial artery (ischemic stroke) which comprises around 80% of the strokes or due to a rupture of an intracranial artery (hemorrhagic stroke).

Ischemic strokes can be classified according to their pathophysiology into large-artery atherosclerosis (including carotid artery disease) cardiogenic embolism, small vessel occlusive disease (lacunar infarcts), stroke of other determined cause (i.e. secondary to sickle cell disease) and stroke of undetermined etiology (cryptogenic strokes).

This classification of ischemic strokes is important since the risk factors treatment, secondary prevention and prognosis of each subtype differs (Box 15.1).

Studies have shown that the long-term survival is better in the small-artery occlusion subgroup. The highest recurrence rates were found for cardioembolic strokes and the lowest for large-artery atherosclerosis subtype.

Highest prevalence of hypertension, diabetes mellitus, hypercholesterolemia, and obesity was found in small-vessel disease.

Patients with diabetes are more prone to lacunar infarcts (small-vessel disease strokes). Stroke subtypes can also vary based on the race and ethnicity. In the West the cardioembolic strokes are more common whereas in the East small-vessel disease is the most common stroke

Box 15.1: Classification of subtypes of acute ischemic stroke.

TOAST classification of subtypes of acute ischemic stroke (Trial of ORG 10172 in acute stroke treatment):

- Large-artery atherosclerosis (embolus/thrombosis)
- Cardioembolism (high-risk/medium-risk)
- Lacunar: Small-vessel occlusion (lacune)
- Other determined etiology
- Undetermined etiology
 - Two or more causes identified
 - Negative evaluation
 - Incomplete evaluation

subtype. Furthermore, diabetes has been shown to be a strong determinant for the presence of multiple lacunar infarcts. Similarly Asians are more prone for intracranial atherosclerosis compared to Western population who are more likely to have extracranial atherosclerosis.

In this chapter, we shall be looking at the risk for stroke in patient with diabetes, and primary stroke prevention strategies. The impact of high sugars on the acute stroke treatment and early post-stroke complications.

Secondary preventive measures to be taken in a diabetic stroke patient and other problem peculiar to a stroke patient with diabetes need to be understood.

The importance of diabetes in patient with transient ischemic attack (TIA) and hemorrhagic strokes will be discussed.

Risk for Stroke in a Patient with Diabetes

Diabetes mellitus is a well-established modifiable risk factor for ischemic stroke. The risk for ischemic stroke in diabetic patients is increased 1.5 to 4 times and this risk is higher in younger patients.

Diabetics more than 65 years have up to a 12-fold increased risk of stroke compared with nondiabetics of similar age.

Chronic hyperglycemia, as indicated by elevated HbA1C levels, is associated with a 17% increase in the risk of stroke with each 1% rise of HbA1C.

Also diabetes is one of the strongest risk factors for stroke recurrence.

In a patient with diabetes the following are markers for a higher stroke risk

- Diabetic retinopathy
- *Hyperuricemia*: Strong predictor of stroke in type 2 diabetes (independent of other cardiovascular risk).
- Proteinuria of more than 300 mg/day is an independent and strong risk factor for stroke in subjects with type 2 diabetes mellitus. However, there is no direct evidence that decreasing urinary protein excretion can delay or prevent stroke.
- Concomitant hypertension.

Primary and Secondary Stroke Prevention Strategies in Diabetics

Multifactorial approaches with intensive treatments to control hyperglycemia, hypertension, dyslipidemia, and microalbuminuria have demonstrated reductions in the risk of cardiovascular events.

Tight glucose control targeting HbA1C less than 7% is recommended, however in the elderly this may not apply as discussed in chapter 23.

In diabetics who have hypertension, control of blood pressure using an ACE inhibitor or an ARB is useful in stroke prevention. In the United Kingdom Prospective Diabetes Study (UKPDS), diabetic patients with controlled BP (mean BP, 144/82 mm Hg) had a 44% reduced relative risk (RR) of stroke compared with diabetics with poorer BP control (mean BP, 154/87 mm Hg; 95% CI, 11–65; $P = 0.013$).

Statins can provide benefit for stroke prevention in diabetics independent of baseline lipid levels. LDL cholesterol targets should be as low as 100 mg/dL in patients with diabetes.

For primary stroke prevention the benefit of aspirin is not established. However, this can be given in diabetics with other atherosclerotic risks.

Diabetes in the Setting of Acute Ischemic Stroke

It is mandatory to have blood sugars checked in all patients presenting with symptoms of an acute stroke. Hypoglycemia can mimic a stroke or a transient ischemic attack and a sugar of less than 60 mg% should be corrected, before interpreting any event as stroke.

An elevated blood sugar can be seen in more than 40% of patients with acute ischemic stroke especially in diabetics.

There is a clear association between admission hyperglycemia and poor outcome in ischemic strokes. This is seen even in patients without diabetes.

There are several mechanisms postulated for this. Following an acute ischemic stroke there is an area of the brain which is acutely damaged called the infarct core (Fig. 15.1). Surrounding this is a larger area called the penumbra. This is an ischemic region at risk for further ischemic damage in the immediate hours following the stroke. Most of the acute therapies for stroke are aimed at saving this penumbra.

Normally glucose is metabolized to pyruvate which enters the Krebs's cycle. In the ischemic brain, the pyruvate is metabolized to lactate. Thus there is an accumulation of lactate and intracellular acidosis in the ischemic brain especially in the setting of hyperglycemia. This will cause accumulation of intracellular calcium which triggers glutamate-dependent excitotoxicity and cell death.

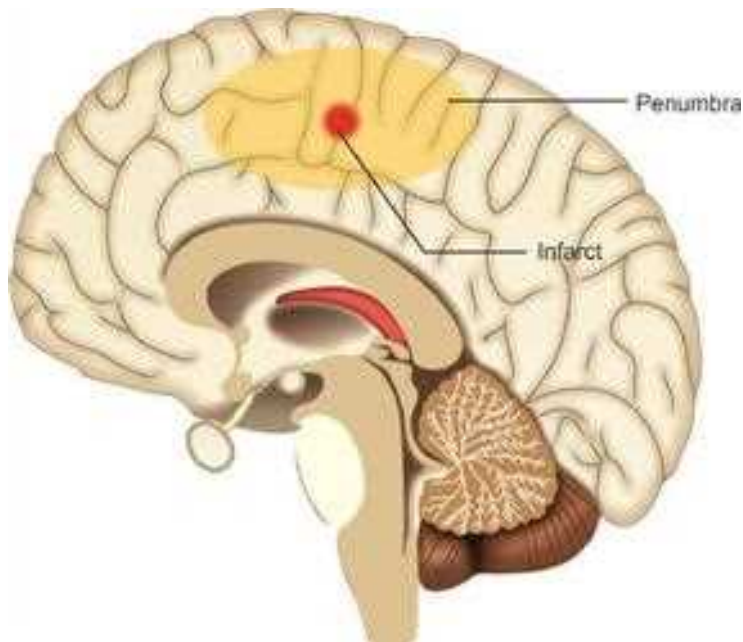


Fig. 15.1: The area of infarct surround by the penumbra.

The current standard of care for patients presenting with acute ischemic stroke is systemic thrombolysis with intravenous recombinant tissue plasminogen activator (rtPA) and intracranial hemorrhage is one of the complications of intravenous rtPA. Hyperglycemia has been shown to be one of the important risk factors for developing symptomatic intracranial hemorrhage in patients treated with intravenous rtPA.

However, there is no clear clinical evidence to show that aggressive treatment of blood glucose will improve outcomes. It is recommended that in the setting of an acute ischemic stroke the blood sugars should be carefully maintained below 180 mg/dL with insulin. Hypoglycemia should be avoided at all costs.

Patients with diabetes are also more prone for the acute post-stroke complications like pneumonia and urinary tract infections. In patients with diabetes, the stroke recovery can be affected as high sugars may impair brain plasticity and functional recovery following ischemic stroke.

Other Special Considerations in a Diabetic Patient with a Stroke

Carotid Atherosclerotic Disease

Carotid atherosclerosis is an important cause for ischemic stroke. The atherosclerotic plaque is usually situated at the carotid bifurcation with extension into the proximal segment of the internal carotid artery. The atherosclerotic plaque can progress or a thrombus can form on it. This can cause ischemic stroke or TIA from artery to artery embolization, or hemodynamic compromise. For suitable patients carotid endarterectomy (CEA) is recommended for stroke prevention.

Atherosclerotic plaques in patients with diabetes are unstable and have an increased chance for rupture and causing perioperative strokes during intervention.

Intracranial atherosclerosis: It is an important and often unrecognized cause for acute ischemic strokes. Diabetes is one of the important risk factors for developing intracranial atherosclerosis. Intracranial narrowing of blood vessels can cause low flow TIAs and watershed infarcts. This is important in long standing diabetics who would have developed diabetic autonomic dysfunction and orthostatic hypotension making them vulnerable to such hemodynamic strokes and TIAs.

Antiplatelet Agents

Oxidative stress (hyperglycemia) results in increasing thromboxane A₂ (TXA₂) which causes platelet aggregation, also in the setting of hyperglycemia there is endothelial dysfunction—diminished vascular responsiveness to nitric oxide (NO). Thus, the effect of antiplatelet therapy is blunted in the presence of uncontrolled sugars.

SUGGESTED READING

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SELF-ASSESSMENT

I. 58-years-old Mr A presented to the emergency department with one-day history of worsening dyspnea. Two days ago he was referred to an orthopedician by his GP when he had presented with acute onset neck pain, shoulder pain and vomiting. He was on irregular drug therapy for diabetes mellitus for the last 8 years. He had quit smoking two years ago subsequent to the development of right leg claudication. On examination his BP was 100/60 mm Hg, had crepitations over lung base and absent right leg pulse. ECG showed fully evolved MI with Q-waves in the anterior leads.

1. What should the GP have done when the patient presented to him initially?

- (a) Taken ECG and given aspirin
- (b) Checked his blood glucose and urine ketones
- (c) Referred to physician or cardiologist
- (d) All of the above

2. What is the most appropriate management of diabetes in this patient?

- (a) To regularize oral drug therapy
- (b) To add premixed insulin therapy to the existing oral drugs
- (c) To stop oral drugs and initiate insulin

3. What is the line of medical therapy to be followed on a short-term basis?

- (a) Insulin infusion followed by SC insulin therapy
- (b) Anticoagulants, antiplatelet drugs and ACE inhibitors
- (c) Patient education on insulin therapy, diet, cessation of smoking and drug compliance.
- (d) All of the above

4. The following combination of drugs cannot be used in this patient *except*:

- (a) Insulin, aspirin, statins, ACEI
- (b) Glibenclamide, metformin, aspirin, ACEIs
- (c) Aspirin, statins, alpha-blockers, insulin
- (d) Aspirin, pioglitazone, beta-blockers.

II. 66-years-old Mrs Y, with diabetes and hypertension of 16-years duration and on regular treatment with glibenclamide (10 mg BD), metformin (500 mg TID) and enalapril (10 mg BD) for last two years, was brought with history of recurrent hypoglycemic episodes and worsening dyspnea. On examination she appeared pale and her BP was 160/100 mm Hg. Fundus showed severe non-proliferative DR and grade III hypertensive retinopathy. Her serum creatinine was 3.9 mg/dL, hemoglobin 8.8 g%, ECG showed new ST-T changes in the lateral leads and old anterior wall MI.

5. What is the most important cause of repeated hypoglycemic episodes in this patient?

- (a) Age-related poor oral intake
- (b) Renal failure
- (c) High dose of drugs.

6. The reasons that would have contributed for the worsening cardiac status of this patient are:

- (a) Due to the absence of cardioprotective drugs
- (b) Due to the absence of lipid lowering drugs
- (c) Enalapril therapy
- (d) Hypoglycemic episodes precipitating acute ischemia

7. The most appropriate changes in the existing management would be all *except*:

- (a) Reduce the dose of all the drugs
- (b) Stop all the antidiabetic drugs and monitor the glucose values closely
- (c) Start her on anticoagulants, antiplatelets and coronary vasodilators
- (d) Initiate her on insulin only if the glucose values are persistently high.

8. The following statements are true *except*:

- (a) ACEI and ARBs should be used with caution
- (b) Cardiac disease is the major cause of morbidity and mortality in these patients
- (c) Antilipid drugs are contraindicated in renal failure
- (d) The patient needs intervention for the coronary artery disease.

III.

9. Which of the following is true about lipid lowering agents?

- (a) Statins act on PPAR— α receptors and reduce LDL-C levels
- (b) The predominant action of fibrates is to reduce triglyceride production
- (c) Ezetimibe cannot be combined with other agents
- (d) None of the antilipid agents have anti-inflammatory action in the vessels.

10. Pick-out the wrong statement regarding screening for CAD in diabetics:

- (a) An electrocardiogram (ECG) is less sensitive in detection of an ischemic event
- (b) Albuminuria in a patient with diabetes indicates a generalized vascular pathology
- (c) All diabetic subjects irrespective of their age should undergo intensive cardiac testing
- (d) Vascular involvement in other sites should prompt screening for coronary artery involvement

CHAPTER

16

Ocular Disease and Retinopathy

Saban Horo, Elizabeth Tharion, Padma Paul

*"If it's early there's frequently hard exudate,
With good control these generally abate,
Later on there may be proliferation,
So laser over fundus is a common decision."*

Ocular complications in diabetes mellitus (DM) are frequent, distressing and destined to become one of the challenging problems of the future. In fact diabetic patients are 25 times more likely to suffer blindness than nondiabetic patients matched for age and gender.

INTRODUCTION

Diabetes can affect any part of the eye including the orbital socket. In this chapter, the ocular changes in DM are revised, with special emphasis on diabetic retinopathy (DR).

CORNEAL CHANGES

Diabetes mellitus significantly affects all the layers of the cornea. Of importance are the damage to the epithelial basement membrane (causing impaired healing and therefore persistent epithelial defects) and diabetic corneal neuropathy (resulting in reduced corneal sensations). This combination renders patients with diabetes more susceptible to infectious keratitis (corneal ulcers) and makes the patient an ideal candidate for an urgent ophthalmology referral when any corneal pathology is suspected.

Stromal and endothelial changes are important in patients undergoing intraocular surgery as any compromise can lead to corneal decompensation.

LENS AND CATARACT

Noncataractous changes include increased sagittal thickness, light scattering, fluorescence, and brunescence. Refractive changes including a myopic shift, transient myopia or hypermetropia have an obvious significance that an undiagnosed or poorly controlled diabetic

patient ends up in frequent change of spectacles. It may take a few months for the refractive error to normalize, after adequate glycemic control.

Diabetes is an important risk factor for the development of cataract, the proposed mechanisms being, increased oxidative stress, glycation, brunescence, fluorescence and osmotic stress. Cataract in diabetic subjects is associated with age, duration of diabetes, use of diuretics, female gender, glycated hemoglobin and retinopathy.

DIABETES AND GLAUCOMA

Though the prevalence of open angle glaucoma in the population may be low, the fact that majority of them are unaware of their condition (up to 98%) necessitates that they should be recognized by healthcare providers. Various studies have reported from no increase to more than threefold increase in the odds of having open angle glaucoma among diabetics. This being true, every time a diabetic comes in for evaluation of retinal status it makes sense to have a comprehensive eye check including intraocular pressure measurement.

Diabetics are also more prone to angle closure glaucoma for various reasons. As detailed later, any patient with a suspicion of a narrow anterior chamber depth, should be referred for further evaluation especially since diabetics need repeated pupillary dilatation for fundus examination. If found shallow, this can be easily remedied by a laser iridotomy prior to dilatation.

Patients with progressive untreated proliferative diabetic retinopathy can develop neovascular glaucoma which leads to a zippered angle and a painful blind eye which not only indicates inadequate laser therapy to the eye but also poor systemic control of disease.

ORBITAL INVOLVEMENT

In the external eye, ptosis (without third nerve involvement and which improves on instillation of phenylephrine), blepharitis, xanthomas and increased tear film glucose are common.

Extraocular muscle involvement often referred to as vasculopathic mononeuropathy leads to sudden onset diplopia. This occurs due to small vessel infarction and usually recovers in 3–4 months. In patients with pupil sparing third nerve palsy, an ischemic infarct of the core fibers occurs, leaving the superficial fibers including those for the pupil intact. When a patient in the vasculopathic age group (>40 years) presents with such pupil sparing III nerve palsy general medical evaluation may often reveal DM or hypertension (HT).

Diabetic patients are susceptible to both bacterial and fungal orbital infections, however mucormycosis is the most potentially life threatening one caused by filamentous saprophytes of the order Mucorales.

Infection starts when spores are inhaled through the nose and settle in either turbinates or pulmonary alveoli. Thrombosis, hemorrhage, infarction and direct tissue invasion result in profound tissue necrosis. From the nose it spreads to the orbit, paranasal sinuses and eventually to the brain through the cribriform plate or orbital apex. Headache, retrobulbar pain, low grade fever, orbital swelling, loss of vision with or without neurological symptoms may be the presentation. On examination periorbitaledema, proptosis, early blindness, ophthalmoplegia (in some cases a frozen globe), chemosis and opaque cornea are found in varying stages.

If there is an ischemic retinopathy a central retinal artery occlusion may be present. Imaging is required to assess the extent of involvement as in some cases the only sign may be a very minimal proptosis with good vision. Treatment requires a multidisciplinary approach with systemic Amphotericin B. There may be a need for orbital exenteration, best performed in a tertiary care hospital. The mortality rate is very high once the brain is involved.

NEURO-OPHTHALMIC MANIFESTATIONS OF DIABETES

Cranial Neuropathies

The facial, abducens, oculomotor and trochlear nerves in isolation or in combination may be involved, presenting with diplopia or lagophthalmos. They have no gender predilection and are exclusive to adults and therefore a child presenting thus, needs further neurological evaluation.

Third nerve involvement along with restriction of adduction, elevation or depression, ptosis, pupillary dilatation, and impaired accommodation is seen when complete. Recovery is usually complete within 3 months. Pupillary sparing usually differentiates diabetic from aneurysmal third nerve palsy, however in the initial stages of aneurysmal compression there may be pupil sparing and hence the patient's pupil needs to be watched closely during the first week. Also in younger individuals and incomplete palsies, vasculopathic neuropathy will be a diagnosis of exclusion.

Fourth nerve palsied patients complain of vertical or torsional diplopia (images separated vertically or with head tilt to opposite shoulder) acutely and tend to resolve similar to third nerve involvement.

Sixth nerve palsy is common and patient complains of horizontal diplopia which is worse on attempting to look towards the paretic side with limitation of movement. While it recovers in 3–6 months, it has to be differentiated from other intracranial pathology as in the other two ocular motor nerves.

Facial nerve palsy presents as weakness or paresis of one side of the face with difficulty in closing the eye on that side. This is the most common cranial nerve involved. There can be different sides involved at different time periods.

In the event of it being a multiple involvement, the most common occurrence is that of third and sixth. A fourth and sixth without third has never been reported. These recover completely as well. As mentioned earlier, the possibility of rhinocerebral mucormycosis has to be considered in these cases.

Autonomic Dysfunction

Pupil size is a balance between the sympathetic and the parasympathetic supplies. The most common manifestation is an exaggerated miosis due to unopposed constriction caused by overacting parasympathetic due to failing sympathetic tone. The average size of the pupil in diabetics is 4 mm with no shape abnormalities.

Parasympathetic dysfunction is manifested as sluggish pupillary reaction.

Accommodation may be affected in diabetes, as noted by lower amplitudes of accommodation, for which longer duration of DM and old age are risk factors.

Optic Neuropathies

Diabetic papillopathy is seen in patients who are in their second to fourth decade, with optic disk swelling, with telangiectatic dilatation of peripapillary capillaries in one or both eyes, with minimal functional impairment of the optic nerve and resolves by the fourth month with minimal or no visual loss. At presentation, they may either be asymptomatic, complain of transient visual obscurations or decrease in visual acuity not improving with glasses. When bilateral it needs to be distinguished from anterior ischemic optic neuropathy (AION) and papilledema. This, therefore will be a diagnosis of exclusion. Diabetic papillopathy has a poorer outcome if associated with progressive diabetic retinopathy.

Much more often, patients with DM develop nonarteritic anterior ischemic optic neuropathy (NAION). This presents with sudden onset of visual loss, altered color vision, field defects in the form of altitudinal or arcuate defects, an afferent pupillary defect or optic disk edema that is characteristically pale with flame shaped hemorrhages at the disk or peripapillary area.

DIABETIC RETINOPATHY

Diabetic retinopathy is the most common cause of legal blindness between the ages of 20 and 70 years. Blindness usually results from non-resolving vitreous hemorrhage, tractional retinal detachment or diabetic macular edema. However, the 5-year risk of severe visual loss can be reduced if a person with proliferative DR undergoes laser photocoagulation. DR is often asymptomatic in its most treatable stages; hence early detection through regularly scheduled ocular examination is critical (Fig. 16.1).

Epidemiology

The prevalence of retinopathy at the time of diagnosis is much greater in type 2 (6.7–30.2%) as compared to type 1 (0–3%), as the former is more likely to remain undiagnosed for longer periods of time. Approximately one in four diabetics is unaware of their disease.

Prevalence of proliferative DR is more in long standing type 1 diabetes mellitus. However, in type 2 DM patients on insulin, risk is equally high (25%) possibly owing to chronic hyperglycemia. Most of the diabetic retinopathy patients seen in the clinics will be suffering from type 2, rather than type 1 diabetes simply because type 2 is seen more commonly in the population than type 1, though type 1 are more prone to develop retinopathy.

Risk Factors

- Duration of diabetes
 - Most important factor
 - Longer the duration higher the incidence (after 10 years of DM, incidence of retinopathy is 50% in patients less than 30 years of age and 90% in patients more than 30 years)
 - Rare before puberty.

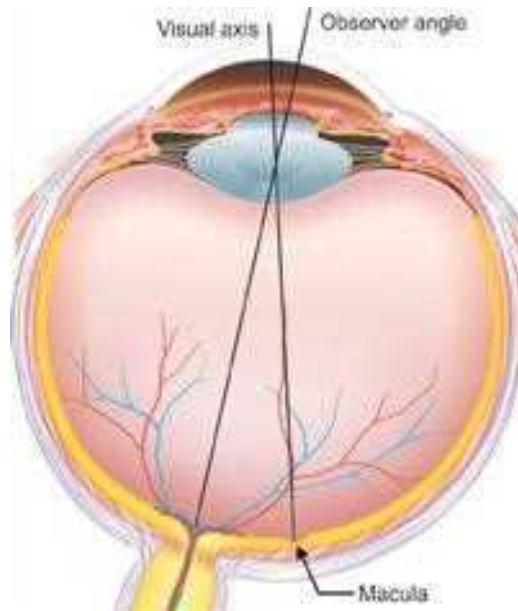
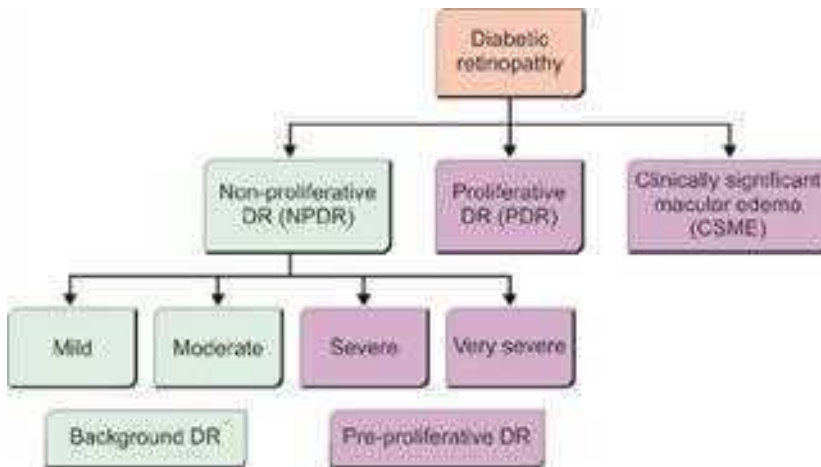


Fig. 16.1: Right eye—the visual axis falls on the macula while the line of observation is aimed at the optic disk, present medial to the macula.

- Poor control of diabetes
 - Worsens the progression
 - Tight control does not guarantee prevention, but delays the onset and slows progression.
- Pregnancy
 - Associated with rapid progression of pre-existent retinopathy especially if pre-pregnancy control was poor
 - Postpartum reversal of retinopathy may occur
 - It is rare for women without retinopathy to develop it during pregnancy
 - *De novo* gestational diabetes has no risk of retinopathy.
- Hypertension is associated with worsening
- Nephropathy
 - Associated with worsening
 - Treatment as with renal transplantation leads to improvement.
- Obesity
- Hyperlipidemia
- Smoking.

CLASSIFICATION AND FEATURES OF DIABETIC RETINOPATHY (FLOWCHART 16.1)

Mild and moderate nonproliferative DR were previously known as background DR. Severe and very severe nonproliferative DR were known as the preproliferative DR.

Flowchart 16.1: Classification of diabetic retinopathy (DR).

Nonproliferative Diabetic Retinopathy

Mild NPDR

- At least one microaneurysm—earliest clinically detectable lesion
- Retinal hemorrhages and hard or soft exudates may be present.

Moderate NPDR (Fig. 16.2A)

- Microaneurysms and/or dot and blot hemorrhages in at least one quadrant
- Soft exudates (Cotton wool spots)
- Venous beading or intraretinal microvascular abnormalities (IRMA).

Severe NPDR (Fig. 16.2B)

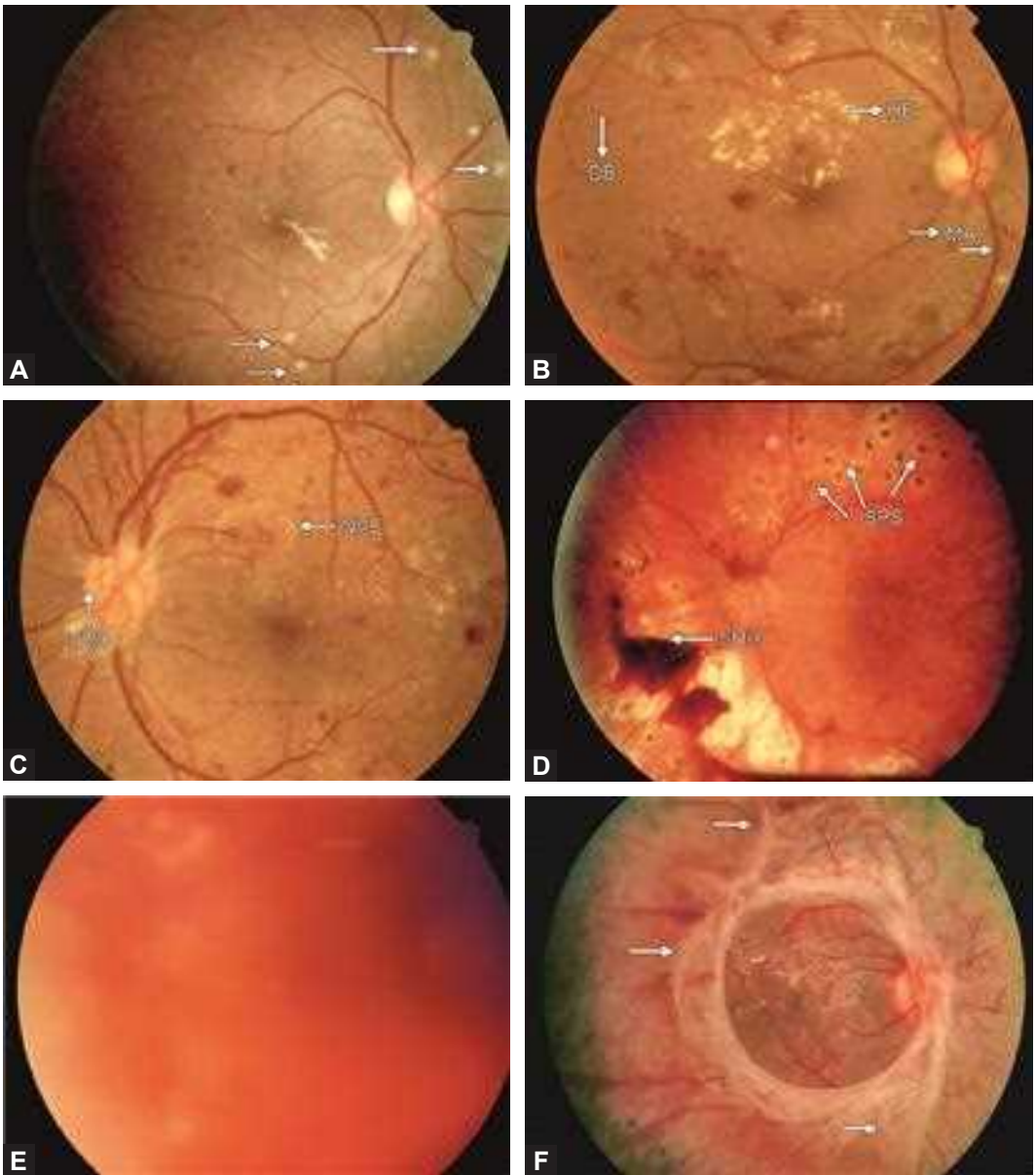
- When any one of the following three features is present
- Microaneurysms and intraretinal hemorrhages in all four quadrants
- Venous beading in two or more quadrants
- Moderate IRMA in at least one quadrant
- Known as the 4-2-1 rule.

Very Severe NPDR

- When any two of the features of the 4-2-1 rule is present.

Proliferative Diabetic Retinopathy (Figs. 16.2C and D)

- Proliferation of new vessels, usually from the veins, is the characteristic feature.
- New vessels on the optic disk (NVD)
- New vessels elsewhere on the retina, along the course of the retinal vessels (NVE).



Figs. 16.2A to F: Diabetic retinopathy. (A) Moderate nonproliferative diabetic retinopathy (NPDR). Cotton wool spots present near major retinal vessels (white arrows); (B) Severe NPDR with clinically significant macular edema (CSME) (DB: Dot and blot hemorrhages; HE: Hard exudates; MA: Microaneurysm; FH: Flame shaped hemorrhage); (C) PDR with New vessels on the optic disk (NVD)—fibrovascular proliferation overlying the optic disk (NVE, loops of new vessels with surrounding hard exudates extending into the macula); (D) PDR with subhyaloid/pre-retinal hemorrhage (SHH) and scatter photocoagulation scars (SPS); (E) Dense vitreous hemorrhage almost completely obscuring the view of the fundus; (F) Tractional retinal detachment (White arrows).

Source: Figures 2A, 2C to 2F are reproduced with permission from Dr Jay M Stewart, Department of Ophthalmology, University of California, San Francisco, United States.

Clinically Significant Macular Edema

- Presents with dimness of vision
- Retinal edema close to fovea
- Hard exudates close to fovea associated with adjacent retinal edema.

PATHOLOGY AND IMPLICATIONS OF THE FEATURES OF DIABETIC RETINOPATHY

Diabetic retinopathy is caused by damage to blood vessels of the retina. Microangiopathy with microvascular leakage and occlusion are its hallmarks. Larger vessels may also be involved.

Saccular outpouchings of the weakened, damaged capillary walls produces microaneurysms. In the earlier and less severe stages of NPDR, these damaged blood vessels become porous and leak fluid into the retina. This breakdown of blood-retinal barrier results in retinal edema and hard exudates. Edema occurring at the macula [clinically significant macular edema (CSME)], causes blurred vision and requires immediate treatment as it can lead to serious loss of vision.

Extensive microaneurysms, hemorrhages in all parts of the retina and venous beading occurring in the later stages of NPDR (severe to very severe NPDR) implies imminent neovascularization (growth of new vessels). Hence, early detection of this stage is crucial.

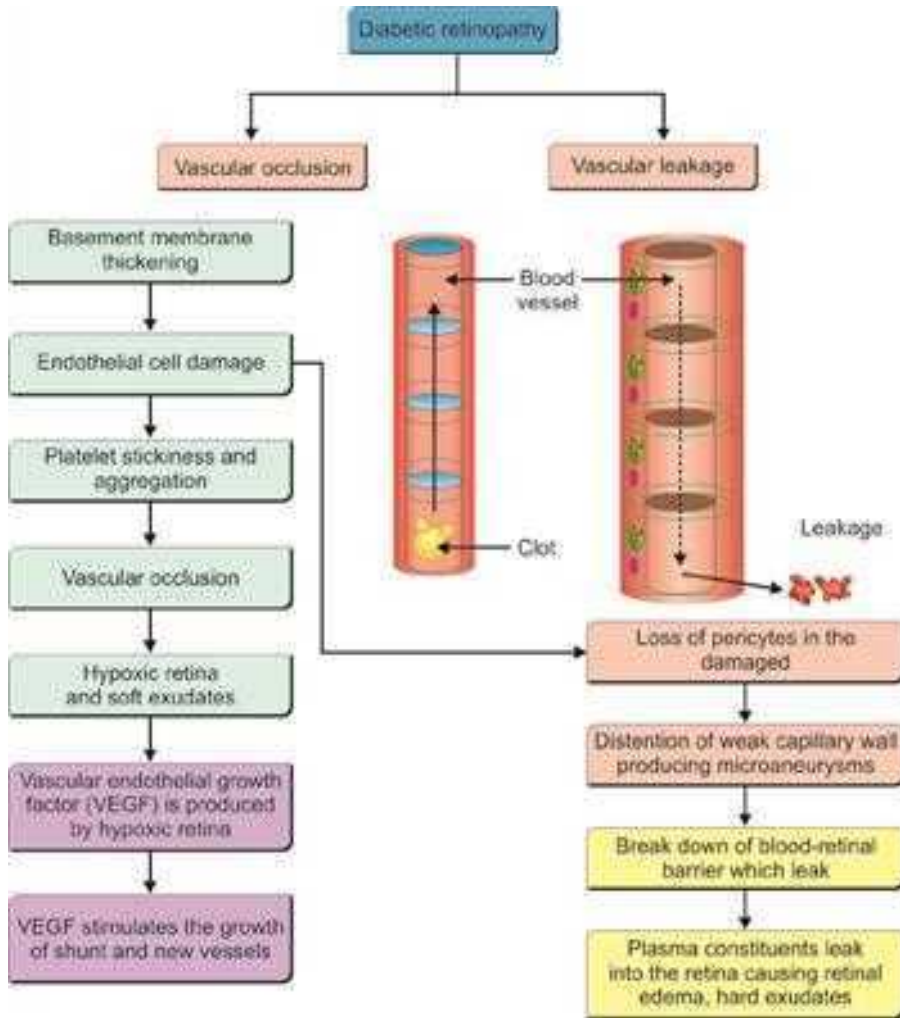
Various diabetes-induced pathologic changes of the capillary walls and the blood cells results in microvascular occlusion, leading to hypoxia of the retina. The hypoxic retina, probably attempting to re-establish circulation, releases large amounts of vascular endothelial growth factor (VEGF). VEGF is a potent stimulator of angiogenesis, the growth of new blood vessels from pre-existing ones (Flowchart 16.2).

Hence, in the more advanced stage of proliferative retinopathy, growth of new blood vessels occurs within the eye. These new vessels are fragile and can bleed causing loss of vision and scarring. This stage is liable to develop complications and therefore requires treatment.

Complications of Diabetic Retinopathy

All are essentially complications of neovascularization.

- *Vitreous hemorrhage*: Patient presents with sudden loss of vision, usually precipitated by straining while lifting a heavy weight or at the toilet and often is the presenting feature of undetected PDR (Fig. 16.2E).
- Tractional retinal detachment (TRD).
- *Rubeosis iridis*: Refers to growth of new vessels on the surface of iris. New vessels first appear at the pupillary margin and then extend radially towards the angle.
- *Glaucoma*: Neovascular glaucoma is a complication of rubeosis iridis, new vessels in angle of anterior chamber cause angle closure leading to mechanical obstruction to outflow of aqueous through channels in the angle. This causes raised intraocular pressure and pupil becomes distorted as iris gets pulled over the angle. Eye becomes painful and red along with progressive loss of vision.

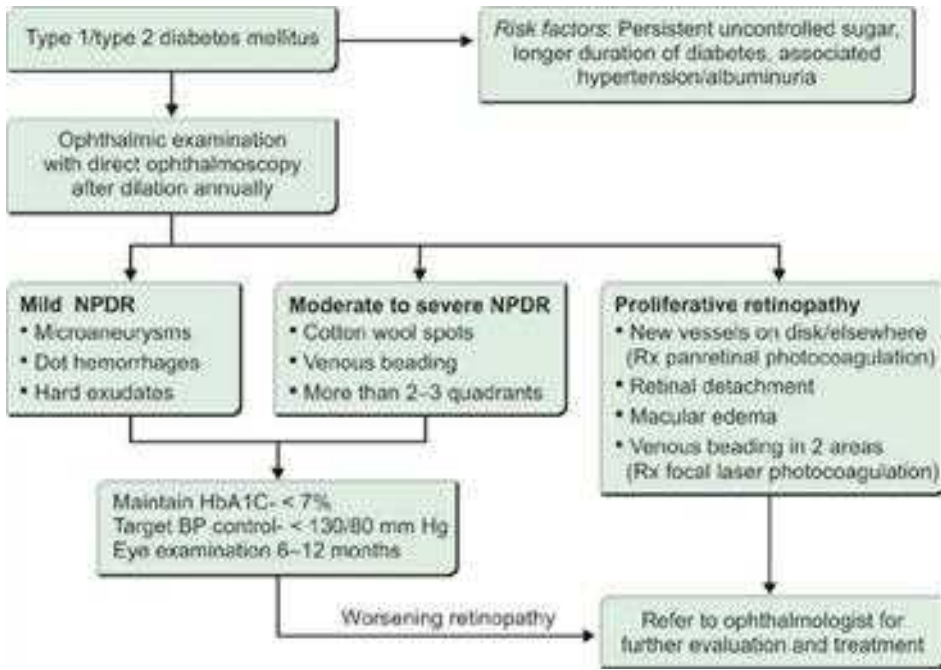
Flowchart 16.2: Pathogenesis of diabetic retinopathy (DR).

- Blindness is due to non-clearing vitreous hemorrhage, neovascular glaucoma, TRD and macular ischemia.

All the earlier complications are preventable, if appropriate treatment is instituted early enough. Herein lays the importance of routine fundus examination of diabetic patients and appropriate referral to ophthalmologists.

MANAGEMENT OF DIABETIC RETINOPATHY (FLOWCHART 16.3)

Good metabolic control of the disease is the mainstay treatment at all stages of DR. Associated hypertension, dyslipidemia, renal failure and anemia also need to be corrected. Other risk factors such as smoking and sedentary life style should be modified. These measures will not reverse existing damage, but will slow the progression of the disease.

Flowchart 16.3: Algorithm for management of retinopathy.

(NPDR: Nonproliferative diabetic retinopathy).

Specific therapy for retinopathy is warranted only in the stage of PDR and CSME, the goal of therapy being to salvage as much central vision as possible, as both conditions can lead to severe vision loss, if untreated.

Mild and Moderate NPDR

No specific treatment for retinopathy is required at this stage. Diabetes should be controlled and the retinopathy followed up with repeated fundus examinations.

Severe and Very Severe NPDR

Warrants close follow-up by an ophthalmologist, in addition to good control of diabetes. Laser photocoagulation may be implemented weighing risk factors such as extent of involvement of the fellow eye, if patient is one-eyed, is unable to be on close follow-up or needs cataract surgery.

Clinically Significant Macular Edema

This requires early focal or grid macular Laser to minimize risk of visual loss. A laser is a powerful light beam that can be precisely focused. Focal laser is used to seal the leaking vessels at the macula, away from the fovea as seen in a Fluorescein angiogram. Grid macular laser

excites the RPE pump to clear the fluid. The optical coherence tomography (OCT) is the other noninvasive investigation which gives a lot of information that guides treatment. OCT gives a cross-section of the retina along with its qualitative assessment and measurement. Laser therapy is essentially painless and is done as an out-patient procedure. Sometimes, there may be a macular ischemia associated with edema wherein macular laser is contraindicated. The patient needs to be on follow-up even after completion of therapy as one in about five may continue to lose vision despite laser treatment. Pars plana vitrectomy is done for relieving vitreomacular traction.

Pharmacologic therapy with intravitreal injection of steroids, Triamcinolone (inflammation is increasingly being considered contributory in its pathogenesis) or anti-VEGF agents like Bevacizumab/Ranibizumab are the alternate adjunct treatments available for CSME and their effects are variable. If the macular edema is more than 400 μm as shown in OCT, then anti-VEGF can be given initially which reduces the edema and followed-up 2 weeks later by macular laser. Intravitreal steroid implants (dexamethasone) can also be used, taking into account the risk of steroid induced glaucoma.

Proliferative Diabetic Retinopathy

Laser photocoagulation of the retina is performed as per the judgment of the ophthalmologist and after a fundus fluorescein angiogram. The ophthalmologist follows certain guidelines to identify eyes with high risk for development of complications and treats them. Laser therapy may be used to seal leaking vessels or to eradicate abnormal fragile vessels and to prevent further extension of neovascularization.

A panretinal photocoagulation (PRP) is done for eyes with risk of severe visual loss. This involves the application of laser [such as Argon/Double frequency neodymium-doped yttrium aluminum garnet (Nd-Yag laser)] to large areas of the retina, sparing the macula. The laser burns kill the retina, converting the hypoxic retina to anoxic retina which cannot produce VEGF. Further new vessel formation is thus prevented and the existing new vessels shrink. PRP will result in constriction of peripheral visual field, but greatly reduces the risk of central visual loss due to complications of PDR. Here also, laser therapy is done as an out-patient procedure, but requires several sittings. With the introduction of Pattern scan laser the PRP can be completed in one sitting. Complications include pain during treatment, transient increase in intraocular pressure, corneal abrasions, macular edema, choroidal hemorrhage and detachment, exudative retinal detachment and lens opacities.

Surgical intervention in the form of vitrectomy is indicated firstly to clear media opacities as in non-clearing vitreous hemorrhage, in those who have bled without prior laser therapy, when there is extensive fibrovascular proliferation with traction involving or threatening macula, tractional or combined retinal detachment, glaucoma and when the fellow eye has had a poor outcome or is blind. Ultrasonography of the eye is a useful adjunct to determine the status of the retina (attached or detached) when visualization is difficult.

Secondly, it is done to remove or relieve anteroposterior or tangential vitreoretinal traction underlying diabetic macular edema and tractional retinal detachment. In addition intraoperative laser may be given to prevent postoperative recurrence of complications. The standard three-port pars plana vitrectomy is the procedure of choice; transconjunctival

sutureless 23 and 25 gauge (G) vitrectomy has been producing successful results visually and anatomically. Recently, micro-incision vitrectomy surgery (MIVS) with 27 G is gaining more popularity now. Better visual outcomes are obtained with only vitreous hemorrhage and TRD not involving the macula. Poorer outcomes are seen in those with similar fate in the fellow eye, TRD involving the macula and those who have not received prior laser.

Complications of vitrectomy are recurrence of vitreous hemorrhage, retinal detachment and rubeosis irides.

It may or may not be combined with cataract extraction depending upon the maturity of the cataract and also its hindrance to clarity to the operating surgeon.

Intravitreal injections of anti-VEGF agents such as Bevacizumab are popular, newer alternative or adjunctive treatments. Anti-VEGF agents are humanized full length immunoglobulin G which binds to all types of VEGF, produced by recombinant DNA technique. They prevent the growth of new blood vessels by inhibiting VEGF. They are especially useful when laser therapy is not possible due to nonvisualization of the retina, as in the case of vitreous hemorrhage prior to surgery or along with PRP. The challenge at present is their short half-life which necessitates repeated injections.

Screening Protocol for Diabetic Retinopathy

Screening involves examination of the fundus following pupillary dilatation of both eyes. Initial screening should be done at diagnosis of type 2 diabetes and within 5 years of diagnosis of type 1 diabetic in adults and children aged 10 years or elder.

The purpose is to detect DR when it is in its asymptomatic treatable phase and therefore prevent blindness.

- Screening once in a year
 - Diabetics with normal fundus
 - Mild NPDR.
- Screening once in 6–8 months
 - Moderate NPDR.
- Screening at 3–4 months
 - Severe and Very severe NPDR
 - CSME postmacular laser.

Referral to Ophthalmologist

It is cost-effective and time-conserving to follow-up the patient at the diabetic clinic without referring to an ophthalmologist, unless warranted by the following conditions.

- Visual symptoms such as
 - Diminished visual acuity
 - Seeing floaters
 - Painful eye
 - Red eye.
- Fundus findings such as
 - Moderate to severe and very severe NPDR
 - Macular edema/hard exudates close to fovea

- Proliferative DR
- Vitreous hemorrhage
- Retinal detachment
- Cataract or corneal opacity precluding fundus examination.

The patient may be asymptomatic even with severe NPDR or PDR and may not be motivated to visit an ophthalmologist. It is important to educate the patients about the associated vision threatening complications and about the preventable nature of the blindness, if early treatment is instituted. Severe NPDR, very severe NPDR and PDR need follow-up every 3–6 months even after treatment, especially in the presence of diabetic macular edema and therefore need to be encouraged to visit their ophthalmologist as advised.

- Presence of risk factors such as
 - Pregnancy
 - Nephropathy.

It would be advisable to refer the patient to a well-equipped ophthalmic clinic with facilities for performing detailed fundus examination, fundus fluorescein angiogram, argon laser therapy and a vitrectomy if necessary, as the case may be. A set-up where just ophthalmic refraction is done and corrective spectacles are prescribed may not be sufficient.

OPHTHALMOSCOPY

Ophthalmoscopy is an examination of the fundus of the eye, which includes the retina, optic disk, choroid, and blood vessels. It is a valuable test to detect early effects of diabetes on the retinal blood vessels and to screen for DR.

There are three types of Ophthalmoscopy—(1) Slit-lamp ophthalmoscopy (or slit-lamp biomicroscopy), (2) Indirect ophthalmoscopy, and (3) Direct ophthalmoscopy. The former two methods require more skill, equipment and time than the direct ophthalmoscopy.

Direct ophthalmoscopy is performed by projecting a beam of light from an ophthalmoscope through the pupil to view the fundus, preferably in a darkened room, or at least with the lights dimmed. In practice, direct ophthalmoscopy can be performed with or without dilatation of the pupil. However, to obtain a good view of the fundus, it is advisable to dilate both eyes. The dilating drops used are 0.5% tropicamide drops alone or in conjunction with 2.5% phenylephrine. The eye drops take about 15–20 minutes to dilate the pupil fully. Before dilatation verify whether the patient has any of the following:

- Allergy to any medications
- Glaucoma or a family history of glaucoma
- Hypertension or history of myocardial infarction—dilating drops containing phenylephrine should not be used in them.

Occasionally, in susceptible patients, the pupillary dilatation may precipitate an attack of narrow angle glaucoma, characterized by sudden onset of severe pain in the eye accompanied by redness and dimness of vision. This warrants immediate referral to an Ophthalmologist. Hence, it is advisable to dilate a patient with history of narrow angle glaucoma only if a prophylactic iridotomy has been done.

The Flashlight test done prior to dilatation may be helpful in detecting susceptible eyes. Here light is directed into the anterior chamber (AC) through the lateral side of the eye, parallel

to the plane of the iris attempting to illuminate the opposite side of the iris or the nasal iris. If the AC is deep due to a flat iris, both the temporal and nasal iris on either side of the pupil is fully illuminated. If the AC is shallow due to the forward bowing of the iris, then a shadow will be cast on the nasal iris. If more than half of the nasal iris is in shadow it will be advisable not to dilate the eye.

The dilating drops may impair focusing of the eyes for several hours. Therefore the patient should be warned that he/she may not be able to read or drive for a few hours after the examination. Wearing sunglasses or tinted lenses will make the patient with dilated pupils more comfortable.

It is important to be familiar with the direct ophthalmoscope, its various apertures and filters and lenses before embarking on the examination. The rotating lenses incorporated in the instrument are used to compensate for the refractive error of the examiner or the patient being examined. A 15 times magnification is obtained by using the direct ophthalmoscope.

Procedure

- Seat the patient comfortably and adjust the patient height such that the examiner will not have to stoop uncomfortably.
- Instruct the patient to look steadily at a distant target. Explain to him that even if the examiner's head obstructs his view of the target, he should pretend to keep looking at it. Allow the patient to blink as required.
- To examine the right eye, stand on the patient's right side. Similarly stand on the left side to examine the left eye.
- Both patient and observer should remove their glasses, but contact lenses do not need to be removed.
- Holding the ophthalmoscope vertically with the right hand and looking through it with the right eye, examine the patient's right eye. Similarly the patient's left eye is examined, using the examiner's left hand and left eye. (Even though only one eye is used for ophthalmoscopy, it is advisable to keep both eyes open, suppressing the image of the other eye. This requires some practice to accomplish).
- The index finger is placed on the edge of the lens dial so that the lenses can be changed easily.
- Set the diopter power of the ophthalmoscope to "0", and turn on the light to about one-half the maximum intensity to begin with.

Hold the ophthalmoscope about 10–12 inches in front of and 15–20 degrees temporal or lateral to the line of visual axis of the patient and direct the light beam into the pupil to get the red reflex. Absence of red reflex or dark spots in the red reflex indicates opacities in the cornea, lens (cataract) or vitreous.

- Keeping the red reflex in view, move closer till the optic disk comes into view (about 1–2 inches in front of patient). Adjust the focus of the ophthalmoscope with the index finger to sharpen the view as much as possible and adjust the intensity of light to optimum illumination. Ideally the optic nerve head should be the first target seen.
- If this procedure does not bring the disc into view, move back slightly and repeat the process using a slightly different angle. It is important to learn to find the viewing angle

necessary to locate the optic disk, with least effort. A short search for the optic disk may be done by following the retinal vessels. An extended search can cause patient fatigue due to the bright light.

- Note the color and cup size of the disc, the presence of hemorrhages or new vessels on the disk, and the nature and caliber of the central retinal vessels.
- Imaginary horizontal and vertical lines passing through the center of the optic disk may be used to divide the fundus into four quadrants. They are the upper nasal and lower nasal quadrants and the upper temporal and lower temporal quadrants (nasal quadrants being medial and the temporal quadrants being lateral).
- Follow the retinal blood vessels as far to the periphery as possible in all four quadrants, noting the caliber and color of the vessels, and searching for microaneurysms, hemorrhages, new vessels and exudates in each area. This may be facilitated by instructing the patient to move his eyes in different directions without moving his head.
- To locate the macula, focus on the disc, then move the light approximately two disk diameters temporally on the retina by moving the ophthalmoscope nasally in the direction of the visual axis of the patient (this will obscure the patient's view of the distant target). This brings the macula which is the central part of the retina into view. Alternatively the patient may be asked to look straight into the light of the ophthalmoscope which will automatically place the macula in full view.
- Observe the foveal reflex seen at the center of the macula as a bright light reflection. Note any hemorrhages, exudates or pigmentary clumping that may be present.
- For future reference note the clarity of the view of the fundus and any observational difficulties.

Allow the patient to occasionally rest for 10–15 seconds or so during a prolonged examination.

Fundus Findings of Diabetic Retinopathy

Microaneurysms

- Saccular outpouchings of damaged retinal capillaries
- Seen as small, distinctly round, bright red spots, with smooth borders and central light reflex
- Appears first temporal to the fovea.

Hard Exudates

- Lipid deposits due to chronic leakage from weakened and damaged vessel walls
- Waxy, yellow, glistening lesions with distinct margins
- Appears individually or in clusters or as a ring around leaking microaneurysms (circinate retinopathy)
- Can be reabsorbed spontaneously or following laser photocoagulation
- May be confused with a drusen, also seen as discrete yellow spots. They arise from beneath the retinal pigment epithelium and have a propensity to be seen in the macular region.

Hemorrhages

- Intraretinal dot and blot hemorrhages from rupture of microaneurysms, capillaries or venules
 - Dot hemorrhage has distinct border (may be confused with microaneurysm)
 - Blot hemorrhage has fuzzy border
 - Usually resolves in 6 weeks to 3–4 months.
- Subhyaloid or pre-retinal hemorrhage (rupture of new vessels)
 - Blood is trapped between the retina and the detaching vitreous in a boat like configuration
- Vitreous hemorrhage—bleeding into the vitreous due to rupture of new vessels.

Soft Exudates (Cotton Wool Spots)

- Localized nerve fiber layer infarcts
- White, fluffy lesions with ill-defined margins
- Overlies blood vessels
- Indicates worsening of NPDR.

Venous Beading

- Focal areas of venous dilatation.

Intraretinal Microvascular Abnormalities

- Dilated tortuous channels between diseased arterioles and venules (shunt vessels)
- Usually recognized only by slit lamp biomicroscopy.

Neovascularization

- New vessels on the disk
- New vessels elsewhere on the retina
- Network of fine wisps or strands, sometimes looping across blood vessels
- May be flat or elevated
- May be associated with fibrosis
- Often adherent to the posterior surface of the vitreous.

Tractional Retinal Detachment (Fig. 16.2F)

- Due to contraction of the fibrovascular mass formed by the fibrous proliferations that develop along new vessels
- The mass is adherent to the vitreous and exerts traction on the retina.

RECORDING OF FUNDUS FINDINGS

- Mention whether the fundus could be viewed clearly or was obscured due to media opacities

- Draw a fundus picture of the two eyes, marking the position of the optic disk, macula and the major retinal vessel arcades
- Note the position, number and the extent of the particular lesions on the picture
- Ideally the microaneurysms and hemorrhages are marked with red color, the hard exudates with yellow color and cotton wool spots and vitreous/subhyaloid hemorrhage with green color
- Alternatively, the fundus findings may be described in words, with special reference to the position and extent of lesions
- Conclude with a note on the stage of the DR.

SUGGESTED READING

1. Dedania VS, Bakri SJ. Novel pharmacotherapies in diabetic retinopathy. Middle East Afr J Ophthalmol. 2015;22(2):164-73.

SELF-ASSESSMENT

1. **A diabetic patient with nonproliferative diabetic retinopathy tells you that he has heard of “laser” treatment for diabetic retinopathy. You would tell him that:**
 - (a) Laser treatment would help him as he has only early stages of diabetic retinopathy
 - (b) Laser treatment is a very painful procedure
 - (c) Laser treatment would prevent worsening of proliferative diabetic retinopathy
 - (d) Laser treatment would completely reverse visual loss
2. **A noncompliant diabetic patient with proliferative diabetic retinopathy is seen by you. You have to impress upon him the need for regular ophthalmic checkups. The complications that he should be aware of are all of the following, *except*:**
 - (a) Development of retinal detachment
 - (b) Development of tumors of the retina
 - (c) Loss of vision due to glaucoma
 - (d) Loss of vision due to persistent vitreous hemorrhage
3. **A fully dilated fundus examination of a diabetic patient, revealed some abnormalities in the right eye, while the left eye was normal. Retina of right eye was noted to have a microaneurysm and a hard exudate, away from the macula. The impression you get is that:**
 - (a) Urgent referral to ophthalmologist is necessary
 - (b) Good control of blood sugar is not necessary
 - (c) Only the right eye need be followed up in the next visit
 - (d) The patient has nonproliferative diabetic retinopathy
4. **The referral letter of a diabetic patient has “background diabetic retinopathy” written on it. The term means that:**
 - (a) The patient has not yet developed diabetic retinopathy
 - (b) Patient has mild to moderate NPDR
 - (c) The retinopathy is in the advanced stage
 - (d) Term is used to describe the retina of all diabetic patients

- 5. The most common form of laser therapy used from the following for retinopathy is:**
- (a) Argon
 - (b) Neon
 - (c) Xenon
 - (d) Frequency-doubled Nd-Yag Laser
- 6. Basic pathology of diabetic retinopathy includes all of the following, *except*:**
- (a) Involvement of large blood vessels only
 - (b) Occlusion of blood vessels
 - (c) Hypoxia of retina
 - (d) Leakage of blood vessels
- 7. Risk factors for the development of diabetic retinopathy are all of the following, *except*:**
- (a) Hypertension
 - (b) Obesity
 - (c) Well controlled sugars
 - (d) Hyperlipidemia dyslipidemia
- 8. Appearance of soft exudates in the retina:**
- (a) Indicates worsening of diabetic retinopathy
 - (b) Implies need for laser treatment
 - (c) Is diagnostic of diabetic retinopathy
 - (d) Requires urgent referral to ophthalmologist
- 9. A thorough fundus examination in a diabetic:**
- (a) Done every visit will delay the onset of retinopathy
 - (b) Will help in the early detection of retinopathy
 - (c) Does not require dilatation of pupils
 - (d) None of the above
- 10. A 55-year-old diabetic patient reports to your clinic with a history of sudden loss of vision of left eye precipitated by lifting a heavy suitcase:**
- (a) He must have had a heavy vitreous bleed of left eye as a result of proliferative diabetic retinopathy
 - (b) He requires to be referred to an ophthalmologist
 - (c) Fundus examination of both eyes should be done
 - (d) All of the above

CHAPTER

17

Autonomic Neuropathy

Kanakamani Jeyaraman

*“An early problem in men is at night,
Irregular heart beats can cause quite a fright,
Dry skin on the shins—a common precedent,
Gastric fullness can be rather unpleasant.”*

Autonomic nervous system (ANS) is crucial for the maintenance of normal body homeostasis. Given the widespread functions of the ANS, it is not surprising that its dysfunction affects every organ and system of the body. It has been rightly said that “knowing autonomic dysfunction is to know the whole medicine”. Autonomic neuropathy is one of the dreaded and troublesome complications of diabetes. Diabetic autonomic neuropathy (DAN) has a significant negative impact on survival and quality of life in patients with diabetes. 25–50% of the patients with DAN die within 5–10 years of diagnosis. It is also a major factor increasing the cost of care of a patient with diabetes. However, it is one of the least recognized and understood complications of diabetes.

INTRODUCTION

Autonomic nervous system (ANS), also called as the visceral or involuntary nervous system, innervates cardiac muscle, smooth muscle, and various endocrine and exocrine glands. Hence, this nervous system influences the activity of almost all tissues and organ systems in the body. The ANS contains two anatomically and functionally different divisions—the sympathetic and parasympathetic systems. Many tissues are innervated by both divisions, typically exerting the opposite effects on a given tissue. However, the two are dominant under different conditions. In general, sympathetic system is active during stressful (“fight-flight”) reactions and exercise, whereas parasympathetic predominates during quiet conditions (“rest-digest”).

Autonomic neuropathy is one of the dreaded and troublesome complications of diabetes. The 5-year mortality rate is 3–5 times higher in diabetic patients with autonomic neuropathy than in those without. Studies have shown that diabetic autonomic neuropathy (DAN) is a marker of adverse cardiovascular, renal and cerebrovascular outcomes.

EPIDEMIOLOGY OF DAN

The prevalence of DAN has been varyingly reported from 5% to 35%. This variability is probably due to the differences in the criteria used for definition of DAN, the study population and

the study setting (hospital based or community based). For example, in a population-based study of diabetic patients in Rochester, the prevalence of symptomatic visceral autonomic neuropathy was 5.5%. However, a community based study from Oxford reported a prevalence of 16.7%, autonomic neuropathy being defined by one or more abnormal heart rate variability tests. In a multicenter study involving 1,171 diabetic patients from Germany, Austria, and Switzerland, 25.3% of patients with type 1 diabetes and 34.3% of patients with type 2 diabetes had abnormal findings in more than two of six autonomic function tests. In the Steno type 2 trial, the prevalence of DAN at baseline was 28%.

PATHOGENESIS

The most important risk factors associated with DAN are poor glycemic control, long duration of diabetes, increasing age, female sex, and higher body mass index. Some studies have also shown smoking and elevated triglycerides to be associated with DAN (Fig. 17.1).

Hypotheses concerning the pathomechanisms of diabetic neuropathy include a metabolic insult to nerve fibers, neurovascular insufficiency, autoimmune damage, and neurohormonal growth factor deficiency. Flux of excess glucose into the polyol pathway leading to accumulation of sorbitol, may cause direct neuronal damage and/or decreased nerve blood flow. Formation of advanced glycosylation end-products in the endoneurial blood vessels, may cause reduced endoneurial blood flow. Impaired neuronal blood flow, may cause direct neuronal damage and/or decreased nerve blood flow. Formation of advanced glycosylation end-products in the endoneurial blood vessels, may cause reduced endoneurial blood flow. Impaired neuronal blood flow, may cause direct neuronal damage and/or decreased nerve blood flow.

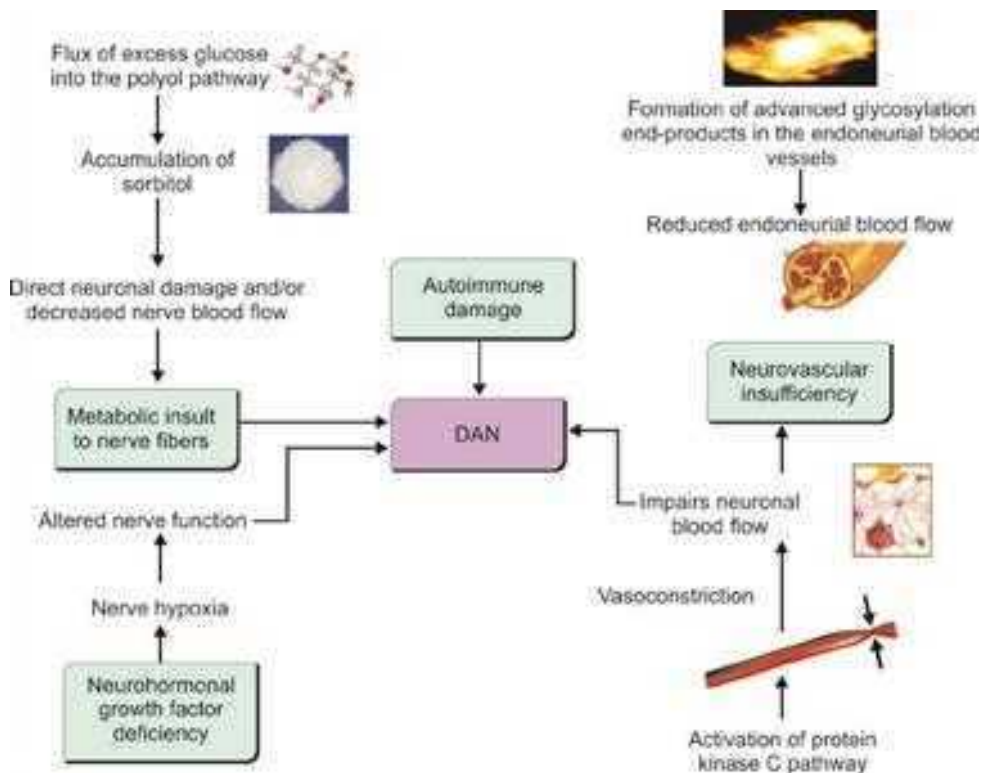


Fig. 17.1: Risk factors associated with diabetic autonomic neuropathy (DAN).

of advanced glycosylation end products in the endoneurial blood vessels result in reduced endoneurial blood flow. Activation of protein kinase C pathway induces vasoconstriction and impairs neuronal blood flow. Free radical production and formation of peroxynitrite lead to oxidative stress and nitrosative stress, respectively. In a subgroup of patients with neuropathy, immune mechanisms may also be involved. Deficiency of neurotrophic growth factors and essential fatty acids may result in nerve hypoxia with altered nerve function.

CLINICAL MANIFESTATIONS OF DAN

Symptomatic autonomic neuropathy generally does not occur until long after the onset of diabetes. But subclinical autonomic dysfunction can occur within a year of diagnosis in type 2 diabetes patients and within two years in type 1 diabetes patients. DAN can involve the entire ANS visceromotor, vasomotor and sensory fibers. The ubiquitous distribution of the ANS renders virtually all organs susceptible to autonomic dysfunction. The vagus nerve which accounts for almost 75% of all parasympathetic activity, being the longest of the ANS nerves is the earliest nerve to be involved in DAN. Hence, even early affects of diabetic autonomic neuropathy are widespread. However, symptoms may be restricted to a single organ or system. The organ systems that frequently exhibit prominent clinical autonomic signs and symptoms in diabetes include the cardiovascular system, gastrointestinal tract, genitourinary system, adrenal medullary system, peripheral vasomotor and sudomotor system and pupils. Table 17.1 summarizes the clinical manifestations of DAN.

Cardiovascular Autonomic Neuropathy (CAN)

Clinical Manifestations

Heart rate variability (HRV): Persistent sinus tachycardia can occur and there may be no variation in heart rate during activities that normally increase parasympathetic vagal tone, such as deep breathing and the Valsalva maneuver. Sympathetic tone may be increased during the day and parasympathetic tone decreased at night, which may predispose to nocturnal arrhythmogenesis. Abnormal myocardial electrical activity with QT prolongation and altered ventricular repolarization has also been implicated in the arrhythmogenesis. Ultimately, cardiac denervation can occur which can lead to fixed heart rate and can be associated with painless myocardial infarction and sudden death.

Limited exercise tolerance: The autonomic tone that normally augments the cardiac output and redirects the blood flow from skeletal muscles, is impaired in CAN and hence the exercise tolerance is limited. This is usually due to impaired augmentation of cardiac output resulting from inadequate sympathetic modulation. Exercise tolerance is also compromised by a reduced ejection fraction, systolic dysfunction, and decreased diastolic filling.

Orthostatic hypotension (OH): It is defined as a fall in blood pressure of more than or equal to 20 mm Hg for systolic or more than or equal to 10 mm Hg for diastolic blood pressure in response to postural change, from supine to standing. It reflects failure of vasoconstriction in both the splanchnic and peripheral vascular beds. Anemia resulting from erythropoietin

Table 17.1: Clinical manifestations of diabetic autonomic neuropathy (DAN).

Organ system	Sympathetic function	Parasympathetic function	Clinical manifestations
Cardiovascular	↑ in heart rate ↑ contractility	↓ in heart rate ↓ contractility	Resting tachycardia, exercise intolerance, orthostatic hypotension, silent myocardial ischemia, intraoperative cardiovascular lability
Gastrointestinal	↓ motility and secretion, ↑ sphincter tone	↑ motility and secretion ↓ sphincter tone	Esophageal dysmotility, gastroparesis, diarrhea, constipation, fecal incontinence, gall bladder atony
Genitourinary	Detrusor relaxation and trigone/sphincter contraction, ejaculation	Detrusor contraction and trigone/sphincter relaxation, erection	Neurogenic bladder, erectile dysfunction, retrograde ejaculation, female sexual dysfunction
Hypoglycemia counter regulatory	Secretion of epinephrine and norepinephrine from adrenal medulla	—	Hypoglycemia unawareness, hypoglycemia associated autonomic failure
Sudomotor	Slight localized secretion	Generalized secretion	Anhidrosis, hyperhidrosis, gustatory sweating
Peripheral microvascular	Constriction	Dilation	Dry skin, loss of nails, peripheral edema, venous prominence, high bone blood flow contributing to reduced bone density and Charcot's neuroarthropathy (?)
Pupillary	Mydriasis and ciliary relaxation for far vision	Miosis and ciliary contraction for near vision	Decreased resting and dark adapted pupil diameter and Argyll Robertson pupil

deficiency secondary to renal denervation may exacerbate orthostatic symptoms. In its most severe form, postural hypotension can be refractory to treatment and can be disabling making the patient wheelchair bound and unable to stand. This orthostasis has the following hemodynamic characteristics—

- There is a loss of the diurnal variation in blood pressure, with supine hypertension occurring at night.
- There is day-to-day variability of symptoms that may be exacerbated by insulin therapy, which can provoke hypotension.
- In occasional patients, supine and standing systolic blood pressures may fall profoundly after meals. The mechanism of postprandial hypotension in DAN is unclear. Inadequate sympathetic compensation to meal-induced pooling of blood in the splanchnic circulation and stimulation of vasodilatory gut peptides may contribute.

Silent myocardial ischemia: In non-diabetic patients, the risk of acute MI is highest in the morning. This diurnal pattern is altered in diabetic patients, who have a higher frequency of infarctions during the evening. Altered sympathovagal balance and reduced nocturnal vagal

activity in patients with CAN results in the blunting of the morning peak. Silent myocardial ischemia is more frequent in diabetic patients with CAN. The cause is unclear, however, it is said that the neuropathic damage of the myocardial sensory afferent fibers reduces the pain perception. A metaanalysis of 12 cross-sectional studies reported that silent myocardial ischemia occurs more frequently in patients with CAN than without CAN with a pooled prevalence rate ratio of 1.96 (1.53–2.51). However, the presence of CAN does not rule out myocardial ischemia as a cause of chest pain in a diabetic patient. Therefore, chest pain in any location in a diabetic patient should be considered of myocardial origin until proven otherwise. MI can also present atypically as unexplained fatigue, confusion, edema, hemoptysis, nausea and vomiting, diaphoresis, cough, and dyspnea.

Intraoperative cardiovascular lability: In patients with CAN, the normal autonomic response of vasoconstriction and tachycardia does not completely compensate for the vasodilating effects of anesthesia. CAN may be associated with more severe intraoperative hypothermia, which in turn can give rise to decreased drug metabolism and impaired wound healing. Some diabetic patients with autonomic neuropathy may have a reduced hypoxia-induced ventilatory drive.

Prognostic implications of CAN

Increased mortality: Longitudinal studies have shown that mortality rates over 5 years in patients with CAN are between 16% and 53%. Many deaths are due to associated macro and microvascular diseases. Few deaths have been attributed to cardiorespiratory arrest secondary to autonomic denervation. In the ACCORD trial, over 3.5 years, the overall mortality was 1.6–2.1 times higher in those with CAN at baseline.

Evaluation of CAN

Adverse cerebrovascular and renal outcomes—similarly, presence of CAN has been showed to be an independent risk factor for stroke and renal complications. In one particular study of 1,523 patients with diabetes followed for 16 years, higher resting HR and lower HRV was associated with increases risk of end stage renal disease.

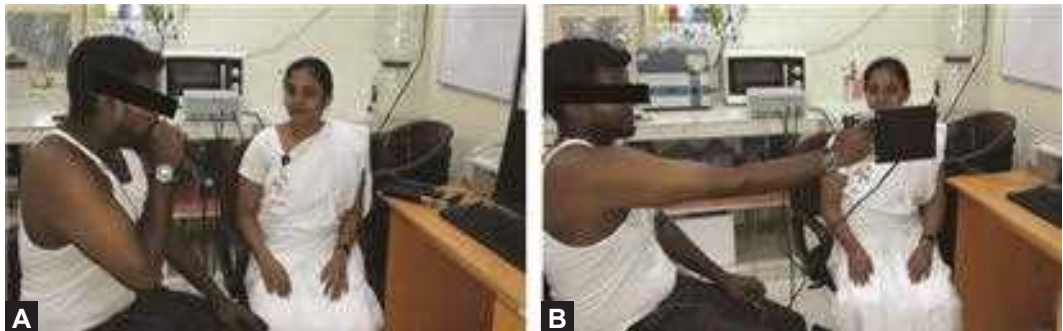
Sleep apnea: One quarter to half of type 1 diabetic patients with CAN have obstructive and/or central sleep apnea. In non-obese subjects with CAN and postural hypotension, the frequency of OSA is more than 30%. Ewing et al. in early 1970s, introduced five noninvasive cardiovascular reflex tests:

- Valsalva maneuver
- Heart rate response to deep breathing
- Heart rate response to standing up
- Blood pressure response to standing up
- Blood pressure response to sustained handgrip.

These tests are simple and reproducible (Table 17.2) and have been applied successfully for past few decades. Recently, automated computer based analyzers are available for use in office which analyze both the sympathetic and parasympathetic nervous systems (Figs. 17.2A and B). The system uses an ECG Cardio-Tochogram (R-R interval) and an advanced automatic noninvasive blood pressure module to conduct a battery of tests. Resting tachycardia and loss

Table 17.2: Diagnostic tests for cardiovascular autonomic neuropathy.

Test	Technique	Interpretation
HR response to Deep breathing	Patient lies quietly and breathes deeply at a rate of six breaths per minute and ECG is recorded The difference between the maximum and minimum heart rate and Expiration to Inspiration (E:I) R-R interval ratio are calculated	A difference in HR of < 10 bpm and E: I ratio is >1.17 are abnormal
HR response to Standing	ECG is recorded in lying followed by full upright position. The R-R interval is measured at beats 15 and 30 after the patient stands	A 30:15 ratio of < 1.03 is abnormal
HR response to Valsalva	The patient forcibly exhales into the mouth-piece of a manometer, exerting a pressure of 40 mm Hg for 15 seconds. There are 4 phases during this maneuver. The longest and shortest R-R intervals are measured. The ratio is called Valsalva ratio	Valsalva ratio of < 1.2 is abnormal
BP response to standing	BP is measured when the patient is lying down and 2 minutes after the patient stands	A systolic BP fall of ≥ 20 mm Hg or diastolic BP fall of ≥ 10 mm Hg is abnormal
BP response to isometric exercise	The patient squeezes a handgrip dynamometer to establish his or her maximum. The patient then maintains the grip at 30% maximum for 5 minutes. BP is measured in the contralateral arm	A diastolic BP rise of < 16 mm Hg is abnormal
Power spectral analysis by ECG	Frequency domain analyses on short R-R sequences (e.g. 7 min) or on 24-hour ECG recording. The heart rate power spectrum is typically divided into low (LF - 0.04 to 0.15 Hz) and high frequency (HF - 0.15 to 0.4 Hz) bands	A QTc of > 440 ms is abnormal. Depressed LF peak indicate sympathetic dysfunction Depressed HF peak indicates parasympathetic dysfunction. Lowered LF/HF ratio indicates sympathetic imbalance



Figs. 17.2A and B: Cardiac autonomic neuropathy analyzer is a simple bedside noninvasive system to assess the five cardiovascular reflexes. (A) Patient doing isometric exercise using dynamometer; (B) Patient performing Valsalva maneuver.

of heart-rate variation in response to deep breathing indicate parasympathetic dysfunction. Sympathetic function is tested using heart rate and blood pressure responses to standing, exercise and handgrip. The results of all these reflex tests need to be interpreted with reference to age-matched normal subjects. In general, for a confident diagnosis of CAN, the patient should have abnormalities in more than one test, which evaluate different limbs of the reflex arc.

The sympathetic innervation of the heart can also be noninvasively visualized and quantified by single photon emission computed tomography with Iodine-123 (I-123) metaiodobenzylguanidine (MIBG-SPECT) or 11-C-hydroxyephedrine scintigraphy. These tests are expensive, not widely available and are of limited clinical utility.

Treatment of CAN

Nonpharmacological measures: Cessation of smoking and tailored exercise programs are shown to improve autonomic function. In patients with OH, measures aimed at increasing peripheral vascular tone (such as body stockings and gravity suits) are often tried. However, they may not be effective since blood pooling probably occurs in the large splanchnic vascular bed. The following simple measures may also be helpful—(i) Changes in posture to be made slowly in “stages”. (ii) Tensing the legs by crossing them while actively standing on both legs. This procedure is shown to rise the cardiac output by 16% and the systemic blood pressure by 13%. (iii) Dorsiflexing the feet or doing handgrip exercise before standing can help reducing postural symptoms.

Pharmacological measures: Intensive glycemic control and stepwise implementation of multifactorial risk reduction including good BP and lipid control can slow the progression of CAN. For HRV, various drugs targeting the pathomechanisms of diabetic neuropathy have been studied in clinical trials. These include antioxidants, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone agonists, beta blockers and calcium channel blockers. Alpha lipoic acid, an antioxidant can slow down the progression and can even reverse autonomic neuropathy. Among the ACEIs, quinapril has been shown to improve parasympathetic activity after 3 months of treatment. Beta blockers that are cardioselective (e.g. atenolol) or lipophilic (e.g. propranolol) can block sympathetic stimuli either centrally or peripherally and thereby restore parasympathetic-sympathetic balance. Clinical trials have shown that with β -blockers there is significant reduction in mortality in post-MI diabetic patients.

In patients with OH, the major form of medical therapy is to increase the plasma volume with the mineralocorticoid fludrocortisone (0.1–0.4 mg/day). This regimen may be helpful in more severe cases but the dose needed for relief of symptoms can cause hypertension or peripheral edema. A high salt diet and increase in water consumption will also help. Atrial tachypacing, α adrenoreceptor agonist—midodrine, the β -blocker with intrinsic sympathomimetic activity—pindolol, fluoxetine and intranasal or oral desmopressin have also been tried with variable success. Clonidine has also been successfully used in few patients with OH with supine hypertension. The somatostatin analog octreotide may be useful in some patients with refractory and postprandial hypotension. Care should be taken to avoid drugs that can

exacerbate postural hypotension. Hematocrit should be checked and associated anemia should be treated, including the judicious use of erythropoietin.

Management of severe supine hypertension with OH is often challenging. In people with CAN, supine hypertension frequently occurs at night. To avoid hypotension at daytime, short acting antihypertensive agents like diltiazem, captopril and verapamil can be given at bedtime. Because of safety concerns, it is preferable to treat OH first.

Gastrointestinal (GI) Autonomic Neuropathy

Clinical Manifestations

Gastrointestinal symptoms are very common in diabetic patients but are more likely to be due to factors other than autonomic neuropathy. The involvement of GI tract is diverse in autonomic neuropathy and has a wide variety of manifestations.

Esophageal dysmotility: Gastroesophageal reflux disease (GERD) is a common symptom in diabetic patients and is possibly due to autonomic neuropathy causing decreased lower esophageal sphincter pressure, impaired clearance function of the tubular esophagus, or delayed gastric emptying. Even when there is abnormality of esophageal peristalsis in esophageal manometry, dysphagia is not a common symptom in patients with DAN. Therefore, dysphagia in diabetes mellitus is more suspicious of organic diseases such as peptic stenosis, esophageal cancer, etc. rather than dysmotility.

Gastroparesis diabetorum: Gastroparesis is defined as delayed gastric emptying. The classic symptoms include bloating, early satiety and postprandial fullness. However, the relationship between the common “dyspeptic” symptoms and the magnitude of delay in gastric emptying do not correlate well. Only a minority of patients with symptoms like epigastric pain, nausea, vomiting, early satiety, postprandial fullness and/or anorexia will be found to have significant abnormalities in gastric emptying. On the other hand, patients with significant delay in gastric emptying may not be symptomatic and may just present with poor glycemic control due to variability in glucose or oral hypoglycemic drug absorption. They can present with apparent “brittle diabetes” with wide swings of glucose levels and unexpected episodes of postprandial hypoglycemia.

The pathophysiology of diabetic gastroparesis is not straight forward, because the abnormalities in gastric emptying do not strongly correlate with the clinical indices of autonomic function. It may result from impaired neural control of gastric function. Abnormal myenteric neurotransmission, impairment of the inhibitory nitric oxide-containing nerves, damage of the pacemaker interstitial cells of Cajal, and underlying smooth muscle dysfunction have been described. In older studies, morphologic abnormalities like inflammatory changes in some autonomic ganglia and dropout of vagal myelinated fibers were reported. Apart from these, there is also a role of acute elevations of blood glucose in the impairment of gastric motility. The role of chronic hyperglycemia in its pathogenesis is not clear.

Diabetic enteropathy: Diarrhea and rarely steatorrhea can occur in diabetics, particularly those with advanced disease. Diarrhea is usually nocturnal, watery and painless and may be associated with fecal incontinence. Episodes of diarrhea may be alternating with normal

bowel habits or even with periods of constipation. The prevalence of diabetic diarrhea has been reported to be between 8% and 22%. The etiology of diabetic diarrhea is multiple and the putative mechanisms can be divided as those due to the autonomic neuropathy and those due to associated factors.

Causes of diarrhea due to autonomic neuropathy:

- Abnormal small intestinal and colonic motility
- Bacterial overgrowth leading to bile acid deconjugation and fat malabsorption
- Anorectal dysfunction—lowered rectal sensory threshold, weak internal anal sphincter
- Increased intestinal secretion—passive secretion due to osmotic gradient caused by altered motility and active secretion due to altered mucosal water transport and ion fluxes can cause this
- Exocrine pancreatic insufficiency.

Causes of diarrhea due to associated factors:

- Dietetic foods—sorbitol
- Concurrent celiac sprue—similar genetic predisposition in type 1 DM
- Altered bile acid pool and increased fecal secretion of hydroxyl fatty acids
- Bile acid malabsorption. Medications like metformin.

Constipation: The most common lower GI symptom occurring in approximately 60% of diabetic patients is constipation. It may be present alone or may be alternating with diarrhea. Rarely severe constipation may lead to fecal impaction and perforation. It is caused by the dysfunction of intrinsic and extrinsic intestinal neurons and decreased or absent gastrocolic reflex. Metformin therapy may also contribute to constipation.

Fecal incontinence: Fecal incontinence due to anorectal impairment is one of the distressing manifestations of GI autonomic neuropathy. It is thought to be relatively common, being present in 9% of diabetics with other diabetes-related complications but only 4% of those without complications. Abnormal internal anal sphincter tone, impaired anorectal sensation, abnormal external sphincter can often be demonstrated by anorectal manometry. Internal prolapse of the rectal anterior wall during straining may contribute to functional obstruction, incomplete evacuation, and fecal incontinence.

Gall bladder atony and enlargement: It is one of the infrequent manifestations of the autonomic involvement of GI tract.

Evaluation of GI Autonomic Neuropathy

GERD does not need any specific investigation; however, dysphagia needs investigations like endoscopy and barium swallow to rule out organic diseases. The diagnosis of gastroparesis is based upon the presence of classical clinical features, delayed gastric emptying, and the absence of an obstructing structural lesion in the stomach or small intestine by endoscopy or barium radiography. The presence of residual food in the stomach after an overnight fast during upper GI endoscopy is suggestive of gastroparesis. Stable isotope breath tests, scintigraphy, ultrasonography, and magnetic resonance imaging are the direct noninvasive means of measuring liquid and solid gastric emptying.

The traditional ideal method to establish the diagnosis of gastroparesis is solid-phase scintigraphic measurement of gastric emptying (Figs. 17.3A and B). Consensus statement regarding gastric emptying scintigraphy is given by the American neurogastroenterology and Motility Society and the Society of Nuclear Medicine. It suggests a protocol that involves a low fat, egg-white meal with imaging at 0, 1, 2, and 4 hours after meal ingestion. Normal values for the percent remaining in the stomach are 37–90% at 1 hour, 30–60% at 2 hours, and 0–10% at 4 hours. In clinical practice, the most useful values for diagnosis of delayed gastric emptying are retention of more than 10% at 4 hours, and more than 70% at 2 hours. Blood glucose should be well controlled at the time of testing, because hyperglycemia can alter gastric motility. With the increase in use of incretin-based therapies like GLP-1 analogues, iatrogenic gastroparesis should also be considered. Since the mechanisms of chronic diarrhea are multiple, the investigations should sequentially and systemically examine all those factors.

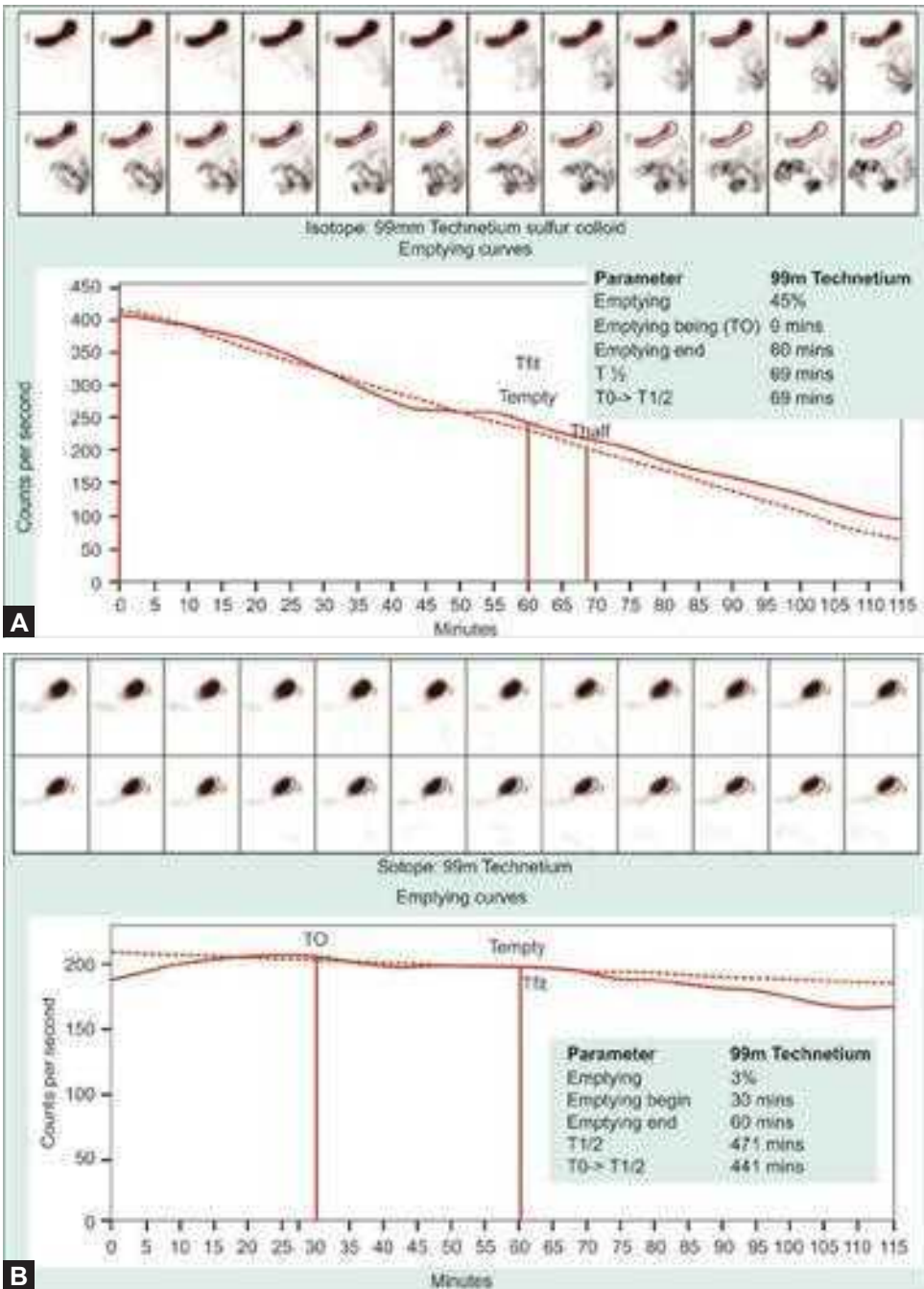
Table 17.3 summarizes the investigations for chronic diarrhea in a diabetic individual.

Treatment

While treating gastroparesis, it should be kept in mind that the treatment is symptomatic and that the correlation between the gastric emptying and the symptoms is poor. Primary treatment includes proper glycemic control, dietary changes, antiemetic and prokinetic agents. Dietary changes include multiple small meals (4–6 times per day), reducing fat content and restricting fiber intake to prevent bezoar formation. Drug therapy includes metoclopramide, domperidone, erythromycin and levosulpiride. Metoclopramide (10 mg orally 30 minutes before meals and at bedtime) accelerates gastric emptying and has a central antiemetic action.

Table 17.3: Investigations for chronic diarrhea in a diabetic individual.

Level of investigation	Tests
First line	Blood biochemistry
	Stool— weight, 72 hour fecal fat, elastase, chymotrypsin, leukocytes, parasites, occult blood
	Upper GI Barium studies with dedicated small bowel follow through—for gastric retention, pattern of malabsorption, small intestinal and colonic wall thickness
	D-Xylose test for small intestinal malabsorption
Second line	Upper GI endoscopy with duodenal biopsy for histology and bacteriology
	Colonoscopy and biopsy for histology
	¹³ C acetate breath test
	Glucose hydrogen breath test for bacterial overgrowth
Third line	Anorectal manometry and sensory testing if fecal incontinence is present
	Ambulatory small intestinal manometry for intestinal pseudo-obstruction
	Empiric cholestyramine for possible bile acid malabsorption
	Enteroscopy with biopsy and enteroclysis
	Secretin-pancreozymin test for pancreatic exocrine insufficiency



Figs. 17.3A and B: Gastric emptying study was done following oral administration of semisolid meal mixed with Tc-99m sulphur colloid. Dynamic images were acquired over 120 minutes. (A) Normal gastric emptying with an emptying time of 69 minutes (Normal 45–90 min); (B) Gastric half emptying > 120 minutes which is markedly prolonged, confirming gastroparesis.

The other possible mechanisms of action of metoclopramide are release of acetylcholine from intramural cholinergic neurons and direct stimulation of antral muscle. Domperidone (10–20 mg four times a day), a peripheral D2 receptor antagonist, can also be useful. Erythromycin and related macrolide compounds have motilin agonist properties. Intravenous and oral erythromycin (250 mg three times a day) improves gastric-emptying time in diabetic patients with gastroparesis. Majority of patients respond to drug therapy and jejunostomy tube placement is rarely necessary. Severe cases with intractable vomiting may benefit from nasogastric suctioning.

In patients with chronic diarrhea, initial management should focus on correction of water and electrolyte imbalance and nutritional deficiencies. Parenteral hyperalimentation may be needed in few patients with frequent hypoglycemic episodes. Long-term management of diarrhea should be planned according to the specific cause. Bacterial overgrowth should be treated with a course of antibiotics like metronidazole. Celiac disease and pancreatic exocrine dysfunction should be treated with gluten-free diet and pancreatic enzyme supplements, respectively. In patients with accelerated intestinal transit, antidiarrheal agents like loperamide, codeine and diphenoxylate may be helpful. Clonidine in the dose of as high as 0.6 mg thrice daily, has been shown to significantly reduce stool volume and frequency in patients with accelerated intestinal transit and increased intestinal secretion. In refractory cases, octreotide 50–75 µg twice or thrice daily may be tried. However, octreotide may worsen hypoglycemic episodes and may inhibit pancreatic exocrine secretion, exacerbating steatorrhea.

Fecal incontinence can be managed with two important measures—drugs to reduce stool volume like loperamide and biofeedback exercise with toilet training. With biofeedback training the threshold of conscious rectal sensation is lowered as far as possible (by training with a rectal balloon distended by progressively smaller volumes of air) and to increase the strength of the external anal sphincter contraction (by training with a surface electromyography electrode which registers the anal squeeze contraction force). Toilet training is done with controlled emptying of the rectal ampulla by using microclists or CO₂-suppositories. Biofeedback training is performed on an ambulatory basis and the patient is taught to do home exercises two to three times daily, each lasting 20–30 minutes. With this technique, improvement in incontinence can be expected in 3–6 months of training.

Genitourinary Autonomic Neuropathy

Clinical Manifestations

Neurogenic bladder: Approximately, 35–50% of patients with diabetes have symptoms of bladder dysfunction. Afferent sensations from the bladder are carried by sympathetic, parasympathetic and somatic nerves. The earliest autonomic dysfunction in diabetes is impairment of bladder sensation resulting in increase in the threshold for micturition reflex. The bladder capacity is increased and there may be decrease in the frequency of urination. The major excitatory input (nerve of emptying) is the parasympathetic system. When these efferent nerves are damaged, there may be symptoms like hesitancy, thin stream of urine and dribbling. Later, detrusor areflexia leads to incomplete evacuation, increased post voidal residue (PVR), bladder over

distension and urinary retention. The bladder dysfunction predisposes patients to frequent urinary tract infections (UTI), pyelonephritis and ultimately, renal dysfunction.

Erectile dysfunction (ED): Erectile dysfunction is the consistent inability to attain and maintain an erection adequate for sexual intercourse. It is usually qualified by being present for several months and occurring at least 50% of the time. It is the most common form of sexual dysfunction in males with diabetes. The etiology in diabetes is multifactorial, including neuropathy, vascular disease, metabolic control, nutrition, endocrine disorders, psychogenic factors, and drugs. Autonomic neuropathy contributes to ED through the loss of cholinergic activation of the erectile process. Acetylcholine acts upon the vascular endothelium to release nitric oxide and prostacyclin, both of which are required for the relaxation of the corpora cavernosa. This relaxation is essential for the increase in blood flow that causes an erection, which is impaired in ED. Nonadrenergic/noncholinergic nerve function may also be hampered which lead to decreased vasodilating neurotransmitters like vasoactive intestinal polypeptide, substance P, and others. Retrograde ejaculation into the bladder also occurs in diabetic males. It is due to loss of coordinated internal sphincter closure with external sphincter relaxation during ejaculation.

Sexual dysfunction in women: Women with diabetes are more prone to have decreased sexual desire and vaginal lubrication leading to dyspareunia.

Evaluation of Genitourinary Autonomic Neuropathy

Bladder function should be tested in all diabetic patients with bladder symptoms, palpable bladder, frequent UTI (> 2 per year) and pyelonephritis. Investigations should include renal function tests, urine culture and PVR by ultrasonography. PVR of more than 150 mL is suggestive of neurogenic bladder if other causes of obstruction are ruled out. Cystometry and voiding cystometrogram (Figs. 17.4A and B) can be done to assess the bladder sensations and pressure-volume changes by filling the bladder with known volumes of water and then voiding. The multiple potential etiologies for ED in a diabetic male makes it difficult to establish a diagnosis. Table 17.4 illustrates the steps involved in the investigation of ED.

Azoospermia along with spermaturia in the postcoital urine specimen confirms the diagnosis of retrograde ejaculation. There are no standard tests for diagnosing female sexual dysfunction. Vaginal plethysmography for measuring vaginal lubrication and flushing is not well established.

Treatment

A grossly over distended bladder should be catheterized and drained to improve contractility. Initial treatment consists of a strict voluntary urination schedule by the clock, frequently coupled with the Crede maneuver (manual abdominal pressure). Such scheduled urinations can be coupled with cholinergic agents like bethanechol (10–30 mg thrice daily). Extended sphincter relaxation can be achieved with a α 1-blocker, such as doxazosin. More advanced cases require clean intermittent self-catheterization, and in extreme cases, resection of the internal sphincter at the bladder neck may be required. Treatment for ED includes withdrawal of offending drugs, psychological counseling, medical treatment or surgery. Most men

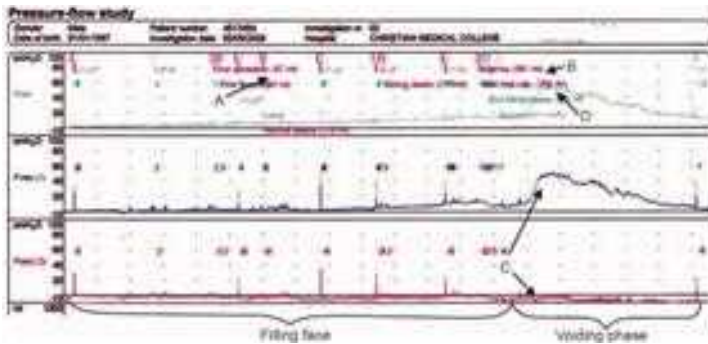


Fig. 17.4A: Normal cystometrogram showing normal sensation (A), compliance and bladder capacity (B) during filling. The voiding pressure is normal without abdominal straining (C) during the voiding phase indicating normal detrusor contraction (D).

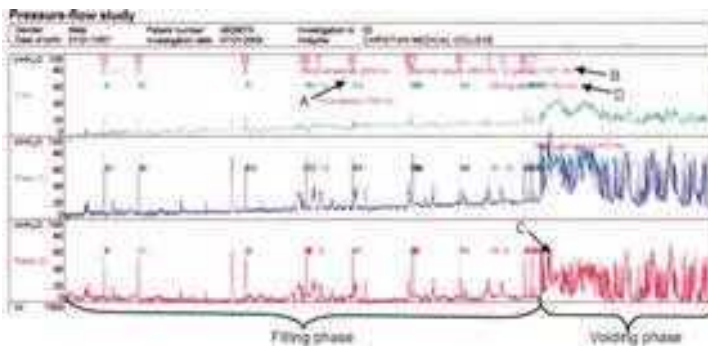


Fig. 17.4B: Cystometrogram of a patient with diabetic cystopathy showing first sensation to void at 660 mL (A) and maximum bladder capacity of 1220 mL (B), during filling phase. When asked to void, he voided with abdominal straining (C) with a postvoid residue of 1250 mL. This study is suggestive of a large capacity hyposensate bladder with hypocontractile detrusor (D) and large volume residual urine.

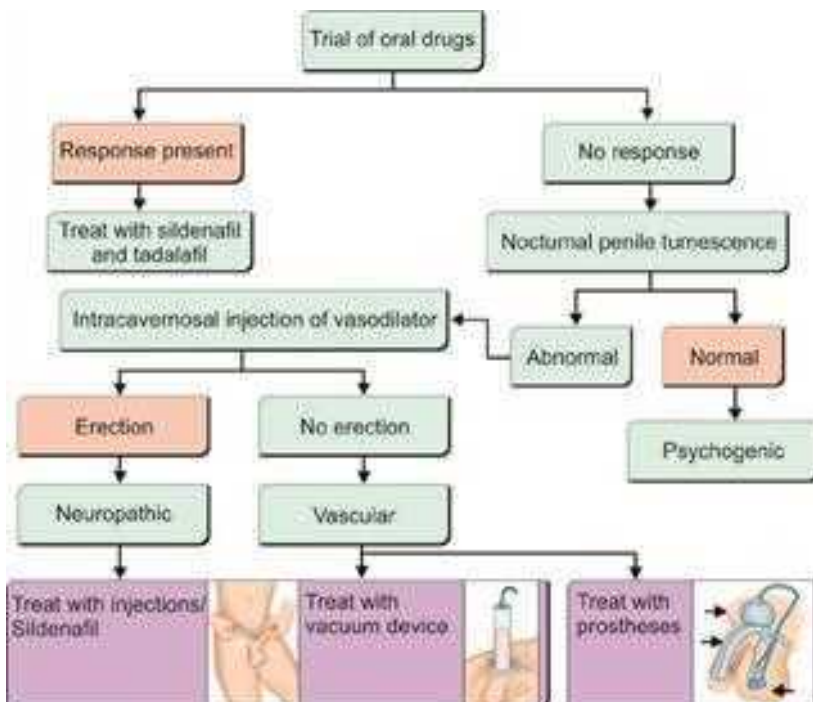
respond to 5-phosphodiesterase inhibitors. Sildenafil at a dose of 50 mg can be prescribed with the usual precautions regarding ischemic heart disease and nitrates. Tadalafil (20 mg) and vardenafil (20 mg) are the newer agents effective in more than 60% of diabetic patients with ED. Other therapies include the intracavernosal injection of vasoactive substances such as papaverine, phentolamine, and prostaglandin E1, transurethral delivery of vasoactive agents and the use of mechanical devices such as the vacuum erection device or constricting rings. Penile prosthetic implants may be used if these therapies fail or are not tolerated by the patient. Vaginal dryness can be treated with lubricants and estrogen cream. Retrograde ejaculation may respond to an antihistaminic drug. A stepwise Algorithm to manage erecting dysfunction is summarized in Flowchart 17.1.

Metabolic Manifestations of DAN

Hypoglycemia unawareness: The relationship between hypoglycemia unawareness and DAN is not clear. Patients with hypoglycemia unawareness or impaired hypoglycemia counter regulation may not have DAN. Similarly, it is not essential for all patients with DAN to be

Table 17.4: Evaluation of erectile dysfunction in diabetic patients.

History regarding	Drugs like antihypertensives and antidepressants
	Trauma
	Androgenisation
	Sexual function (libido, erectile and ejaculatory function)
	Autonomic nerve function
	Vascular function
↓	
Physical examination	Sexual development (penis, scrotum, breasts, hair, visual fields),
	Somatic nerve function (perianal sensation, anal wink, bulbocavernosus reflex and anal sphincter tone)
	Peripheral pulses
↓	
Investigations	Liver and renal function tests
	Serum testosterone and prolactin
	Autonomic function tests
	Vascular tests (penile Doppler with penile brachial index)

Flowchart 17.1: Algorithm for management of erectile dysfunction.

unaware of their hypoglycemia episodes. However, this relationship may be complex and there is some overlap between DAN and impaired hypoglycemia counter-regulation. Recent data suggest that autonomic neuropathy attenuates the epinephrine response to hypoglycemia in diabetic individuals after recent hypoglycemia episodes.

Hypoglycemic autonomic failure: The spectrum of reduced counter-regulatory hormone responses, in particular epinephrine and decreased perception of hypoglycemia symptoms due to decreased ANS activation, after recent antecedent hypoglycemia has been termed “hypoglycemia-induced autonomic failure”. This impaired counter-regulation and autonomic failure lead to frequent hypoglycemia episodes and this continues as a vicious cycle.

Sudomotor and Peripheral Microvascular Manifestations of DAN

Clinical Manifestations

Sudomotor involvement is common in diabetic autonomic neuropathy. This generally manifests as loss of sweating and dry skin in the extremities, which may be accompanied by excessive sweating in the trunk. Excessive sweating may occur as a compensatory phenomenon involving proximal regions such as the head and trunk that are spared in the dying-back neuropathy. Ultimately, there may be global anhidrosis. Gustatory sweating, the abnormal appearance of sweat over the face, head, neck, shoulders, and chest after eating, is less common.

Microvascular skin flow is regulated by ANS and the rhythmic contractions of arterioles and small arteries are disordered in DAN. Clinically, this manifests as changes in the texture of skin, loss of nails, anhidrosis, callus formation and the development of fissures and cracks that are portals of entry for microorganisms leading to infectious ulcers and ultimately gangrene. Peripheral edema and venous prominence occur and are often associated with poor wound healing. The loss of sympathetic vascular innervation results in high peripheral blood flow through arteriovenous (AV) shunts and abnormal local reflex vascular control. This leads to increased osteoclastic activity resulting in reduced bone density, proneness to fractures and is also thought to contribute to the pathogenesis of Charcot’s neuroarthropathy.

Evaluation

Sudomotor testing includes quantitative sudomotor axon reflex test (QSART), the sweat imprint, the thermoregulatory sweat test (TST), and the sympathetic skin response. The QSART involves iontophoresis of a cholinergic agonist to measure axon reflex-mediated sudomotor responses quantitatively to evaluate postganglionic sudomotor function. Sweat imprinting includes secretion of sweat glands into a plastic or silicone mold in response to iontophoresis of a cholinergic agonist. This test can determine sweat gland density, sweat droplet size, and sweat volume per area. TST is a well-standardized test and it evaluates the distribution of sweat by a change in color of an indicator powder on the skin after exposure to infrared light. The sympathetic skin response tests the peripheral autonomic surface potential generated by the sweat glands and overlying epidermis. This surface potential can be recorded using a surface electrode connected to a standard electromyogram instrument. Peripheral neurovascular responses can be assessed by measuring the alterations in the skin blood flow following hand grip, cold exposure and heating. These tests are particularly useful in the assessment of feet at risk for ulceration.

Treatment

Therapy for peripheral autonomic neuropathy centers on prevention of foot infection and ulceration. Proper foot care has to be taught to all these patients. Hyperhidrosis may be treated with anticholinergic agents such as trihexyphenidyl, propantheline, or scopolamine. High doses are usually required and hence therapy is complicated by other anticholinergic side effects, such as, urinary retention, dry mouth, and constipation. Glycopyrrolate may benefit diabetic patients with gustatory sweating. In addition, local intracutaneous injection of botulinum toxin type A may also be useful. If neuropathic peripheral edema is present, it can be distinguished from renal or cardiac cause by history and absence of elevation of jugular venous pressure. Such edema can be treated with simple measures like support stockings, foot elevation and diuretics. Sympathomimetic drugs may decrease edema by decreasing the AV shunting. Previously ephedrine was used in the dose of 30 mg thrice daily. Because of its prominent side effects, presently the drug of choice is midodrine (10 mg thrice daily). By decreasing the high bone blood flow, these sympathomimetic are also thought to be beneficial in the treatment of Charcot's neuroarthropathy.

Miscellaneous Manifestations of DAN

Pupillary involvement: Pupillomotor function impairment and Argyll-Robertson pupil are the pupillary manifestations of DAN. There may be delayed or absent reflex response to light, diminished hippus due to decreased sympathetic activity and reduced resting and dark adapted pupillary diameter.

Anemia of autonomic dysfunction: Type 1 diabetic individuals with early nephropathy and symptomatic autonomic neuropathy have been shown to have inappropriately low levels of erythropoietin (EPO) for the severity of their anemia. These individuals can, however, mount an appropriate EPO response to moderate hypoxia. The pathogenesis of this erythropoietin-deficient anemia is unclear. It has been hypothesized that reduced sympathetic stimulation of EPO production is the cause of ineffective erythropoiesis resulting in anemia.

CURRENT GUIDELINES FOR THE DIAGNOSIS OF DAN

The 1988 San Antonio conference, jointly sponsored by American Diabetes Association (ADA) and American Academy of Neurology (AAN), offered a consensus statement on testing for diabetic neuropathy including autonomic neuropathy. The following are the important general recommendations made by the panel:

- Symptoms possibly reflecting DAN should not, by themselves, be considered as markers of its presence.
- Noninvasive validated autonomic function tests should be used for diagnosis of DAN, after carefully excluding end organ failure and taking into account confounding factors like concomitant drug use, concurrent illness, age, etc.
- Abnormality in more than one test on more than one occasion is desirable for establishing a diagnosis of DAN.

- Both sympathetic and parasympathetic functions should be tested independently.
- While monitoring improvement or deterioration in the autonomic function, quantitative measures of autonomic reflexes should be used.

For the assessment of CAN, the panel recognized three tests of heart rate control, mainly for parasympathetic system (heart rate response to breathing, standing, and the Valsalva maneuver). Two tests of BP control were also recommended—BP response to standing or passive tilting and sustained handgrip. These tests were judged suitable for both routine screening and monitoring the progress of autonomic neuropathy. No other tests including those for GI, genitourinary, sudomotor, microvascular skin blood flow and pupillary function were considered to be sufficiently well standardized for routine clinical use. The San Antonio consensus panel also proposed staging of patients with DAN using the tests for cardiovascular autonomic function. This three stage model is as follows:

- *Early stage:* Abnormality of heart rate response during deep breathing alone
- *Intermediate stage:* An abnormality of Valsalva response
- *Severe stage:* The presence of postural hypotension.

However, these criteria appear to be arbitrary and not clearly evidence based. The second conference held in 1992 revised its recommendations to include three tests for longitudinal monitoring for cardiovascular autonomic function:

- Heart rate response to deep breathing
- Valsalva maneuver
- Postural BP response.

The panel also recognized that though there is an association between peripheral somatic neuropathy and DAN, parasympathetic dysfunction may appear independent of peripheral neuropathy. Hence, tests for sensory and motor nerve functions (e.g. monofilament, quantitative sensory testing, nerve conduction studies, muscle strength testing) may not be effective in detecting CAN that cardiovascular autonomic function testing can detect at early stage of emergence. Thus, tests for other forms of diabetic peripheral nerve dysfunction should not substitute for the tests for cardiovascular autonomic dysfunction.

The American Diabetes Association (ADA) recommends screening for DAN at the time of diagnosis of type 2 diabetes and five years after the diagnosis of type 1 diabetes. Screening should include a history and physical examination for autonomic dysfunction. Tests of heart rate variability may be indicated and if initial screening is negative, it should be repeated annually.

An expert panel from AAN reviewed the safety of these noninvasive testing procedures. They found that these tests carry a high value-to-risk ratio. Some tests may have few adverse effects. Valsalva maneuver can cause transient increase in intracranial, intrathoracic and intra-abdominal pressures with a theoretical possibility of intraocular hemorrhage and lens dislocation. However, there is no evidence in the published literature for deaths or adverse events attributable to these tests. When used properly by trained staff, autonomic function tests are safe and effective in diagnosis. There may be difficulty in performing these tests in children and mentally disabled, since patient cooperation is very essential. Elderly patients may pose similar challenges and deterioration of physiologic response due to aging may be of concern.

MANAGEMENT IMPLICATIONS OF DAN

After identification of DAN, management should be done accordingly, as discussed earlier. Unfortunately, physicians feel that screening for DAN is not of value because treatment options for the identified complications are limited. But the results of autonomic function tests can contribute to good diabetes management in the following ways.

To assist in the establishment of tight glycemic control—intensive glycemic control has been shown to delay the onset as well as slow the progression of DAN, especially in its earliest stages. Evidence of early autonomic dysfunction may bring patients to medical attention before serious complications emerge, making proactive treatment, especially intensive diabetes care, possible. Also, in patients with hypoglycemia unawareness, raising the blood glucose target may be necessary to prevent repeat hypoglycemia episodes. Thus, tight control in patients with DAN includes increased vigilance in glucose monitoring and re-education of the patient regarding hypoglycemia.

To facilitate decision to initiate treatment for CAN—Timely identification of autonomic dysfunction may expedite end-organ prophylaxis such as the use of ACE inhibitors, aspirin, tight BP and lipid control.

To modify lifestyle interventions—Determination of early stages of autonomic dysfunction could intensify the salience of measures such as diet and exercise. Recommendations with regard to exercise for individuals with CAN should be given with care. This does not mean that exercise is inappropriate for patients with CAN. In fact, studies have shown that physical training improved heart rate variation in insulin requiring diabetic individuals with early CAN. Appropriate exercise program should be developed to yield maximum benefits.

CONCLUSION

Autonomic dysfunction is a prevalent and serious complication for individuals with diabetes. The clinical manifestations of DAN produce troubling symptoms, and cause lethal dysfunction. History and physical examination are not sensitive for identification of early DAN and therefore noninvasive tests have been recommended. This does not diminish the importance of clinical evaluation and patient observation. The economic impact of autonomic function testing is minimal compared with that of the costs of treating a catastrophic event that would eventually occur. Given these economic and clinical implications, testing for cardiovascular autonomic dysfunction should be part of the standard of care for all diabetic patients. Identification of early DAN also has management implications encouraging patients and physicians to improve metabolic control and to use therapies proven to be effective in the treatment of DAN.

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2. Nanaiah A, Chowdhury SD, Jeyaraman K, et al. Prevalence of cardiac autonomic neuropathy in Asian Indian patients with fibrocalculous pancreatic diabetes. *Indian J Endocrinol Metab.* 2012; 16 (5):749-53.
3. Serhiyenko VA, Serhiyenko AA. Diabetic cardiac autonomic neuropathy: Do we have any treatment perspectives? *World J Diabetes.* 2015;6(2):245-58.

SELF-ASSESSMENT

- 1. Which one of the following imaging is used to assess cardiac autonomic innervation?**
 - (a) Stress echocardiography
 - (b) MIBI scan
 - (c) MIBG SPECT scan
 - (d) FDG-PET scan
- 2. Which of the following drug is used for treating orthostatic hypotension?**
 - (a) Hydrocortisone
 - (b) Fludrocortisone
 - (c) Carvedilol
 - (d) Prazosin
- 3. Which of the following cardiovascular autonomic test result is abnormal?**
 - (a) Expiration to inspiration R-R interval ratio < 1.17
 - (b) Valsalva ratio < 1.2
 - (c) BP response to isometric exercise > 16 mm Hg
 - (d) A 30:15 R-R interval ratio on standing > 1.03
- 4. The most common cause of dysphagia in a diabetic patient is:**
 - (a) Functional
 - (b) Esophageal dysmotility due to autonomic neuropathy
 - (c) Organic causes like candidiasis, stenosis, cancer, etc.
 - (d) Delayed gastric emptying
- 5. The pathogenetic mechanisms of diarrhea in type 2 diabetes mellitus (T2DM) are:**
 - (a) Abnormal intestinal motility
 - (b) Anorectal dysfunction
 - (c) Bacterial overgrowth
 - (d) Celiac disease
- 6. What is the traditional method used to confirm gastroparesis?**
 - (a) Upper GI endoscopy
 - (b) Electrogastrography
 - (c) CT scan of abdomen
 - (d) Gastric emptying scintigraphy
- 7. Which of the following is used to treat gastroparesis?**
 - (a) Domperidone 10 mg thrice a day
 - (b) Pantoprazole 40 mg once a day
 - (c) Erythromycin 500 mg four times a day
 - (d) Ondansetron 4 mg thrice a day
- 8. All the following are manifestations of neurogenic bladder *except*:**
 - (a) Decrease in frequency of urination
 - (b) Hesitancy
 - (c) Urgency
 - (d) Urine retention
- 9. What is significant post-voidal residue of urine?**
 - (a) 60 mL
 - (b) 100 mL
 - (c) 250 mL
 - (d) 150 mL
- 10. Which one of the following can be used to treat neurogenic bladder?**
 - (a) Bethanechol
 - (b) Prazosin
 - (c) Oxybutynin
 - (d) Transurethral vasoactive agents

CHAPTER

18

Infections in Diabetes

George M Varghese, Ravikar Ralph, Abraham OC

*“When I go to the loo, my urine it bakes,
I have high fever and my body it shakes,
Bugs are growing in the cultures they say,
I will need antibiotics for many a day.”*

Infections are common in patients with diabetes mellitus and such infections result in complications and death more frequently than would be anticipated in otherwise healthy individuals. Patients with diabetes mellitus type 1 and 2 are at increased risk for infections, commonly of the lower respiratory tract, urinary tract, skin and soft tissue. Many specific infections are more common in diabetic patients and some occur almost exclusively in them. Others occur with increased severity and are associated with an increased risk of complications in patients with diabetes.

INTRODUCTION

Infections in diabetes mellitus are relatively more common which can be serious and result in worse outcome. Acute metabolic decompensations in patients with diabetes during infections are common, and conversely patients with metabolic decompensation are at higher risk of certain infections. Several limitations exist in management of infections in subjects with diabetes. The most important factor is to determine an appropriate estimate of the population at risk and the appropriate form of antimicrobial therapy. A number of variables, including the duration of illness, the severity of noninfectious complications, concurrent illnesses and the degree of hyperglycemia result in a heterogeneous group of individuals at risk.

Predisposing Factors

These are host and organism-specific factors that may explain why people with diabetes are more susceptible to particular infections.

Host Factors

1. *Impairment of immune response:* Hyperglycemia impairs neutrophil chemotaxis and adherence to vascular endothelium. Opsonophagocytosis is impaired because NADPH

is diverted from superoxide production into the polyol pathway. Intracellular bactericidal activity and cell-mediated immunity are also depressed in diabetic patients.

2. *Vascular insufficiency* this results in local tissue ischemia, enhancing the growth of microaerophilic and anaerobic organisms. There is also impairment of the oxygen-dependent bactericidal functions of leukocytes. Vascular disease related to diabetes may also impair the local inflammatory response and the absorption of antibiotics.
3. *Sensory neuropathy*: Unnoticed local trauma in patients with diabetes-associated peripheral neuropathy may result in skin ulcers resulting in diabetic foot infections.
4. *Autonomic neuropathy*: Sudomotor involvement leads to dry skin in the periphery especially in the feet leading to fissures giving way to foot ulcers. Bladder involvement leads to urinary retention and stasis that, in turn, predisposes them to develop urinary tract infections.
5. *Increased skin and mucosal colonization*: Patients with diabetes, particularly those who are on insulin, often have asymptomatic nasal and skin colonization with *Staphylococcus aureus* which are more likely to be methicillin-resistant. This colonization may predispose to cutaneous or incisional Staphylococcal infections as well as transient bacteremia, resulting in infection at distant sites such as damaged muscle. Mucosal colonization with *Candida albicans* is also common.

Organism Specific Factors

There are several organism-specific factors that predispose diabetics to infection.

1. *Candida albicans* has glucose-inducible proteins which promote adhesion to buccal or vaginal epithelium. This gives the organism an advantage over the host because adhesion impairs phagocytosis.
2. *Rhizopus* species have ketone reductases which allow them to thrive in high glucose, acidic conditions typically seen in diabetic ketoacidosis (DKA).

Infections with an Increased Prevalence in Patients with Diabetes

Head and Neck

- Oral and esophageal candidiasis.

Genitourinary

- Bacteriuria and cystitis in women
- Pyelonephritis and perinephric abscess.

Skin and Soft Tissue

- Surgical site infection
- Cellulitis and osteomyelitis of the extremities
- Pyomyositis.

Pulmonary

- Tuberculosis
- Staphylococcal and Gram-negative pneumonia.

Abdominal

- Emphysematous cholecystitis
- Infections with *Salmonella enteritidis*, *Campylobacter jejuni* and *Listeria monocytogenes*.

Certain infections occur more commonly in patients with diabetes, while certain other infections tend to be more severe in diabetic hosts.

Infections Unique to Patients with Diabetes

Head and Neck

- Rhinocerebral mucormycosis
- Malignant otitis externa.

Urinary Tract

- Emphysematous cystitis
- Emphysematous pyelitis and pyelonephritis.

Skin and Soft Tissue

- Synergistic necrotizing cellulitis
- Fournier's gangrene.

It should be noted that good glycemic control can rectify some of the phagocytic defects. This is best illustrated in the reduction of postoperative wound infection in patients with better perioperative glycemic control.

SPECIFIC INFECTIONS

Head and Neck Infections

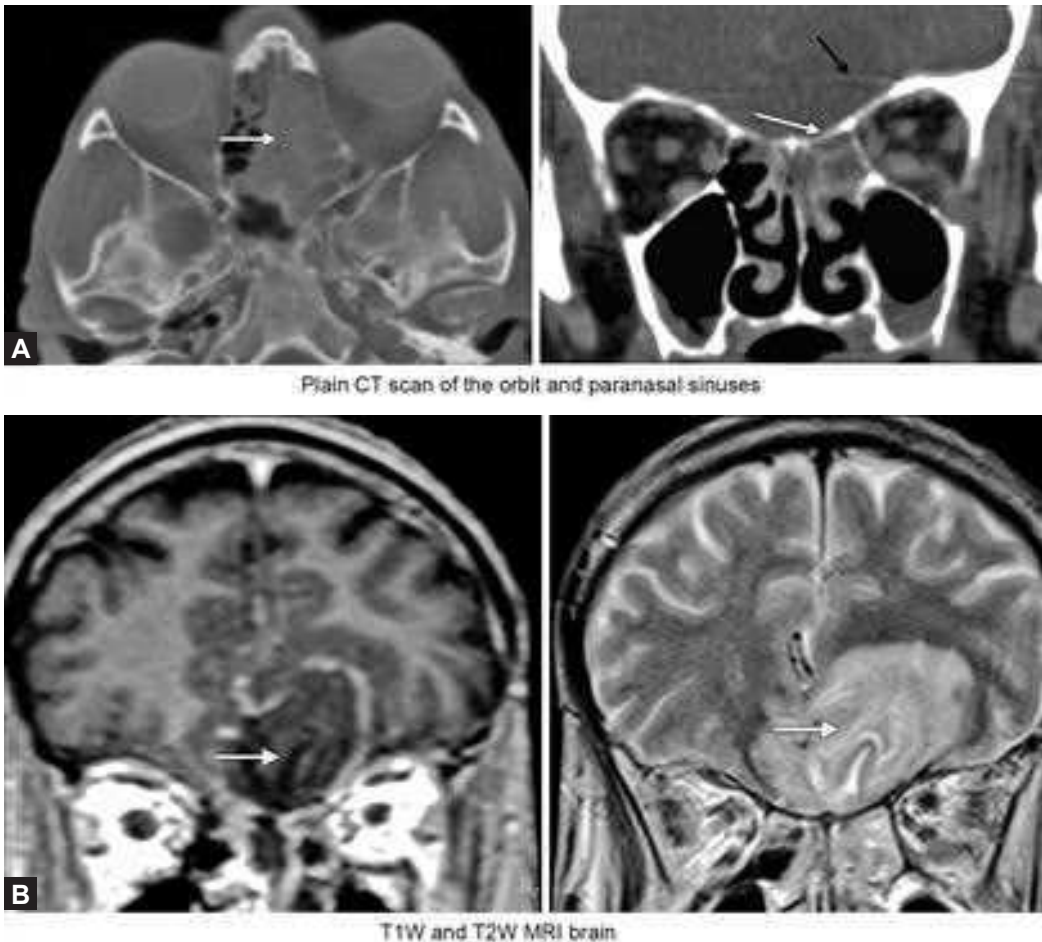
The two important infections that occur in patients with diabetes are rhinocerebral mucormycosis and malignant otitis externa. Although rare, these diseases can be life-threatening.

Rhinocerebral Mucormycosis

This fungal infection is caused by members of the order Mucorales (*Rhizopus*, *Absidia*, *Mucor*, etc.) and is promoted by DKA. The pathogenicity of these organisms is characterized by a ketone reductase system, allowing them to thrive in an acidic pH and glucose rich medium and the ability to invade arterial blood vessels. Upon inhalation, the air-borne spores reach the paranasal sinuses, germinate and spread to invade the palate, sphenoid bone, cavernous sinus, the orbit and the brain. The patient presents with headache, facial pain and swelling,

ocular pain or periorbital swelling and nasal obstruction with discharge. Progression is rapid and extension into the cranial cavity with involvement of the vasculature (carotid artery) can lead on to neurological deficits. Other signs of extension include proptosis, ophthalmoplegia and visual loss and cranial nerve palsies.

Imaging by computed tomography (CT) scan can confirm the diagnosis and extent of the lesions. Biopsy from the lesion can demonstrate broad, aseptate fungal hyphae. The organism also grows in fungal culture media like Sabouraud's dextrose agar, though culture often yields no growth (Figs. 18.1A and B).



Figs. 18.1A and B: Rhinocerebral mucormycosis. A 66-year-old elderly gentleman with long-term uncontrolled diabetes presented with left sided headache and orbital pain. Rigid nasal endoscopy showed mucopurulent discharge from left middle meatus. His nasal swab fungal culture showed broad aseptate fungal hyphae—*Rhizopus arrhizus*. (A) Opacified ethmoid sinuses on the left with defect in the anterior ethmoid roof (white arrow). The adjoining basifrontal region shows hypodensity suggestive of contiguous inflammation and infection (black arrow); (B) An abscess in evolution (hypointense on T1W with peripheral subtle enhancement and hyperintense on T2W) involving bilateral basifrontal regions, left more than the right, contiguous with the left ethmoid involvement and posterior ethmoid defect (white arrow).

The management consists of extensive surgical debridement, systemic antifungal therapy and control of the predisposing condition (hyperglycemia and metabolic acidosis). Surgery (extensive debridement of necrotic lesions) should be undertaken as soon as the diagnosis is suspected. Intravenous (IV) amphotericin B is essential for initial therapy following surgery. Considering the toxicity profile and outcome, liposomal amphotericin (5 mg/kg IV Q 24 hours in 5% dextrose) is preferred over amphotericin B deoxycholate (0.7–1.5 mg/kg/day in 5% dextrose solution over 4 hours). Infusion related reactions like fever and chills can be controlled with the use of paracetamol and antihistamines prior to infusion and in some cases pethidine may be required. Long-term toxicity primarily involves the kidney and for this reason, routine regular monitoring (every 2nd to 3rd day) of serum creatinine and potassium is required. Potassium replacements may be required and should always be administered orally or parenterally through the central line. In the event of worsening of renal function, the daily dose needs to be reduced. Prolonging the duration of infusion has been shown to decrease toxicity. As therapy is prolonged, a central venous access is ideal. Lipid coformulations permit larger doses to be administered daily with lesser toxicity, however, they are expensive. Posaconazole, an orally available broad spectrum triazole (400 mg twice a day) is the only azole that has proven efficacy in mucormycosis. Oral therapy is recommended for continuation therapy after the initial IV therapy. Side effects associated with Posaconazole therapy include QT prolongation and Torsades and hepatic dysfunction. Concomitant administration with proton pump inhibitors decreases its bioavailability and must thus be avoided. If combination with a proton pump inhibitor cannot be avoided, serum levels of Posaconazole should be monitored at all times to evaluate absorption, or antifungal therapy should be switched to an alternative compound. Optimum duration of therapy is debated and is based on individual judgment. One should consider clinical as well as radiological resolution, negative culture and biopsies with recovery from immunosuppression. Mortality is up to 20% despite adequate therapy. Voriconazole, fluconazole and echinocandins have not been shown to be effective.

Malignant Otitis Externa

Most patients (90%) with this condition have some form of glucose intolerance including diabetes. Other than poor glycemic control, risk factors include aging, swimming and use of a hearing aid. The patient presents with severe earache, with inflammation of the canal, which is evident on otoscopic examination. The infection spreads to the temporal bone and involves the facial nerve frequently. Involvement of the other lower cranial nerves, the sigmoid sinus, the meninges and the mastoid air cells are infrequent. *Pseudomonas aeruginosa* is the causative organism in majority of cases. Other rare organisms include *Staphylococcus aureus*, *Proteus mirabilis*, *Klebsiella oxytoca* and *Burkholderia cepacia*.

Magnetic resonance imaging (MRI) or CT scan will delineate the extent of involvement, but cannot reliably rule out squamous cell carcinoma and a biopsy may be indicated in this situation. *Pseudomonas aeruginosa* can be isolated on bacterial culture from the involved tissue.

Aggressive surgical debridement followed by IV antipseudomonal antibiotic therapy like Ceftazidime at a dose of 2 g every 8 hours or Cefepime 2 g twice daily is required. If underlying osteomyelitis is suspected at the time of surgery, antibiotics should be given for 4–6 weeks.

In this situation, ciprofloxacin at a dose of 750 mg twice daily orally is a suitable agent. Drug resistant pseudomonas is on the rise and many patients may require prolonged hospital stay with parenteral antibiotics like piperacillin or carbapenems with or without aminoglycosides after culture susceptibility report. There is no role for topical antimicrobial agents. In spite of early diagnosis and treatment, mortality approaches 20%. Relapses are frequent and may be prevented by prolonging antibiotic therapy.

Periodontal Infections

The risk of oral infections, particularly periodontitis amongst patients with uncontrolled or poorly controlled diabetes is generally two to four times higher than in healthy individuals. Periodontitis is associated with substantial morbidity in the form of tooth loss, which directly affects nutritional status and the quality of life.

Pulmonary Infections

Diabetes is associated with an increase in severity as well as recurrence of community acquired pneumonia. Two patterns of susceptibility to pneumonia in patients with diabetes have been noted. Infections caused by certain microorganisms (*Staphylococcus aureus*, Gram-negative organisms and *Mycobacterium tuberculosis*) occur with increased frequency. Infections due to other microorganisms (*Streptococcus pneumoniae* and influenza virus) are associated with increased mortality and morbidity.

Initial antibiotic therapy in diabetics with respiratory tract infections should target common community acquired pathogens including atypical bacterial organisms such as *Mycoplasma* and *Legionella*. The preferred agent for lobar pneumonia is still crystalline penicillin (at a dose of 0.2 million units every 4 hours intravenously if the patient is not allergic), as the organism (*Pneumococcus*) is exquisitely sensitive. Pneumococcal resistance to penicillin is not significant even in tertiary care centers.

As the risk of severe bacteremia, ketoacidosis and mortality of community acquired pneumonia in hospitalized patients is higher in those with diabetes, pneumococcal vaccination may be offered. Guidelines recommend pneumococcal vaccines for all patients with diabetes.

The relative risk of developing pulmonary tuberculosis and mortality is several times higher in patients with diabetes mellitus than in matched controls. But the clinical symptoms and presentation of pulmonary tuberculosis is similar with or without diabetes mellitus and so are the bacteriological conversion rates and relapse rates. Treatment regimens are the same as in nondiabetic individuals. An increase in the doses of oral hypoglycemic drugs is needed because of the interaction with rifampicin.

Urinary Tract Infections

Bacteriuria and Cystitis in Women

Asymptomatic bacteriuria (ASB) refers to the presence of high quantities of a uropathogen in the urine of an asymptomatic person. The 2005 Infectious Diseases Society of America (IDSA) guidelines recommend the following criteria for the diagnosis of ASB in adults:

- For asymptomatic women, bacteriuria is defined as two consecutive clean-catch voided urine specimens with isolation of the same bacterial strain in counts $\geq 10^5$ cfu/mL
- For any asymptomatic patient, bacteriuria is defined as a single catheterized urine specimen with one bacterial species isolated in counts $\geq 10^2$ cfu/mL.

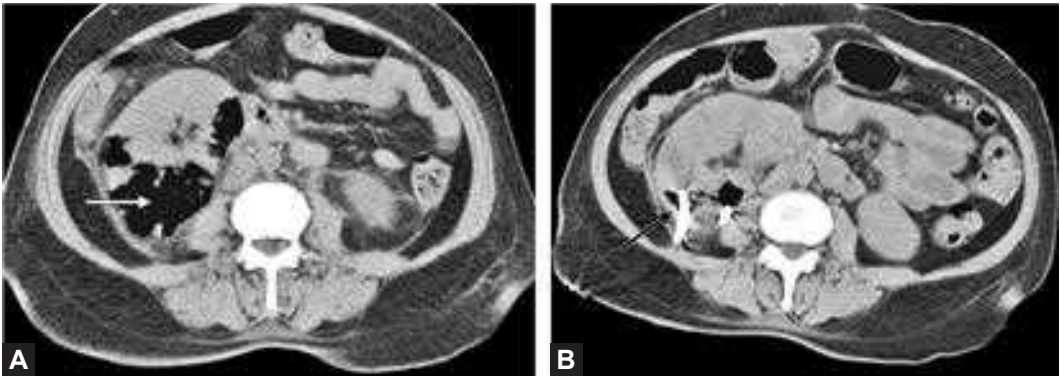
Women with diabetes have a three to fourfold increased risk of bacteriuria and the risk is higher in those with advanced or severe disease.

Asymptomatic bacteriuria often precedes symptomatic urinary tract infection in diabetes and the risk of progression to upper urinary tract infection is higher. The overall prevalence of ASB is around 26% in diabetic women. Routine screening of women with diabetes is not considered cost-effective. Although persons with bacteriuria are at an increased risk of symptomatic urinary infection, treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic infection or improve other outcomes. Thus, in populations other than those for whom treatment has been documented to be beneficial, pregnant women and patients undergoing urological interventions, screening for or treatment of ASB is not appropriate and should be discouraged.

Cystitis can be diagnosed by the presence of dysuria, the triad of suprapubic pain, frequency and urgency. The presence of fever, flank pain, costovertebral angle tenderness and nausea or vomiting suggests an upper tract infection and warrant more aggressive diagnostic and therapeutic measures. The bacteriology is similar to those with ASB. A urine culture should be checked whenever possible and antibiotic choices should be made according to microbiology and *in vitro* susceptibility data. The choice of antibiotics in symptomatic infection is the same as in a nondiabetic person. Double strength cotrimoxazole twice daily or ciprofloxacin 500 mg twice daily, need to be given for a longer duration (7–14 days) as compared to the 3–5 days regimen. Cotrimoxazole may be associated with hypoglycemia which may be wrongly attributed to antidiabetic agents. Attempts must be made to confirm cure after treatment. Recurrences are common.

Acute Pyelonephritis

Pyelonephritis is more common in those with diabetes and is more likely to involve both kidneys. The patient presents with fever, dysuria and loin pain radiating to groin. There is an increased risk of complications—perinephric abscess, emphysematous pyelonephritis and renal papillary necrosis. Ultrasound scan of the abdomen should be obtained to look for any features of obstruction or abscess. *E. coli* and *Klebsiella* are the common causative agents and extended-spectrum beta-lactamase (ESBL)-producing bacteria have become wide spread. ESBLs are beta-lactamase enzymes that can be produced by bacteria (*E. coli*, *Klebsiella*, etc.) making them resistant to penicillins, third generation cephalosporins and aztreonam. Carbapenems are the most effective and reliable options as they are highly resistant to the hydrolytic activity of all ESBL enzymes. For community acquired strains of Enterobacteriaceae, Ertapenem 1 g intravenously has been found to be effective. Patients with nonsevere pyelonephritis and no features of systemic inflammatory response, a betalactam-betalactam inhibitor combination such as cefoperazone-sulbactam 3 g IV Q 12 hours may be used. If fever persists beyond 4–5 days in spite of adequate antimicrobial therapy, a search



Figs. 18.2A and B: A 48-year-old postmenopausal lady with diabetes presented with high grade fever with chills, vomiting and right flank pain. Her urine culture grew extended spectrum beta lactamase (ESBL) producing *E. coli*. (A) Noncontrast CT abdomen showed bulky right kidney with extensive air in the renal parenchyma (white arrow); (B) Repeat CT after percutaneous nephrostomy (PCN) shows bulky right kidney with significant reduction in the air. The black arrow shows the PCN tube *in situ*.

for complications should be made and an ultrasonography, CT scan or MRI is ideal. Surgical drainage of the abscess is indicated if it is large, or if fever persists for more than a week after starting antimicrobial therapy (Figs. 18.2A and B).

Emphysematous Pyelonephritis

This severe form of acute multifocal bacterial nephritis occurs almost exclusively in diabetics. The risk is enhanced in women with obstruction to drainage of urine. *E. coli* and Gram-negative coliforms are the usual causative pathogens. The patient presents with a flank mass in addition to features of acute pyelonephritis and sometimes crepitus may be elicited. Gas can be demonstrated on plain film, but CT scan is more sensitive and can assess the extent of involvement.

Based upon CT scan findings, four prognostic classes can be identified:

- *Class 1:* Gas in the collecting system only (i.e. emphysematous pyelitis).
- *Class 2:* Gas in the renal parenchyma without extension to the extrarenal space.
- *Class 3A:* Extension of gas or abscess to the perinephric space (defined as the area between the fibrous renal capsule and the renal fascia).
- *Class 3B:* Extension of gas or abscess to the paranephric space (defined as the space beyond the renal fascia) and/or extension to adjacent tissues such as the psoas muscle.
- *Class 4:* Bilateral or a solitary functioning kidney with emphysematous pyelonephritis.

Although surgery (nephrectomy) was performed routinely, consensus now favors conservative therapy including placement of percutaneous catheter drainage nephrostomy (PCN) for drainage.

- All patients are treated with parenteral antibiotics and obstruction, if present should be relieved
- Class 1 disease (pyelitis without abscess or obstruction) can be treated with antibiotics alone. Other patients with class I disease and patients with class II disease should be treated with antibiotics plus percutaneous catheter drainage (PCD)

- Patients with class 3A or 3B disease at low-risk (defined as none or only one of the following risk factors: thrombocytopenia, acute renal failure, impaired consciousness, or shock) can initially be treated with antibiotics plus PCD. However, given the lack of evidence some urologists still go for early nephrectomy in all patients with class 3 disease
- Patients with class 3A or 3B disease with two or more of the above risk factors should be treated with antibiotics plus immediate nephrectomy
- Patients with class 4 disease (bilateral involvement or infection is a solitary functioning kidney) should initially be treated with antibiotics plus bilateral PCD. Nephrectomy is a last option
- Nephrectomy is indicated in all patients in whom PCD is unsuccessful.

Mortality with medical therapy is 60–80%, but can be reduced to 20% with surgical drainage.

Patients who present with sepsis and disseminated intravascular coagulation, shock or renal failure have a higher mortality.

Abdominal and Gastrointestinal Infections

Emphysematous Cholecystitis

Emphysematous cholecystitis is a rare and serious infection, more commonly in those with diabetes. In addition to the usual clinical presentation of uncomplicated cholecystitis, fever with chills, pain in the right upper abdomen and crepitus may be present. The infection is usually polybacterial (*E. coli*, *Bacteroides* and *Clostridium*) and the diagnosis can be confirmed by plain films or CT scan which shows gas in the region of the gall bladder. Rapid surgical excision and broad spectrum antibiotics (piperacillin-tazobactam 4.5 g every 8 hours or ertapenem 1 g once a day) can limit mortality to less than 20%.

Enteric Pathogens

Patients with diabetic autonomic neuropathy causing gastrointestinal dysmotility are at an increased risk to infections caused by many pathogens, especially *Salmonella* and *Campylobacter*. Clinical presentation, diagnosis, complications and treatment of typhoid is as in those without diabetes (oral ciprofloxacin 750 mg twice daily for 14 days).

Skin and Soft Tissue Infections

Intertrigo

This is an inflammatory condition of two closely apposed skin surfaces that is common in diabetics. Heat, moisture and friction lead to irritation of the skin and predispose to fungal infection. The lesions are usually weeping red patches or plaques with surrounding satellite papules. Diagnosis is by clinical examination, but can be confirmed by staining scrapings with potassium hydroxide (KOH) and examination under the microscope. The involved area should be kept dry and topical agents like clotrimazole, miconazole or ketoconazole could be used two to four times a day.

Dermatophyte (Tinea) Infections

Three types of superficial fungi/dermatophytes account for the majority of infections—*Epidermophyton*, *Trichophyton* and *Microsporum*. The infestations with varied presentation are named by location and have similar treatment. It is always worthwhile confirming the diagnosis by a scraping mounted with KOH, to avoid unnecessary use of steroid combinations and to avoid misdiagnosing conditions like eczema that can mimic a dermatophyte infection. In case of lesions involving the scalp (tinea capitis), oral therapy is preferred with terbinafine 250 mg daily for a span of 6–12 weeks. Patients with involvement of the trunk or feet are best treated with topical antifungal creams like 1% terbinafine, 1% miconazole, 2% ketoconazole or 2% miconazole for 6 weeks.

Pyomyositis

This is a bacterial infection of skeletal muscle characterized by muscle pain and swelling, more commonly seen in the tropics. It occurs at two age groups—(1) 2–5 years of age and (2) again between 35 years and 40 years. Although most patients do not have diabetes, those with diabetes have a higher chance of developing this infection. More than 90% of the infection is due to *S. aureus*. There is leukocytosis with elevation of the erythrocyte sedimentation rate (ESR) and creatine kinase. Blood cultures have a poor yield, but tissue cultures are useful in isolating the organism. Surgical drainage of abscesses along with antibiotics like cloxacillin 2 g every 4–6 hours or cefazolin 2 g every 8 hours is indicated. In patients with hypersensitivity to penicillin, vancomycin can be used. The duration of therapy is usually 4–6 weeks. Recurrences can occur.

Synergistic Necrotizing Cellulitis

This severe form of necrotizing fasciitis, with extensive involvement of underlying muscles, is unusual in those without diabetes. Patients present subacutely—the soft tissues of the perineum and lower limb are very painful, with areas of skin necrosis and ulcers with drainage of foul smelling fluid. The skin, muscle, fat and fascia are infiltrated by the infection. In the absence of prompt therapy, the patient can progress to ketoacidosis. The infection is usually polybacterial and cultures from the involved tissues are not always useful. Imaging is also not useful in delineating the amount of involvement and surgical exploration takes priority over imaging or culture reports if the diagnosis is suspected. Extensive surgical debridement and broad spectrum antibiotics (crystalline penicillin 20 L units iv Q4H with clindamycin 600 mg every 8 hours) should be initiated early. If the patient has had previous antibiotic therapy, penicillin should be substituted by piperacillin/tazobactam 4.5 g every 6 hours.

Fournier's Gangrene

This is a form of necrotizing fasciitis occurring in the genitalia of males with diabetes, particularly in the elderly. Predisposing genitourinary defects may be identified in most cases—urethral stricture with extravasation of urine, urinary tract trauma caused by instrumentation, perianal fissure or abscess, chronic disease or trauma of the perineal skin. There is extensive tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial

planes and infiltration by acute inflammatory cells. The patient experiences scrotal discomfort progressing to erythema, edema and skin necrosis. This may then spread along the abdominal wall, buttocks or thighs. The infection is usually polybacterial and can be confirmed by tissue cultures. Deeper samples taken during surgery are often more useful in identifying the organisms involved. Extensive debridement is necessary but orchidectomy and penile amputation is usually not required. The choice of antibiotics is the same as in synergistic necrotizing fasciitis. Despite good antimicrobial therapy, the mortality is 25–35%.

Diabetic Foot Infections

Diabetic foot infections span a spectrum including paronychia, cellulitis, myositis, necrotizing fasciitis, osteomyelitis and the classic foot ulcer.

The predominant organisms in the diabetic foot infections and ulcers are aerobic Gram-positive cocci namely *S. aureus* and *Streptococci*.

The severity of the infection can be clinically classified using the IDSA, 2004 guidelines on diabetic foot infections:

1. *Uninfected*: Wound lacking purulence or any manifestations of inflammation.
2. *Mild*: Presence of two manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness.
3. *Moderate*: Infection (as earlier) in a patient who is systemically well and metabolically stable but which has one of the following characteristics: cellulitis extending more than 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone.
4. *Severe*: Infection in a patient with systemic toxicity or metabolic instability (e.g. fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia).

Diagnosis of diabetic foot infection is best made clinically. Laboratory evaluation should include complete blood count, blood glucose and electrolytes. Baseline and subsequent inflammatory markers such as ESR and C-reactive protein (CRP) can be useful for monitoring response to therapy. Newer inflammatory markers such as procalcitonin (PCT) may also be useful although further studies are needed to determine its clinical utility.

Organisms cultured from superficial swabs usually do not represent the pathogens responsible for deeper infection. Preferred clinical specimens for reliable culture include aspirate from an abscess and curettage from the ulcer base, after superficial debridement of necrotic tissue. Deep tissue or bone biopsies can be obtained during surgical debridement if deep tissue infection or osteomyelitis is suspected. Formal neurological and/or vascular evaluation should be done to determine the extent of surgical intervention.

Mild to moderate infections with no systemic symptoms where Gram-positive bacteria are usually the causative agents, treatment is initiated in the outpatient department with oral cloxacillin 1,000 mg orally, every 6 hours for 7–10 days, cephalexin 500 mg orally 6 hourly for 7–10 days; cefazolin 1 g intravenously 8 hourly is an alternative.

For severe extensive infections which are limb and life threatening, appropriate surgical debridement and drainage is paramount. As these infections are polymicrobial in etiology (*S. aureus*, Group A *Streptococcus*, aerobic Gram-negative bacilli, anaerobes), cefazolin

1 g intravenously 8 hourly with gentamicin 5 mg/kg intravenously every 24 hours or ciprofloxacin 400 mg intravenously every 12 hours + metronidazole 500 mg intravenously every 8 hours should be used. Alternate regimens are Ertapenem 1 g intravenously once a day or piperacillin-tazobactam 4.5 g intravenously every 8 hours.

The duration of antibiotic therapy should be tailored to individual clinical circumstances and should be continued in conjunction with attentive wound care until there is evidence that the infection has resolved.

Patients with mild infection usually need about 1–2 weeks of therapy. Antibiotics need not be administered for the entire duration that the wound remains open. Patients requiring surgical debridement should receive intravenous antibiotic therapy perioperatively. In the absence of osteomyelitis, they usually need 2–4 weeks of antibiotic therapy. If there is a good response to parenteral therapy, oral agents can be used to complete the course of treatment. In the setting of osteomyelitis, parenteral antibiotic should be continued at least for 6 weeks after the last debridement. In patients requiring amputation, if the entire area of infection is fully resected, perioperative parenteral followed by a brief course of oral antibiotic therapy (about a week) following surgery is usually sufficient.

If clinical evidence of infection persists beyond the expected duration, patient compliance, development of antibiotic resistance, an undiagnosed deep abscess, or ischemia should be considered.

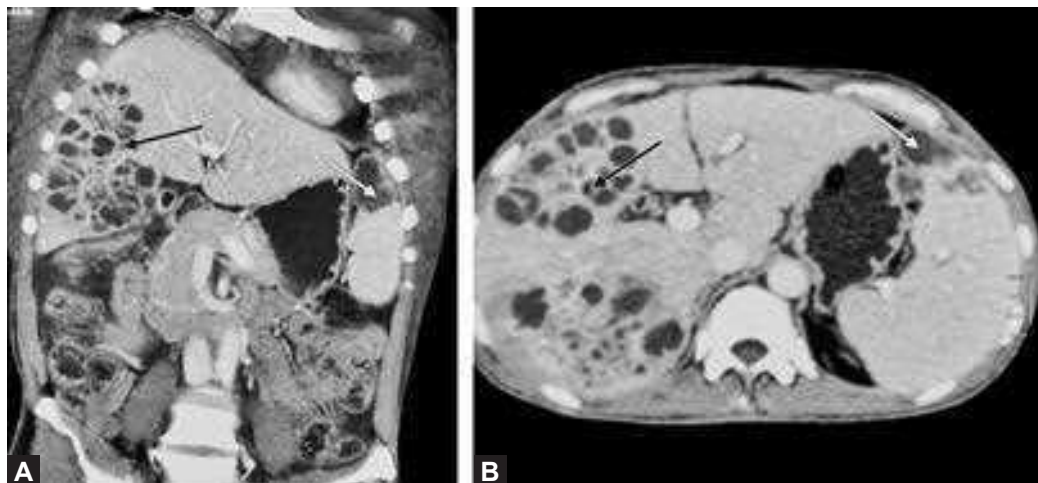
Melioidosis

Melioidosis is an infectious disease caused by the bacterium *Burkholderia pseudomallei*. Though endemic in south Asia, it is often undiagnosed and under reported. The bacterium is an environmental saprophyte and spreads to humans and animals through direct contact with the contaminated soil and water especially through skin abrasions. Diabetics have an increased risk for asymptomatic infection, clinical disease and bacteremia. In a series of cases from South India, 75% of patients with melioidosis were diabetic. The clinical spectrum of disease ranges from skin nodules, pulmonary infections, encephalomyelitis acute bloodstream infections to chronic suppurative infections of the joints, viscera, lymph nodes and spleen.

Melioidosis is diagnosed with a high index of suspicion and isolation of *B. pseudomallei* from the blood, urine, sputum, or pus from involved area. Ashdown's medium, a gentamicin containing liquid transport broth allows selective growth of *B. pseudomallei*. On Gram's stain, they have characteristic bipolar staining with a "safety pin" appearance. It should be treated with initial intensive therapy (at least 2 weeks of IV therapy) followed by eradication therapy orally for 6 months. Ceftazidime 2 g intravenously thrice daily for 14 days should be followed by cotrimoxazole (TMX at 10 mg/kg/day) for 20 weeks. In the intensive phase, carbapenems may also be used in bacteremic patients or central nervous system involvement (Figs. 18.3A and B).

Immunizations Recommended in Diabetes

Recommendations in this schedule given in Table 18.1 were approved by the Centers for Disease Control and Prevention (CDC), Advisory Committee on Immunization Practices (ACIP),



Figs. 18.3A and B: A 48-year-old gentleman with poor glycemic control presented with weight loss, anorexia and low grade fever. Ultrasonography followed by CT of the abdomen showed few multiloculated abscesses in the right lobe of liver (black arrows) and an abscess in the spleen (white arrows). His urine culture and blood culture repeated thrice showed *Burkholderia pseudomallei*.

Table 18.1: Recommended adult immunization schedule in diabetes.

Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 years
Human papillomavirus (HPV)	3 doses for females through age 26 years
Varicella	2 doses
Zoster	1 dose
Measles, mumps, rubella (MMR)	1 or 2 doses
Influenza (TIV)*	1 dose annually
Pneumococcal (polysaccharide)	1 or 2 doses
Hepatitis A	2 doses
Hepatitis B	3 doses
Meningococcal	1 or more doses

All persons in this category who meet the age requirements and who lack evidence of immunity (e.g. lack documentation of vaccination or have no evidence of prior infection)

Recommended if some other risk factor is present (e.g. on the basis of medical, occupational, lifestyle, or other indications)

* TIV, seasonal inactivated vaccine.

the American Academy of Family Physicians (AAFP), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Physicians (ACP).

People with diabetes are at increased risk of bacteremic form of pneumococcal infection which has a very high mortality rate.

The CDC advisory committee on immunization practices recommends influenza and pneumococcal vaccines to all individuals with diabetes.

The recommendation regarding immunizing all or some adults with diabetes for hepatitis B is awaited.

CONCLUSION

Infections in diabetes are relatively more common and more serious. These result in extended hospital stay and an additional financial burden. Besides appropriate antimicrobial therapy, equal emphasis must be made on strict glycemic control (Table 18.2).

Common Infections and Suggested Antimicrobial Therapy (Tables 18.3 to 18.5)

The three common sites of infection in patients with diabetes are the respiratory tract, genital tract and feet of diabetes patients. The common micro-organisms and the antibiotic of choice is summarized in the following tables.

Table 18.2: Clinical features, diagnosis, and causative organisms of selected infections in patients with diabetes.

<i>Infection</i>	<i>Clinical features</i>	<i>Diagnostic procedure</i>	<i>Organisms</i>	<i>Comments</i>
Respiratory tract: Community-acquired pneumonia	Cough, fever	Chest radiography	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> , Other Gram-negative bacilli, atypical pathogens	Pneumococcal infection carries a higher risk of death in diabetic than in nondiabetic patients
Urinary tract: Acute bacterial cystitis	Increased urinary frequency, dysuria, suprapubic pain	Urine culture	<i>Escherichia coli</i> , proteus species	Bacteriuria more common in diabetic than in nondiabetic women
Acute pyelonephritis	Fever, flank pain	Urine culture	<i>E. coli</i> , proteus species	Emphysematous infection should be considered
Emphysematous pyelonephritis	Fever, flank pain, poor response to antibiotics	Radiography or CT scanning	<i>E. coli</i> , other Gram-negative bacilli	Emergency nephrectomy often required
Perinephric abscess	Fever, flank pain, poor response to antibiotics	Ultrasonography or CT scanning	<i>E. coli</i> , other Gram-negative bacilli	Surgical drainage usually required

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<i>Infection</i>	<i>Clinical features</i>	<i>Diagnostic procedure</i>	<i>Organisms</i>	<i>Comments</i>
Fungal cystitis	Same as for acute bacterial cystitis	Urine culture	<i>Candida</i> species	Difficult to distinguish colonization from infection
Soft tissue: Necrotizing fasciitis	Local pain, redness, crepitus, bullous skin lesions	Radiography or CT scanning	Gram-negative bacilli, anaerobes (type I), or group A streptococci (type II)	High mortality; emergency surgery required
Other: Invasive otitis externa	Ear pain, otorrhea, hearing loss, cellulitis	Clinical examination, magnetic resonance imaging	<i>Pseudomonas aeruginosa</i>	Prompt otolaryngologic consultation recommended
Rhinocerebral mucormycosis	Facial or ocular pain, fever, lethargy, black nasal eschar	Clinical examination, magnetic resonance imaging, pathological findings	Mucor and rhizopus species	Strong association with ketoacidosis; emergency surgery required
Abdomen: Emphysematous cholecystitis	Fever, right upper quadrant abdominal pain, systemic toxicity	Radiography	Gram-negative bacilli, anaerobes	High mortality; gallstones in 50%; emergency cholecystectomy required

(CT: Computed tomography).

Source: Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. *N Engl J Med.* 1999;341:1906-12; Reproduced with permission.

Table 18.3: Respiratory tract infections.

<i>Condition</i>	<i>Etiology</i>	<i>Antibiotic choice</i>
Acute pharyngitis	Viral Group A B hemolytic <i>Streptococcus</i> (GABHS)	<i>Preferred:</i> Benzathine penicillin 12 L units IM × 1 dose <i>In penicillin allergic patients:</i> Erythromycin 500 mg PO Q6H × 10 days <i>Alternatives:</i> Amoxicillin 500 mg PO Q8H × 10 days
Acute epiglottitis	<i>H. influenzae</i>	Ceftriaxone 1-2 g IV OD × 7 - 10 days
Acute bronchitis	Viral	None required
Acute bacterial rhinosinusitis (Antibiotics if symptoms of fever, facial pain and purulent nasal discharge persist >7 days)	<i>Streptococcus pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i>	Amoxicillin 500 mg PO TID × 10-14 days

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Condition		Etiology	Antibiotic choice
Acute bacterial exacerbation of COPD		<i>Streptococcus pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i>	Preferred: Amoxicillin 500 mg PO TID × 7 days Alternatives: Doxycycline 100 mg PO BD × 7 days Azithromycin 500 mg PO OD × 3 days
Community acquired pneumonia	CURB-65* score 0–1 (out-patient management)	<i>Streptococcus pneumoniae</i>	Preferred: Amoxicillin 500 mg PO Q8H × 7 days Alternatives: Levofloxacin 750 mg PO OD × 5–7 days Azithromycin 500 mg PO OD × 3 days Doxycycline 100 mg PO BID × 7 days
	CURB-65 score 2 (hospitalized patients)	<i>Streptococcus pneumoniae</i>	Preferred: Crystalline penicillin 20 L units IV Q4H × 7 days
	CURB-65 score ≥3 (in ICU)	<i>Streptococcus pneumoniae</i> <i>Legionella spp.</i> Enterobacteriaceae	Preferred: Piperacillin-Tazobactam 4.5 g IV Q6-8H + Azithromycin 500 mg IV OD × 7–10 days
			Alternatives: 1. Crystalline penicillin 20 L units IV Q4H + Azithromycin 500 mg IV OD × 7–10 days 2. Ertapenem 1 G IV OD + Azithromycin 500 mg IV OD × 7–10 days
Nosocomial pneumonia		Gram-negatives: <i>E. coli</i> , <i>Klebsiella</i> , Enterobacter, Pseudomonas	Meropenem 1 g IV Q8H De-escalate as per AST reports/Piperacillin-tazobactam 4.5 g q8h × 8 days

(COPD: Chronic obstructive pulmonary disease).

*CURB-65 scoring system:

- Six point score (range 0–5)
- Gives one point each for:
Confusion (abbreviated mental test score ≤ 8 or new disorientation in person, place, or time)
Urea > 7 mmol/L
Respiratory rate ≥ 30/min
Low blood pressure (systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg)
Age ≥ 65 years
- Severe pneumonia: CURB-65 score of ≥ 3.

Table 18.4: Genitourinary tract infections.

Cystitis in women—dysuria and frequency in healthy, adult, non-pregnant women with normal urinary tract	<i>E. coli</i>	Preferred: Nitrofurantoin 100 mg PO BID × 5–7 days Alternative: Ciprofloxacin 500 mg PO BID × 3 days
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Pyelonephritis—uncomplicated (no underlying GU disease)*	Nonsevere illness: <i>E. coli</i>	Cefoperazone + sulbactam 3g Q12h for 7–10 days
	Severely ill (multi-organ dysfunction/septic shock): <i>E. coli</i>	Ertapenem 1 g IV Q24H for 14 days; hospitalize patient
Pyelonephritis—complicated (underlying GU disease)*	<i>E. coli</i> , <i>Proteus</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter spp.</i>	Carbapenems (Imipenem/Meropenem); deescalate as per antibiotic susceptibility testing (AST) reports. Duration of treatment for 10–14 days.
Foley catheter associated UTI	Gram-negative bacilli	As per AST reports Treat only when patient has symptoms

(GU: Genitourinary; UTI: Urinary tract infection).

*In a setting where high prevalence of ESBL producing strains among *E. coli* and *Klebsiella spp.* are suspected, would suggest injection Ertapenem 1 g IV OD/Tigecycline 100 mg initial dose, followed by 50 mg IV (over 30–60 minutes) Q12H. Antibiotic choice in these settings should be guided by the knowledge of local susceptibility patterns and whenever possible deescalated based on culture and sensitivity. All doses recommended are assuming normal renal and hepatic functions.

Table 18.5: Foot infections in patients with diabetes.

Infection	Diagnostic procedure	Causative organisms	Initial management	
Mild to moderate	Plain radiography, possibly culture*	Primarily aerobic Gram-positive cocci (e.g. <i>Staphylococcus aureus</i> , streptococci)	Oral antibiotics [†] ; wound care [‡] ; outpatient management if there is good home support	<i>First choice:</i> Cefazolin 1 g IV Q8H <i>Alternative:</i> Cloxacillin 500–1,000 mg PO Q6H × 7–10 days Cephalexin 500 mg PO Q6H × 7–10 days
Moderate to severe	Plain radiography; deep cultures; “probe to bone” test [§] , vascular and neurological assessment	Polymicrobial: aerobic Gram-positive cocci, strict anaerobes (e.g. <i>Bacteroides fragilis</i>), and Gram-negative bacilli (e.g. <i>E. coli</i>)	Immediate hospitalization and surgical consultation; broad spectrum intravenous antibiotics; wound care [‡]	<i>First choice:</i> Cefazolin 1 g IV Q8H + Amikacin 15 mg/kg IV Q24H + Metronidazole 500 mg IV Q8H <i>Alternate regimens:</i> 1. Piperacillin-Tazobactam 4.5 g IV Q6-8H 2. Ertapenem 1 g IV OD

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Infection	Diagnostic procedure	Causative organisms	Initial management	
Necrotizing fasciitis	Deep cultures; vascular assessment	Group A <i>Streptococcus</i>	Immediate hospitalization and surgical debridement	crystalline penicillin 20 L Units IV Q4H + Clindamycin 600 mg IV Q6H; Duration: Until clinical cure

(SIRS: Systemic inflammatory response syndrome).

*Since Gram-positive cocci are the anticipated pathogens, cultures are not clearly required in each case.

†Recommended oral antibiotics include cephalexin, clindamycin, and amoxicillin-clavulanate.

*Wound care includes sharp debridement of devitalized tissue and callus, sterile dressings and relief of pressure at the ulcer.

§The ability to touch bone when the wound is gently probed with a sterile surgical probe is predictive of underlying osteomyelitis.

SUGGESTED READING

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SELF-ASSESSMENT

- A 60-year-old lady, with type 2 diabetes mellitus, presented to the OPD with a painful pigmented swelling over her back of 2 days duration. She had low grade fever. Currently, she is on oral hypoglycemic agents (OHAs). Mark the false statement:**
 - The most probable diagnosis is a carbuncle
 - Prophylactic antibiotic therapy required for next 6 months
 - An urgent surgical opinion should be sought as regards the need for a cruciate incision and drainage
 - Antibiotic therapy should cover *Staphylococcus aureus*
 - Insulin may be temporarily added to control blood sugars
- The clinical presentation of mucormycosis includes:**
 - Rhinocerebral
 - Pulmonary
 - Cutaneous
 - Gastrointestinal
 - All of the above
- The most common postoperative infection in a patient with diabetes is:**
 - Urinary tract infection
 - Sternal wound infections following coronary artery bypass graft surgery (CABG)

- (c) Infection of the prosthesis in hip replacement
 - (d) Emphysematous cholecystitis
 - (e) Synergistic necrotizing cellulitis
- 4. All of the following is caused by *Staphylococcus spp.* in individuals with diabetes except:**
- (a) Sternal wound infections following CABG
 - (b) Arthritis
 - (c) Emphysematous pyelonephritis
 - (d) Pyomyositis
 - (e) Catheter infection in continuous ambulatory peritoneal dialysis.
- 5. Which of the following are mainstays of management of rhinocerebral mucormycosis except:**
- (a) Surgical debridement
 - (b) Fluconazole IV
 - (c) Amphotericin IV
 - (d) Oral Posaconazole
- 6. Which of the following statements about tuberculosis in a diabetic are false?**
- (a) Mortality of tuberculosis in diabetes is higher than controls
 - (b) The dose of rifampicin may need to be increased in patients on OHAs
 - (c) The clinical features and symptoms of TB in diabetics are different from that of normal population
 - (d) The Sputum conversion rate of a diabetic on ATT is less than of a normal individual
- 7. Asymptomatic bacteriuria is to be treated in which of the following group of patients?**
- (a) In patients with an indwelling urinary catheter
 - (b) In pregnancy
 - (c) In poorly controlled diabetic patients
 - (d) In immunocompromised patients
- 8. 70-year-old gentleman presents with right ear discharge and pain radiating to the temporomandibular joint. He is on metformin for the past 4 years with poor control. His disease has worsened with topical medications. The auditory canal shows intense cellulitis and edema with formation of granulation tissue. Which is the causative organism?**
- (a) *Staphylococcus aureus*
 - (b) *Pseudomonas*
 - (c) *Klebsiella*
 - (d) *Aspergillus*
 - (e) *Mucormycosis*
- 9. A 50-year-old lady diabetic for the past 5 years presents with pain in the right thigh for the past 5 days. She is febrile (102°F) BP 70/30 mm Hg, Pulse rate 120/minute**

and a RR 28/minute. On examination appears warm and indurated. What would be the next step in management?

- (a) Cloxacillin
- (b) Clindamycin and cloxacillin
- (c) Fluid resuscitation
- (d) Surgical debridement

10. A truck driver presents with a history of pain in the perianal region for the past one week which has worsened over the past three days. He is unable to carry on with his work. He is febrile with a BP 110/70 mm Hg, pulse rate 100/minute. Examination reveals a warm erythematous swelling in the area. What is the most appropriate management?

- (a) Crystalline penicillin
- (b) Cloxacillin and gentamicin
- (c) Surgical debridement
- (d) Await culture report

CHAPTER

19

Hyperglycemic Emergencies

Jubbin Jagan Jacob

*“Sugars are high,
They reach the sky!
Breathe smells of grapes,
I’m under the drapes,
My breathing is fast,
I hope I will last,
Insulin and saline,
They are the lifeline.”*

Diabetic ketoacidosis (DKA) is a state of absolute or relative insulin deficiency aggravated by ensuing hyperglycemia, dehydration and acidosis producing derangements in intermediary metabolism. The most common causes are underlying infection, disruption of insulin treatment and new onset of diabetes. DKA is typically characterized by hyperglycemia over 300 mg/dL, low bicarbonate (< 15 mEq/L) and acidosis (pH < 7.30) with ketonemia and ketonuria. Hyperosmolar hyperglycemic state (HHS) is a metabolic derangement that occurs principally in patients with adult-onset diabetes.

INTRODUCTION

Diabetic ketoacidosis and HHS (also called nonketotic hyperglycemia) are two of the most serious acute complications of diabetes. DKA is characterized by the triad of hyperglycemia, anion gap metabolic acidosis and ketonemia. Blood glucose levels are generally below 800 mg/dL and metabolic acidosis is often the major finding. DKA is characteristically associated with type 1 diabetes. It also occurs in type 2 diabetes under conditions of extreme stress such as serious infection, trauma and cardiovascular emergencies (Table 19.1).

In HHS, there is little or no keto acid accumulation, the serum glucose concentration frequently exceeds 1,000 mg/dL, the plasma osmolality may reach up to 380 mOsm/kg, and neurologic abnormalities are frequently present (including coma in 25–50%). There is no acidosis and urine/serum ketones are usually negative. The rate of hospital admissions for HHS is lower than that of DKA, and accounts for less than 1% of all primary diabetic admissions. It is most commonly seen in individuals older than 65 years with type 2 diabetes. Restricted fluid intake due to illness or immobility compounded with poor thirst response in the elderly contributes to the severe dehydration and hyperosmolality seen in HHS.

Table 19.1: Precipitating factors for diabetic ketoacidosis and hyperosmolar hyperglycemic state.

<i>Diabetic ketoacidosis (DKA)</i>
<ul style="list-style-type: none"> • Inadequate insulin treatment or noncompliance (in young patients with recurrent admissions with DKA secondary to insulin omission, psychological issues and undiagnosed eating disorders should be considered) • Patients on insulin pumps have an increased risk of DKA secondary to pump dysfunction • New onset diabetes (20–25%) • Acute illness—Infection (30–40%), cerebrovascular accident, myocardial infarction, acute pancreatitis • Drugs—Clozapine or olanzapine, cocaine, thiazide diuretics, terbutaline, corticosteroids and dobutamine • Trauma, surgery • Rarely DKA maybe the primary manifestation of acromegaly or Cushing’s disease.
<i>Hyperosmolar hyperglycemic state (HHS)</i>
<ul style="list-style-type: none"> • Inadequate insulin treatment or noncompliance (20–40%) • Acute illness—Infection like pneumonia, urinary tract infection (UTI) and sepsis (30–60%), cerebral vascular accident, myocardial infarction, acute pancreatitis, acute pulmonary embolism, intestinal obstruction, renal failure and subdural hematoma • Drugs/Therapy—Chlorpromazine, clozapine, loxapine, olanzapine, diazoxide, ethacrynic acid, immunosuppressive agents like L-asparaginase, phenytoin, steroids, thiazide diuretics and total parenteral nutrition • Trauma, surgery • Previously undiagnosed diabetes.

PRECIPITATING FACTORS

Precipitating factors for DKA and HHS are listed in Table 19.1.

PATHOPHYSIOLOGY OF DKA AND HHS

Diabetic ketoacidosis is a complex metabolic disorder characterized by hyperglycemia, acidosis and ketonuria. DKA usually occurs as a consequence of absolute or relative insulin deficiency that is accompanied by an increase in counter-regulatory hormones (i.e. glucagon, cortisol, growth hormone and epinephrine). This type of hormonal imbalance enhances hepatic gluconeogenesis, glycogenolysis and lipolysis.

Hepatic gluconeogenesis and glycogenolysis secondary to insulin deficiency, and counter-regulatory hormone excess result in severe hyperglycemia; while lipolysis increases serum free fatty acids. Hepatic metabolism of free fatty acids as an alternative energy source (i.e. ketogenesis) results in accumulation of acidic intermediate and end metabolites (i.e. ketones, keto acids). Ketones include acetone, β -hydroxybutyrate and acetoacetate (Fig. 19.1).

Progressive rise in blood concentration of these acidic organic substances initially leads to a state of ketonemia. Natural body buffers can buffer ketonemia in its early stages. When the accumulated ketones exceed the body’s capacity of extracting them, they overflow into urine (i.e. ketonuria). If the situation is not treated promptly, more accumulation of organic acids leads to frank clinical metabolic acidosis (i.e. ketoacidosis), with a drop in pH and bicarbonate serum levels. Respiratory compensation of this acidotic condition results in rapid shallow breathing (Kussmaul respiration).

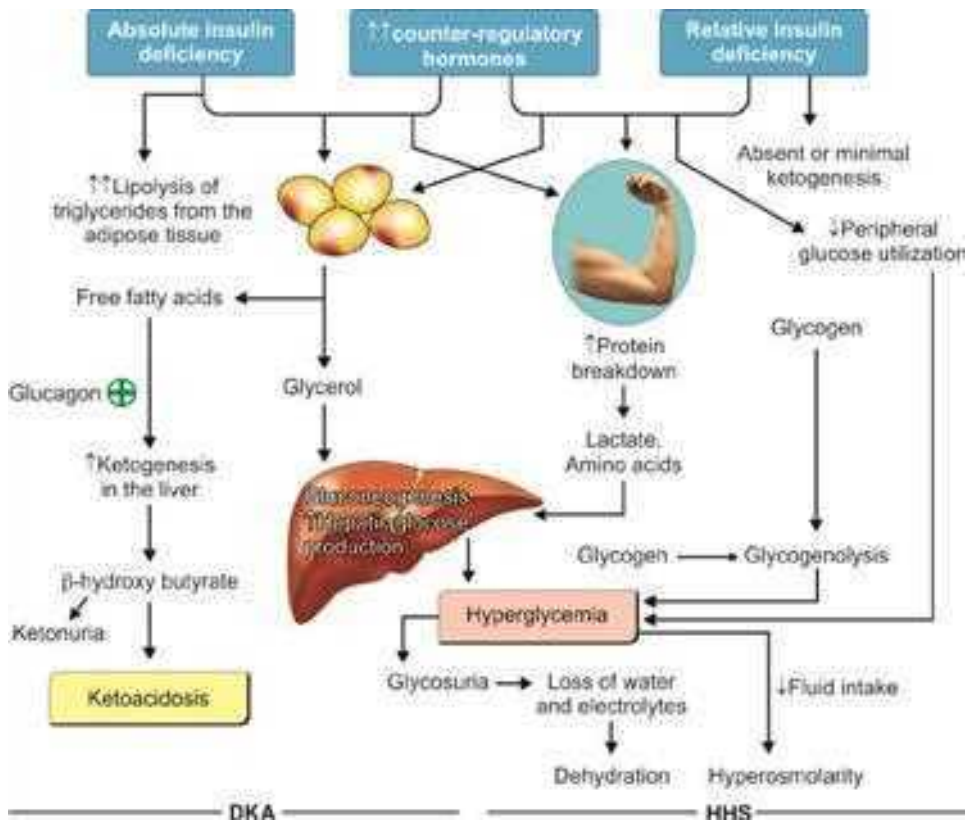


Fig. 19.1: Pathogenesis of diabetic ketoacidosis and hyperosmolar hyperglycemic state.

Ketones, in particular β -hydroxybutyrate, induce nausea and vomiting that consequently aggravate fluid and electrolyte loss, which already exists in DKA. Moreover, acetone produces the characteristic fruity breath odor of ketotic patients.

Hyperglycemia usually exceeds the renal threshold of glucose absorption and results in significant glycosuria. Consequently, water loss in the urine is increased due to osmotic diuresis-induced by glycosuria. Increased water loss results in severe dehydration, thirst, tissue hypoperfusion and possibly lactic acidosis.

Hyperglycemia, osmotic diuresis, serum hyperosmolality and metabolic acidosis result in severe electrolyte disturbances. The most characteristic disturbance is total body potassium loss. This loss is not mirrored in serum potassium levels, which may be low within the reference range, or even high. Potassium loss is caused by a shift of potassium from the intracellular to the extracellular space in exchange with hydrogen ions that accumulate extracellularly in acidosis. A large part of the shifted extracellular potassium is lost in urine because of osmotic diuresis. Patients with initial hypokalemia are considered to have severe and serious total body potassium depletion. High serum osmolality also drives water from intracellular to extracellular space, causing translocational hyponatremia. Sodium also is lost in the urine during the osmotic diuresis.

Hyperosmolar hyperglycemic state most commonly develops in patients with diabetes who have some concomitant illness that leads to a reduced fluid intake. Infection is the most common cause, but many other conditions can cause altered mentation and/or dehydration.

Unlike patients with DKA, patients with HHS do not develop ketoacidosis, but the reason for this is not clear. Contributing factors include the limitation of ketogenesis by hyperosmolarity, the lower levels of free fatty acids available for ketogenesis, the availability of insulin in amounts sufficient to inhibit ketogenesis but not sufficient to prevent hyperglycemia and the hepatic resistance to glucagon in these patients.

CLINICAL RECOGNITION, ESTABLISHING A DIAGNOSIS AND ASSESSMENT OF COMORBIDITIES

History in Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic State

- Insidious increased thirst (i.e. polydipsia) and urination (i.e. polyuria) are the most common early symptoms of DKA
- Nausea and vomiting usually occur and may be associated with diffuse abdominal pain
- Generalized weakness and fatigability may occur
- Altered consciousness is the most common cause for seeking medical attention. It may range from mild disorientation to frank coma. Although frank coma is uncommon, it may occasionally occur when the condition is neglected or if dehydration or acidosis is severe
- Symptoms of possible associated intercurrent infection may include fever, dysuria, cough, malaise and arthralgia
- Acute chest pain or palpitation may occur in association with myocardial infarction. Painless infarction is not uncommon in patients with diabetes and should always be suspected in elderly patients
- Patients may present with a history of failure to comply with insulin therapy or mistaken omission/failure to augment insulin in the setting of an acute illness
- History of rapid weight loss is a symptom in patients who are newly diagnosed with type 1 diabetes
- In HHS, oral hydration usually is impaired by concurrent acute illness or chronic comorbidity (e.g. dementia, immobility and vomiting). There may be variety of focal and global neurological changes.

Physical Findings in DKA and HHS

- *Signs of dehydration:* Weak and rapid pulse, dry tongue and skin, hypotension, and increased capillary refill time
- *Odor of breath:* Characteristic acetone odor in DKA
- *Signs of acidosis:* Shallow rapid breathing or air hunger (Kussmaul or sighing respiration), abdominal tenderness and altered sensorium. Although these signs are not usual in all cases of DKA, their presence signifies a severe form of DKA. It is important to know

that no direct correlation exists between the degree of acidosis, hyperglycemia and the disturbances in the level of consciousness

- *Signs of intercurrent illness:* Myocardial infarction, UTI, pneumonia and perinephric abscess, among others. It should be noted that the body temperature may be within the reference range or low, even in the presence of intercurrent infection. A search for signs of infection is mandatory in all cases.

DIAGNOSTIC EVALUATION AND LABORATORY STUDIES

Urine

- Urine is highly positive for glucose and ketones by dipstick testing (they may be positive in HHS as well). Rarely, urine is negative for ketones because most of the available laboratory tests can detect only acetoacetate, while the predominant ketone in severe untreated DKA is β -hydroxybutyrate. When the clinical condition improves with treatment, the urine test result becomes positive due to the breakdown of β -hydroxybutyrate to acetoacetate. Glucose recommendation is however, no longer recommended.
- Urine culture helps to identify any possible infecting organisms, and blood culture should be collected if patient has high-grade fever.

Blood and Plasma

- *Glucose:* Levels may be as low as 250 mg/dL. The clinician can do finger-stick glucose while waiting for the serum chemistry panel. In HHS it usually is elevated dramatically, often to greater than 800 mg/dL.
- *Sodium:* The osmotic effect of hyperglycemia moves extravascular water to the intravascular space. For each 100 mg/dL of glucose over 100 mg/dL, the serum sodium is lowered by approximately 1.6 mEq/L. When glucose levels fall, the serum sodium will rise by a corresponding amount.
- *Potassium:* This needs to be checked frequently, as values drop very rapidly with treatment. An electrocardiogram may be used to assess the cardiac effects of extremes in potassium levels. Total body potassium is likely low regardless of its serum value.
- *Bicarbonate:* Used in conjunction with the anion gap to assess degree of acidosis.
- *Complete blood count:* High white blood cell (WBC) counts ($> 15,000/\text{mm}^3$) or marked left shift suggest underlying bacterial infection.
- *Arterial blood gases:* pH is often less than 7.3 in DKA. Venous pH may be used to repeat pH measurements, during treatment. In HHS, pH is usually normal and bicarbonate is more than 15 mEq/L.
- *Osmolarity:* Calculated as $2(\text{Na}^+) (\text{mEq/L}) + \text{glucose} (\text{mg/dL})/18 + \text{blood urea nitrogen (BUN)} (\text{mg/dL})/2.8$. Patients with DKA who are in coma typically have osmolarities more than 330 mOsm/kg H_2O . If the osmolarity is less than this in a comatose patient, search for another cause of obtundation. In HHS the serum osmolarity is usually greater than 320 mOsm/kg H_2O .
- *Phosphorous:* Phosphate balance is typically negative in DKA/HHS because of poor intake and osmotic diuresis/phosphaturia. Despite phosphate depletion, serum phosphate

Table 19.2: Comparison of DKA with HHS based on biochemistry.

Variable	Diabetic ketoacidosis			Hyperosmolar
	Mild	Moderate	Severe	hyperglycemic state
Plasma glucose level (mg/dL)	> 250	> 250	> 250	> 600
Arterial pH level	7.25– 7.30	7.00– 7.24	< 7.00	> 7.30
Serum bicarbonate level (mEq/L)	15–18	10 to < 15	< 10	> 15
Urine or serum ketones	Positive	Positive	Positive	Small or negative
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	> 320
Anion gap	> 10	> 12	> 12	Variable
Alteration in sensoria or mental obtundation	Alert	Alert/ drowsy	Stupor/coma	Stupor/coma

Source: Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, et al. Hyperglycemic crises in diabetes. *Diabetes Care*. 2004;27(suppl 1):S95.

level may be normal or even high because insulin deficiency and acidosis cause shift of phosphate out of the cells. Hence, correction of acidosis and insulin therapy can precipitate hypophosphatemia.

- Hyperamylasemia may be seen even in the absence of pancreatitis. The diagnosis of acute pancreatitis in this setting is done with imaging (CT scan).
- Repeated monitoring of biochemistry is critical. Potassium needs to be checked every 1–2 hours during initial treatment. Glucose and other electrolytes should be checked every 2 hours or so during initial aggressive volume replacement, glucose and electrolyte management. If the initial phosphorous was low, it should be monitored every 4 hours during therapy. A data flowsheet as shown in Figure 19.2 is helpful for following up a patient with DKA/HHS. The salient features differentiating these two clinical entities are summarised in Table 19.2.
- While interpreting the biochemistry it should be noted that high serum glucose levels may lead to dilutional hyponatremia; high triglyceride levels may lead to factitious low glucose and high levels of ketone bodies may lead to factitious elevation of creatinine.

Other Tests

Electrocardiogram: Diabetic ketoacidosis/Hyperosmolar hyperglycemic state may be precipitated by a cardiac event and the physiological disturbances of the underlying hyperglycemic state may cause cardiac complications.

- This test may reveal signs of acute myocardial infarction that could be painless in patients with diabetes, particularly in those with autonomic neuropathy
- T-wave changes may produce the first warning sign of disturbed serum potassium levels
- Low T-wave and apparent U-wave always signify hypokalemia, while peaked T-wave is observed in hyperkalemia.

Chest X-ray (CXR): Is done to rule out pulmonary infection.

Patient Name:										
Date:										
Hour										
Mental status*										
Vital signs										
Temperature										
Pulse										
Respiration (rate & depth)										
Blood pressure										
Chemistries										
Serum glucose										
Serum ketones										
Urine ketones										
Serum Na ⁺ (mEq/L)										
Serum K ⁺ (mEq/L)										
Serum Cl ⁻ (mEq/L)										
Serum HCO ₃ ⁻ (mEq/L)										
Serum BUN (mg/dL)										
Effective osmolality Δ										
Anion gap										
Blood gases										
pH specify venous (V) or arterial (A)										
pO ₂										
pCO ₂										
O ₂ sat										
Insulin (units in past hour)										
Route										
IV										
SC										
IM										
Fluid/Metabolites (past hour)										
0.45 percent NaCl (mL)										
0.9 percent NaCl (mL)										
5 percent dextrose (mL)										
Other										
Output										
Urine (mL)										
Other										

Fig. 19.2: Data flowsheet for following up a patient with DKA/HHS.

(DKA: Diabetic ketoacidosis; HHS: Hyperosmolar hyperglycemic state; IV: Intravenous; SC: Subcutaneous; IM: Intramuscular).

CLINICAL MANAGEMENT OF DKA AND RECOGNITION OF COMPLICATIONS

Managing DKA/HHS in an intensive/acute care unit during the first 24–48 hours is always advisable. When treating DKA, the points that must be considered and closely monitored

include correction of fluid loss with intravenous (IV) fluids, correction of hyperglycemia with insulin, correction of electrolyte disturbances, particularly potassium loss, correction of acid-base balance and treatment of concurrent infection if present. Paying great attention to the correction of fluid and electrolyte loss during the first hour of treatment, followed by gradual correction of hyperglycemia and acidosis, is always advisable. Correction of fluid loss makes the clinical picture clearer and may be sufficient to correct acidosis. The presence of even mild signs of dehydration means that at least 3 L of fluid already have been lost.

Fluid Resuscitation

Fluid resuscitation is a critical part of treating DKA and HHS. Intravenous solutions replace extravascular and intravascular fluids and electrolyte losses. Fluid resuscitation in itself produces significant improvements in hyperglycemia as fluids dilute both the circulating glucose levels and the levels of circulating counter-regulatory hormones. Thus adequate rehydration is critical to produce optimal responses to subsequent low-dose insulin therapy, which is needed to help switch from a catabolic to an anabolic state, with uptake of glucose in tissues and the reduction of gluconeogenesis as well as free fatty acid and ketone production.

Choice of Fluids

There is still no consensus on the most appropriate type of fluid to be used in the initial management of DKA. Hypertonic fluids appear to be detrimental though both isotonic and hypotonic fluids are equally effective. Hypotonic solutions may worsen dehydration so most people prefer the use of isotonic fluids in the initial management of DKA. Among isotonic fluids crystalloids (normal saline and Ringers Lactate) require large volumes and would in theory predispose to an increased incidence of cerebral and pulmonary edema in comparison to colloids (dextran and hexastarch). However, recent meta-analysis has not suggested any mortality or morbidity benefits of colloids over crystalloids in critically ill patients with DKA. In view of costs and availability, isotonic crystalloids (normal saline and Ringers lactate) remain the fluid of choice.

- Administer 1 L over the first 30 minutes
- Administer 1 L over the second hour
- Administer 1 L over the following 2 hours
- Administer 1 L every 4 hours, depending on the degree of dehydration and central venous pressure readings.
- When the patient becomes euvolemic, the physician may switch to half-normal (0.45%) sodium chloride solution, particularly if hypernatremia exists.
- When blood sugar decreases to less than 200 mg/dL, isotonic sodium chloride solution is replaced with 5–10% dextrose in half normal sodium chloride solution.
- Fluid deficits in HHS are large; the fluid deficit of an adult may be 10 L or more. Though the above schedule can be used for patients in HHS more fluids would have to be given subsequently.

Insulin Therapy

When insulin treatment is started, several points must be considered.

- A low-dose insulin regimen (1–4%) has the advantage of not inducing severe hypoglycemia or hypokalemia, as may be observed with a high-dose insulin regimen (in 25–30% of patients)
- Subcutaneous absorption of insulin is reduced in DKA because of dehydration; therefore, using IV or intramuscular routes is always preferable. Most of the benefits of IV therapy are in the first 8 hours and subsequently all three routes have similar efficacy
- Only short-acting insulin is used for correction of hyperglycemia
- Continuous insulin infusion is preferred over bolus insulin therapy again because of the lower risk of hypoglycemia (3% vs 27%)
- Priming or bolus dosing prior to starting the insulin infusion with 0.1 unit/kg given stat has recently been shown to be of no additional benefits.

The initial insulin dose is a continuous IV insulin infusion using an infusion pump, if available, at a rate of 0.1 unit/kg/hour. A mix of 24 units of regular insulin in 60 mL of isotonic sodium chloride solution usually is infused at a rate of 15 mL/hour (6 units/hour) until the blood sugar drops to less than 200 mg/dL, then the rate of infusion decreases to 5–7.5 mL/hour (2–3 units/hour) until the ketoacidotic state abates.

Larger volumes of insulin may be easier to administer in the absence of an IV infusion pump (e.g. 60 units of insulin in 500 mL of isotonic sodium chloride solution at a rate of 50 mL/h with a micro-drip set). The infusion rate can be modified depending on the rate of decline of blood sugar values. The drip rate for micro-drip set is 1 mL = 60 micro drops and with the macro-drip set is 1 mL = 16 macro drops.

- The optimal rate of glucose decline is 50–75 mg/dL/hour
- Blood glucose level should not be allowed to fall below 200 mg/dL during the first 4–5 hours of treatment
- Hypoglycemia may develop rapidly with correction of ketoacidosis
- A common mistake is to allow blood glucose to drop to hypoglycemic levels. This mistake usually results in a rebound ketosis derived by counter-regulatory hormones. Rebound ketosis requires a longer duration of treatment. The other hazard is that rapid correction of hyperglycemia and hyperosmolarity may shift water rapidly to the hyperosmolar intracellular space and may induce cerebral edema.

Initial subcutaneous use of insulin analogues in mild and moderate, uncomplicated DKA: Prospective studies have demonstrated safety and cost effectiveness of the use of subcutaneous rapid acting analogue insulin (aspart, lispro and glulisine) in treating uncomplicated mild to moderate DKA. Doses used in two of these studies were 0.2 unit/kg initially followed by hourly injections at the dose of 0.1 unit/kg. This is continued till blood glucose is less than 250 mg/dL and thereafter half the dose of insulin is used till resolution of DKA.

Electrolyte Correction

Potassium

There is a significant decline in the total body potassium levels most of which is lost in the urine during osmotic diuresis. The potassium deficit in the body in a patient with DKA

Table 19.3: Potassium replacement in a patient with diabetic ketoacidosis.

Serum potassium levels in mEq/L	Amount of potassium to be added to 500 mL of fluids
> 6	Hold supplementation
4.5–6	10 mEq
3–4.5	20 mEq
< 3	Hold insulin infusion and administer potassium at the rate of 20 mEq/hour till the serum K is > 3.3 mEq/L

is in the range of 5 mEq/kg. This leads to loss of over 300 mEq of total body potassium in a 60 kg individual with DKA. However, this loss is not reflected in the serum levels of potassium because of the extracellular shift. Hypokalemia in the setting of DKA usually implies severe potassium depletion and treatment of DKA with insulin should only be started after some replacement of potassium is done to prevent serious hypokalemia from developing during the course of treatment of DKA.

- The rate of potassium supplementation based on the serum values is given in Table 19.3
- Monitor serum potassium levels hourly and the infusion must stop if the potassium level is greater than 6.0 mEq/L.
- Monitoring of serum potassium must continue even after potassium infusion is stopped in case of (expected) recurrence of hypokalemia
- If insulin is administered without correcting hypokalemia, there will be further drop in the serum K⁺ level and serious cardiac arrhythmias may result
- Potassium replacement is usually in the form of potassium chloride but it may be preferable to use a combination of potassium chloride and potassium phosphate to replace the deficits.

Correction of Acid-Base Balance

Sodium bicarbonate is not indicated in mild or moderate DKA. In severe DKA the use of sodium bicarbonate is still controversial due to lack of randomized trials. In theory the dangers of bicarbonate therapy includes worsening of hypokalemia, cerebral edema in children and young adults, paradoxical central nervous system and cellular acidosis and an increased risk of peripheral hypoxemia.

However, because severe acidosis can result in impairment of consciousness and impaired cardiac muscle contractility bicarbonate therapy is indicated when decompensated acidosis starts to threaten the patient's life, especially when associated with either sepsis or lactic acidosis. Bicarbonate is also indicated if pH is less than or equal to 6.9.

If the pH is less than or equal to 6.9, 100 mL of sodium bicarbonate is diluted in 400 mL of water and 20 mEq of KCl and is infused over 2 hours.

If subsequent pH is between 6.9 and 7.0, 50 mL of sodium bicarbonate is diluted in 200 mL of water and 10 mEq of KCl is infused. This may be repeated every 2 hours if necessary till the pH is more than or equal to 7.0.

Phosphate Replacement

Whole body phosphate deficits can be around 1 mmol/kg in patients presenting with DKA. Commencement of insulin therapy will further lower phosphate levels in the blood. In studies it was noted that over 90% of patients would develop hypophosphatemia in the course of treatment for DKA. Prospective randomized studies, however, have failed to show any improvement in outcomes with phosphate replacements. Phosphate replacements have been implicated in cases of symptomatic hypocalcemia in patients with DKA. Careful phosphate replacements is indicated in patients with

- Serum phosphate levels less than 1.0 mg/dL.
- Serum phosphate levels between 1.0 mg/dL and 2.0 mg/dL and cardiac dysfunction or respiratory depression.

Treatment of Concurrent Infection

- In the presence of infection, administer proper antibiotics guided by the results of culture and sensitivity results
- Empirical antibiotics on the basis of clinical suspicion of infection while awaiting culture reports.

COMPLICATIONS

- The leading cause of DKA mortality in children is cerebral edema, which occurs 4–12 hours into treatment. Recent research by Glaser et al. indicated that cerebral edema occurs in 1% of children with DKA, with a mortality rate of 21% and neurologic sequelae in another 21% of patients. Cerebral edema begins with mental status changes and is believed to be partially due to “idiogenic osmoles”, which have stabilized brain cells from shrinking while the DKA was developing. Cerebral edema is a complication that affects primarily children.
- Hypokalemia is a complication that is precipitated by failing to rapidly address the total body potassium deficit brought out by rehydration and insulin treatment, which not only reduce acidosis but directly facilitate potassium reentry into the cell.
- Hypoglycemia may result from inadequate monitoring of glucose levels during insulin therapy.
- Acute pulmonary edema potentially is related to aggressive or excessive fluid therapy.
- Other complications:
 - Cortical vein thrombosis
 - Myocardial infarction
 - Acute gastric dilatation
 - Erosive gastritis
 - Late hypoglycemia
 - Respiratory distress
 - Infection

- Hypophosphatemia
- Complications of associated illnesses like sepsis, worsening of ischemia can happen in untreated DKA/HHS.

SPECIAL SITUATIONS

Diabetic Ketoacidosis in Children and Adolescents

The management of DKA in children is complicated by the occurrence of cerebral edema. The onset of cerebral edema is unpredictable and is fatal in 25% of cases. Children are also more likely to develop aspiration pneumonias and should have a nasogastric tube inserted if semiconscious or unconscious. Fluid and insulin management will depend on the weight of the child and it is preferred if the child is weighed on presentation. If weighing the child is not possible the last recorded weight in the charts or parents estimates or an estimated weight from centile charts should be noted.

Fluid resuscitation: If the child presents in shock then give an initial bolus of 10 mL/kg of 0.9% saline over 30 minutes. (Repeat this up to 3 times till effective circulation is restored). After circulation has been restored calculate fluid requirements using the following formula

Requirement = maintenance + deficit - fluids already given

Deficit (liters) = % dehydration × body weight (kg)

Most children with DKA will have 5–8% dehydration. Clinically the percentage of dehydration is assessed as given in Table 19.4

Normal saline is used in the first 12 hours. Once glucose has fallen to less than 250 mg/dL glucose is added to the fluids. After 12 hours half-normal saline can be used if serum sodium is stable or increasing. However, if serum sodium is falling continue using normal saline.

Insulin administration: There is some evidence suggesting an increase in risk of cerebral edema with early use of insulin. In children with DKA start insulin administration only after an hour of fluid resuscitation. Continuous IV infusion is the route of choice at the rate of

Table 19.4: Clinical assessment of dehydration in children with DKA.

Mild (3%)	Only clinically detectable
Moderate (5%)	Dry mucous membranes and reduction in skin turgor
Severe (8%)	Significantly unwell with poor peripheral perfusion with rapid thready pulse. Reduced blood pressure is generally a late sign and need to be treated as shock
<i>Maintenance requirement:</i>	
0–12.9 kg	80/mL/kg/24 hours
13–19.9 kg	65/mL/kg/24 hours
20–34.9 kg	55/mL/kg/24 hours
35–59.9 kg	45/mL/kg/24 hours
Adult (> 60 kg)	35/mL/kg/24 hours
Hourly fluid administration rates = 48 hours maintenance + deficit - resuscitation fluids already given	

0.1 unit/kg/hour. Some pediatricians use lower doses of 0.05 unit/kg/hour. There is a recent trial from Post Graduate Institute, Chandigarh documenting the safety of this lower dose insulin approach. However, most current guidelines still recommend the use of the higher dose of insulin.

Bicarbonate and phosphate administration: In children bicarbonate infusions further increase the risk of cerebral edema and so should only be used in patients with pH less than 6.9 along with hemodynamic instability. Phosphate administration is rarely required in children.

Cerebral edema: Headache, visual symptoms, changes in conscious state, hemodynamic instability including slowing of heart rate and increased blood pressure, abnormal posturing and specific neurological signs are all symptoms of cerebral edema. Presence of papilledema, convulsions and respiratory arrest are late events and usually indicate poor prognosis. The treatment is as follows:

- Exclude hypoglycemia as cause of change in sensorium
- Give hypertonic (3%) saline at the dose of 5mL/kg over 5–10 minutes or mannitol 0.5–1 g/kg (2.5–5 mL of 20% mannitol solution) over 20 minutes. Repeat dose in 2 hours if no response
- Once child is stable exclude other caused by brain imaging
- Restrict fluids to one-half maintenance and replace deficits over 72 hours rather than 48 hours.

Diabetic Ketoacidosis with Pregnancy

The metabolic changes that accompany pregnancy predispose to DKA. Insulin resistance increases through pregnancy and require adequate increase in exogenous insulin to counteract this. Relative starvation ensues in the second and third trimesters of pregnancy when the fetus and the placenta use large amounts of maternal glucose. Early pregnancy is complicated by emesis and in some patients with hyperemesis, which in turn predisposes to ketosis. Finally in pregnancy because of higher minute alveolar ventilation there is some degree of respiratory alkalosis, which leads to loss of bicarbonate in the urine and a general decline in the buffering capacity when exposed to an acid load.

The net effect of the above changes include rapid establishment of DKA in pregnant women along with DKA at much lower blood glucose values compared to nonpregnant women. Precipitating events in addition to those previously noted include hyperemesis, steroid use for lung maturation and use of sympathomimetic drugs for preterm labor.

Keto acids cross the placenta as readily as glucose and maternal metabolic derangement can have a detrimental effect on the fetus. Fetus exposed to maternal ketoacidosis has been shown to have lower IQs.

Management: Treatment is similar to nonpregnant patients with DKA. Pregnant women have larger fluid deficits and have acidosis at lower glucose levels requiring more glucose containing infusions. Additionally, pregnant women need continuous fetal monitoring under obstetric supervision. Magnesium sulphate is the tocolytic of choice in women with DKA and preterm labor.

Diabetic Ketoacidosis in Patients with End-stage Renal Disease/Hemodialysis

Clinically patients with end-stage renal disease (ESRD) and DKA have minimal dehydration. Often they have features of fluid overload. Poor glomerular filtration leads to no osmotic diuresis explaining the lack of dehydration. Fluid and potassium replacements are not usually required and the mainstay of therapy is insulin administration. Occasionally patients with DKA and ESRD may present in pulmonary edema due to the hyperglycemia-induced interstitial hypertonicity. Treatment in this case is again primarily insulin and rarely patients require hemodialysis.

USE OF INPATIENT STANDARD MANAGEMENT PROTOCOLS IN DIABETIC KETOACIDOSIS

Standard inpatient management protocols for DKA have been demonstrated to be safe and efficient. Use of protocols decreases the length of hospital stay without any increase in hypoglycemia or hypokalemia. In one study the use of a standard protocol decreased time to resolution of DKA by 10 hours. The greatest benefits of the protocol are seen in the first 4–6 hours when the patient maybe first attended to by junior medical staff.

CLINICAL MANAGEMENT OF HYPEROSMOLAR HYPERGLYCEMIC STATE

The diagnostic criteria for HHS as currently recommended by the American Diabetes Association includes:

- Plasma glucose more than 600 mg/dL
- Arterial pH more than 7.30
- Serum bicarbonate more than 18 mEq/L
- Negative or small amounts of urine and blood ketones
- Effective serum osmolality more than 320 mOsm/L
- Serum β -hydroxybutyrate less than 3 mmol/L

In the absence of randomized control trials regarding optimal insulin dosing in HHS currently most societies recommend low-dose insulin regimes similar to what is used in DKA. Fluid resuscitation is similar to DKA in the first 4–6 hours. It is important to start insulin only after adequate fluid resuscitation in HHS to prevent hypotension secondary intracellular movement of water. More individualized plans for fluids and electrolytes need to be made because patients with HHS are likely to have multiple comorbidities. Protocol-driven management of HHS may lead to frontline medical staff not paying adequate attention to comorbidities, which in case of HHS can be more life threatening than the hyperosmolar state in itself.

PROGNOSIS

Though the incidence of DKA appears to have gone up, the mortality rate has significantly come down over the past few decades. Younger patients with no other comorbid factors

have excellent prognosis. Mortality is primarily due to the underlying precipitating illness and only rarely attributable to the metabolic complications of hyperglycemia or acidosis. The prognosis of DKA is substantially worse at the extremes of age and in the presence of coma, hypothermia and hypotension. Mortality attributed to HHS varies from 10% to 50%. But as in DKA, mortality is most often due to the underlying illness or comorbidity.

SUGGESTED READING

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SELF-ASSESSMENT

A 28-year-old woman with a 15 years history of diabetes, presented to the hospital casualty with a 5 days history of weakness, nausea and vomiting. She was on insulin regularly, till the time she presented to the casualty.

On examination, her temperature was 99.1°F, blood pressure was 98/64 mm Hg, pulse was 136/minute, and respiration rate was 36. There was strong smell of ketones in the examination room. The patient was drowsy but cogent. Her head and neck exam revealed poor dentition and periodontal disease. Her lung sounds were clear without wheezes or rhonchi. Her heart sounds were normal. The abdominal exam revealed mild periumbilical and epigastric tenderness to deep palpation but no rebound tenderness or guarding. Bowel sounds are normal. Extremities were well perfused with symmetric pulses. She weighed 48 kg.

Laboratory results were remarkable for a room air arterial blood gas with pH of 7.12, pCO₂ of 17 mm Hg and bicarbonate of 5.6 mEq/L. Urinalysis revealed 4+ glucose and 3+ ketones. Chemistry panel revealed glucose of 420 mg/dL, BUN of 16 mg/dL, creatinine of 1.3 mg/dL, sodium of 139 mEq/L, chloride of 112 mEq/L, CO₂ of 11.2 mmol/L, and potassium of 5.2 mEq/L. CXR revealed no infiltrate.

1. What is the osmolarity in the patient?

- | | |
|---------------|---------------|
| (a) 317 mm/kg | (b) 307 mm/kg |
| (c) 298 mm/kg | (d) 408 mm/kg |

2. What fluid will you give to this patient?

- | | |
|---------------------|--------------------------|
| (a) Isotonic saline | (b) Half isotonic saline |
| (c) Ringer lactate | (d) Hypertonic saline |

3. How will you administer K⁺ in this patient?

- (a) 10–20 mEq of K⁺ in each liter of IV fluid
- (b) 20–30 mEq of K⁺ in each liter of fluid
- (c) 20–30 mEq of K⁺/hour
- (d) No need for potassium

4. How will you administer bicarbonate in this patient?

- (a) 100 mmol infused in 2 hours
- (b) 50 mmol infused over 1 hour

- (c) No need for bicarbonate correction
 - (d) 25 mmol infused over 1 hour
- 5. The best way to R/o pancreatitis in this patient is:**
- (a) Amylase
 - (b) Lipase
 - (c) Clinical examination
 - (d) Imaging by CT scan
- 6. A 25-year-old man with type 1 diabetes on self-mixed insulin preparation presented with disorientation and unresponsiveness of 1 hour duration. There is no immediate facility to check blood sugar. What is the most appropriate action?**
- (a) Administration of 10 units of actrapid insulin subcutaneously
 - (b) Administration of 25 mL of 50% dextrose
 - (c) Check urine sugars
 - (d) Shift patient to higher center for appropriate management
- 7. In the above situation, a glucometer reading at the time the patient was brought to the clinician showed blood sugar of 26 mg/dL. 25 mL of 50% dextrose have already been administered and the patient has fully recovered. All of the following are indications for admission of the patient *except*:**
- (a) Use of long acting insulin
 - (b) Concomitant use of sulphonylureas
 - (c) Evidence of infection
 - (d) Use of short acting insulin
- 8. Which one of the following diabetic patient is more prone for HHS?**
- (a) 22 years old type 1 diabetic
 - (b) 48 years old obese type 2 diabetic
 - (c) 48 years old type 1 diabetic with nephropathy
 - (d) 76 years old type 2 diabetic with dementia
- 9. A 20-year-old type 1 DM, who omitted insulin for past 1 week is brought to casualty in comatose state. His urine ketones are negative. He has acidotic breathing and the blood glucose with glucometer was 350 mg/dL. All other lab investigations are awaited. What would be the cause of negative ketones in urine?**
- (a) Patient does not have DKA
 - (b) Patient has renal failure
 - (c) Patient has HHS
 - (d) He would be predominantly excreting β -hydroxyl butyrate
- 10. What would be the most serious complication of bringing down the blood glucose levels rapidly to less than 150 mg/dL, in a setting of DKA?**
- (a) Cerebral edema
 - (b) Hyponatremia
 - (c) Metabolic alkaline
 - (d) Hyperphosphatemia

CHAPTER

20

Hypoglycemia

Nitin Kapoor, Jubbin Jagan Jacob, Nihal Thomas

*“Oh, I’m feeling sweaty, oh, I’m feeling hot,
These palpitations hit me—they put me in a spot,
The hunger pangs—they’re growing and getting sort of bad,
If I get into a coma—would be rather sad.”*

Hypoglycemia as defined by both American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) when serum glucose level is less than 70 mg/dL.¹ However, this level is neither an indication for treatment nor necessitates presence of symptoms but may just suggest a trend towards low sugars and warrants further exploration. Rather it has been shown in an epidemiological study in south India that 23% of normal subjects have a postprandial sugar less than the fasting.² This 70 mg/dL is the lower limit of normal post-absorptive range and is the level at which counter-regulatory hormones get activated in a non-diabetic person. Also, antecedent plasma glucose concentrations of less than or equal to 70 mg/dL reduce sympathoadrenal responses to subsequent hypoglycemia and therefore this criterion sets the conservative lower limit for individuals with diabetes.

An alternative definition of hypoglycemia is a decrease in the blood glucose level or its tissue utilization that results in demonstrable signs or symptoms. These signs or symptoms usually include altered mental status and/or sympathetic nervous system stimulation. The glucose level at which an individual becomes symptomatic is highly variable.

CLINICAL CLASSIFICATION OF HYPOGLYCEMIA

Hypoglycemia in diabetes may be classified into the following six categories:³

1. *Severe hypoglycemia*: An event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions.
2. *Documented symptomatic hypoglycemia*: Typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (≤ 3.9 mmol/L).
3. *Asymptomatic hypoglycemia*: An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (≤ 3.9 mmol/L).

4. *Probable symptomatic hypoglycemia*: An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL (≤ 3.9 mmol/L).
5. *Pseudo-hypoglycemia*: An event when a person experiences typical symptoms of hypoglycemia but with a measured plasma glucose concentration above 70 mg/dL (> 3.9 mmol/L).
6. *Relative hypoglycemia*: An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration more than 70 mg/dL. This is due to the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels more than 70 mg/dL as plasma glucose concentrations decline toward that level. Though these symptoms cause distress and interfere with the patient's sense of well-being and therefore, potentially limit the achievement of optimal glycemic control, such episodes probably pose no direct harm to the patient.

PATHOPHYSIOLOGY OF COUNTER-REGULATION

As the blood glucose concentration begins to fall, an orchestrated neuro-hormonal response comes into action to prevent symptomatic hypoglycemia. The principles of glucose counter-regulation are three:

1. Prevention and correction of hypoglycemia involves both waning of insulin and activation of the counter-regulatory hormones.
2. There are redundant counter-regulatory factors like not only glucagon but other hormones like epinephrine, growth hormone and cortisol. Therefore, there is a fail-safe system that prevents hypoglycemia even if one or more components of the system fail.
3. There is hierarchy among the counter-regulatory hormones. Table 20.1 summarizes the various physiologic responses to falling plasma glucose concentrations.

CAUSES

Causes of hypoglycemia are varied, but in diabetic patients, it is most often iatrogenic.

- Hypoglycemia may result from medication changes or overdoses, infection, diet changes, metabolic changes over time, or activity changes; however, no acute cause may be found. Careful consideration should be given to all diabetic patients presenting with hypoglycemia. New medications, activity changes, and infection should be considered.
- Early in the course of type 2 diabetes, patients may experience episodes of hypoglycemia several hours after meals. The symptoms generally are brief and respond spontaneously.
- *Drugs that may be related to hypoglycemia include the following*: oral hypoglycemic agents, sulfonamides, insulin, salicylates, p-aminobenzoic acid, haloperidol, ethanol, quinine, thiazide diuretics.
- Cultural and social factors, e.g. religious fasting during ramzan⁴
- Other causes in non-diabetic and in patients with diabetes include the following:
 - GI surgery (Especially gastric surgery)
 - Hepatic disease

Table 20.1: Physiologic response to falling plasma glucose.

<i>Hormonal response</i>	<i>Glycemic threshold* (mg/dL)</i>	<i>Effects</i>	<i>Role in hypoglycemia prevention/correction</i>
↓ Insulin	80–85	↑ Ra (↓ Rd)	Primary glucose regulatory factor, first defense against hypoglycemia
↑ Glucagon	65–70	↑ Ra	Primary glucose regulatory factor, second defense against Hypoglycemia
↑ Epinephrine	65–70	↑ Ra, ↓ Rd	Involved, Critical when glucagon is deficient, third defense against hypoglycemia
↑ Cortisol and growth hormone	65–70	↑ Ra, ↓ Rd	Involved, not critical
Symptoms	50–55	↑ Exogenous glucose	Prompt behavioral defense (food ingestion)
↓ Cognition	< 50	—	Compromises behavioral defenses

*Arterialized venous plasma glucose concentration. Ra: Rate of appearance of glucose through production in liver and kidney; Rd: Rate of disappearance of glucose through peripheral utilization in insulin sensitive tissues such as skeletal muscles and not central nervous system. Adapted from William's Textbook of Endocrinology, Eleventh Edition.

- Islet cell tumor/extrapaneatic tumor (Rare)
- Adrenal insufficiency
- Hypopituitarism
- Sepsis
- Starvation.

CLINICAL RECOGNITION OF HYPOGLYCEMIA

History

- A history of insulin usage or ingestion of an oral hypoglycemic agent may be known, and possible toxic ingestion should be considered. Inquire if the patient is taking any new medications
- Obtaining an accurate medical history may be difficult if the patient's mental status is altered
- The medical history may include diabetes mellitus, renal insufficiency/failure, alcoholism, hepatic cirrhosis/failure, other endocrine diseases, or recent surgery
- Review systems for weight reduction, fatigue, somnolence, nausea and vomiting, and headache
- Look for other symptoms suggesting infection.
- Adrenergic symptoms and neuroglycopenic symptoms summarized in Table 20.2.

Hypoglycemia may be suspected in the following category of patients:

- Being a male: young adult or elderly
- Low HbA1c (<5.0%)

Table 20.2: Symptoms of hypoglycemia.

<i>Neurogenic</i>	<i>Neuroglycopenic</i>
Adrenergic <ul style="list-style-type: none"> - Palpitations - Tremor - Anxiety/arousal Cholinergic <ul style="list-style-type: none"> - Sweating - Hunger - Paresthesia 	Cognitive impairments Behavioral changes Psychomotor abnormalities Seizure Coma

- Long duration of diabetes
- A history of hypoglycemia
- Hypoglycemia unawareness
- Recent bouts of severe hypoglycemia
- Low C-peptide level, daily insulin dose
- insulin dosage > 0.85 U/kg/day
- Recreationally active

Physical Examination

Physical findings are nonspecific in hypoglycemia and generally are related to the central and autonomic nervous systems.

- Assess vital signs for hypothermia, tachypnea, tachycardia, hypertension, and bradycardia (neonates)
- Cardiovascular disturbances may include tachycardia (bradycardia in children), hypertension or hypotension and dysrhythmias. Respiratory disturbances may include dyspnea, tachypnea, and acute pulmonary edema
- GI disturbances may include nausea and vomiting, dyspepsia, and abdominal cramping
- Skin may be diaphoretic and warm or show signs of dehydration with decrease in turgor
- Neurologic conditions include coma, confusion, and fatigue, loss of coordination, combative or agitated disposition, stroke syndrome, tremors, convulsions, and diplopia.

Laboratory Studies

- Treatment and disposition of hypoglycemia are guided by the history and the clinical picture. Serum glucose should be measured frequently and used to guide treatment, because clinical appearance alone may not reflect the seriousness of the situation.
- Hypoglycemia is defined according to the following serum glucose levels:^{5*}
 - <50 mg/dL in men
 - <45 mg/dL in women
 - <40 mg/dL in infants and children

*More than definition these are operational thresholds

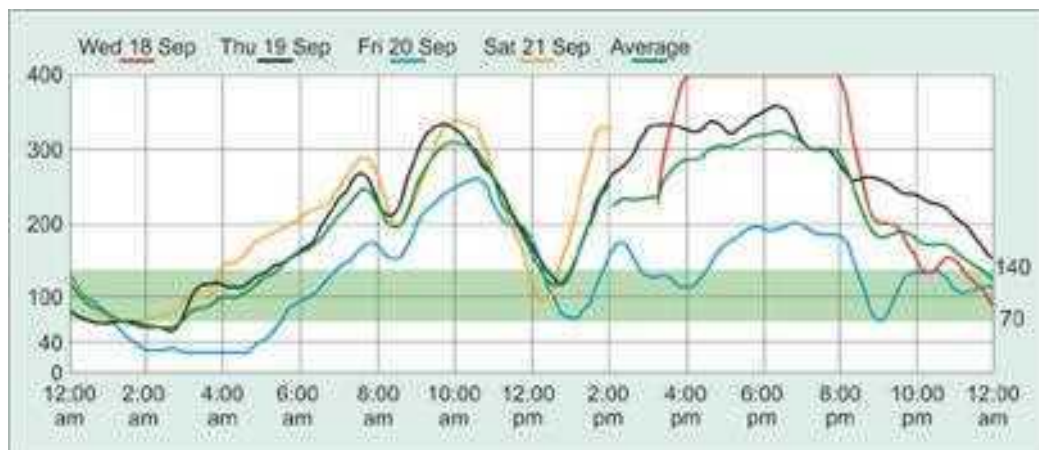


Fig. 20.1: Somogyii effect: Hypoglycemia leading on to hyperglycemia in an asymptomatic patient.

- If the cause of hypoglycemia is other than oral hypoglycemic agents or insulin in a diabetic patient, other lab tests may be necessary. Check liver function tests, cortisol and thyroid levels (if clinically indicated)
- Search for a source of infection. Studies should be considered to rule out the possibility of a concurrent occult infection contributing to the new hypoglycemic episode
- Complete physical examination
- Blood counts and chest radiograph (if indicated)
- Urinalysis and renal function tests.
- Continuous glucose monitoring system is useful in identifying asymptomatic or subtle hypoglycemias as shown in Figure 20.1.

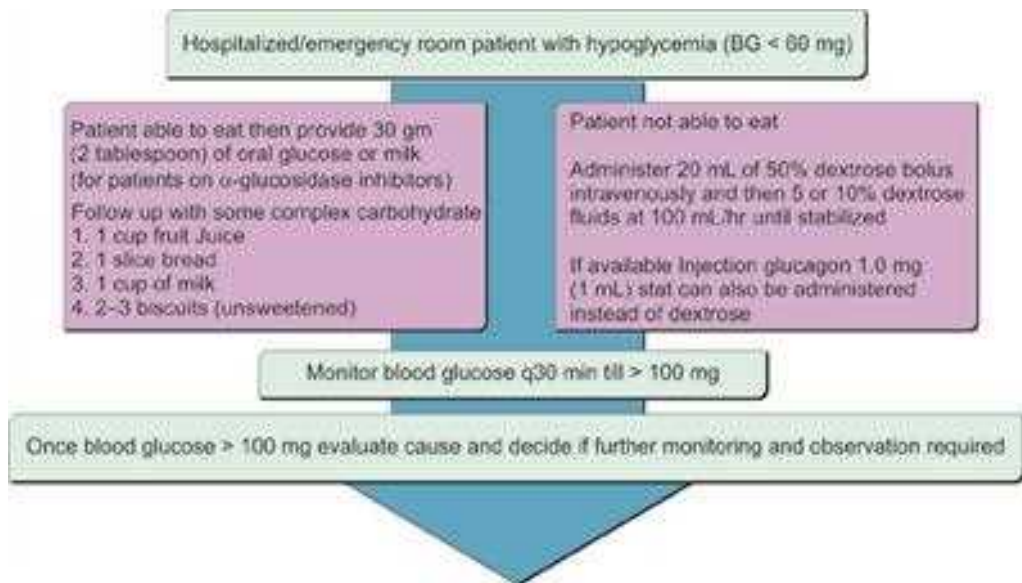
CLINICAL MANAGEMENT OF HYPOGLYCEMIA (FLOWCHART 20.1)

- Treatment should not be withheld while waiting for a laboratory glucose value, since the brain uses glucose as its primary energy source, neuronal damage may occur if treatment of hypoglycemia is delayed
- A hyperglycemic patient with an altered mental status may receive a bolus of glucose. This procedure is unlikely to harm the patient with high glucose; however, the delay in giving glucose to the hypoglycemic patient may be detrimental
- The mainstay of therapy for hypoglycemia is glucose or carbohydrates.

LONG-TERM MANAGEMENT

Ten percent glucose IV infusion in water by venous line at 100 mL/hr; avoid vein sclerosis that may occur with peripheral infusion

- The following patients require admission and 10% dextrose infusion after initial hypoglycemia is corrected because of the risk of further hypoglycemia

Flowchart 20.1: Management of hypoglycemia.

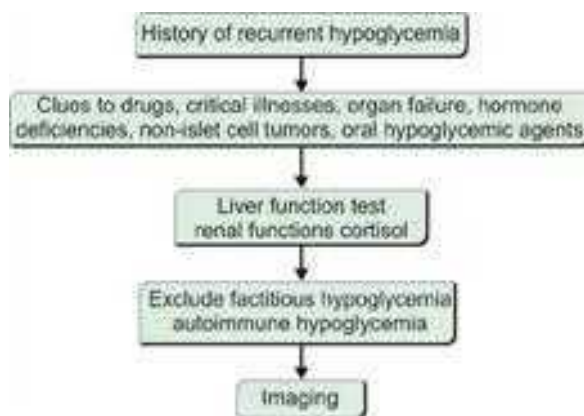
- No obvious cause
- Oral hypoglycemic agent
- Long-acting insulin
- Persistent neurologic deficits
- *Education/Prevention:* Patients must be counseled as to the causes and the early signs and symptoms of hypoglycemia. General outpatient diabetic education or inpatient diabetic teaching is indicated.⁶

RECURRENT HYPOGLYCEMIA

The following protocol is suggested in individuals with recurrent hypoglycemia in whom over dosage of medications and life style change alone cannot explain the hypoglycemia. Though rare, if all the mentioned causes are excluded then rarely patient may require evaluation and imaging for insulinoma.⁷ The protocol is summarized in Flowchart 20.2.

CONSEQUENCES

- Delay in treatment can result in profound sequelae, including death, though uncommon⁸
- Acute sequelae include coma, cardiac dysrhythmia and death
- The risk of permanent neurological deficits increases with prolonged hypoglycemia; such deficits can include hemiparesis, memory impairment, diminished language skills, decreased abstract thinking capabilities and ataxia
- Because the consequences of hypoglycemia can be devastating and an antidote is readily available, diagnosis and treatment must be rapid in any patient with suspected hypoglycemia, regardless of the cause

Flowchart 20.2: Evaluation of recurrent hypoglycemia.

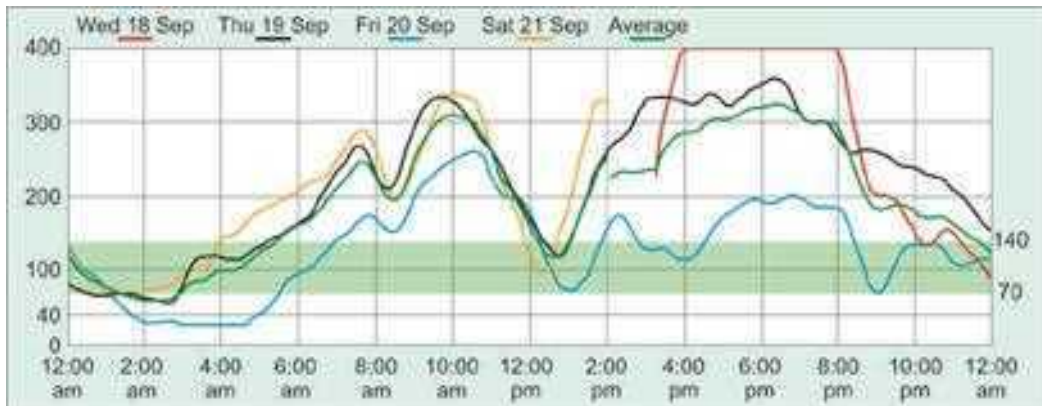
- In patients with cardiac autonomic neuropathy, repetitive hypoglycemia may lead to unresponsiveness and ultimately death which is known as death in bed syndrome. Cardiac autonomic neuropathy is more seen in patients with fibrocalcific pancreatic diabetes.⁹
- Recurrent hypoglycemia in children can cause intellectual impairment as therefore have relaxed glycemic targets. They also require additional care during adolescence due to the higher incidence in this age group. This is often due to lack of motivation busy educational responsibilities, changing physical activities and poor dietary habits.

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SELF-ASSESSMENT

1. A 68-year-old gentleman known to have type 2 diabetes mellitus for past 10 years, on twice daily premixed insulin, presented with concerns of recent onset fasting hyperglycemias. He has an HbA1c -5.6%. On further history he often misses his bed time snack. He was put on a continuous glucose monitors for diabetes (CGMS) device which showed the following pattern. What is your diagnosis?



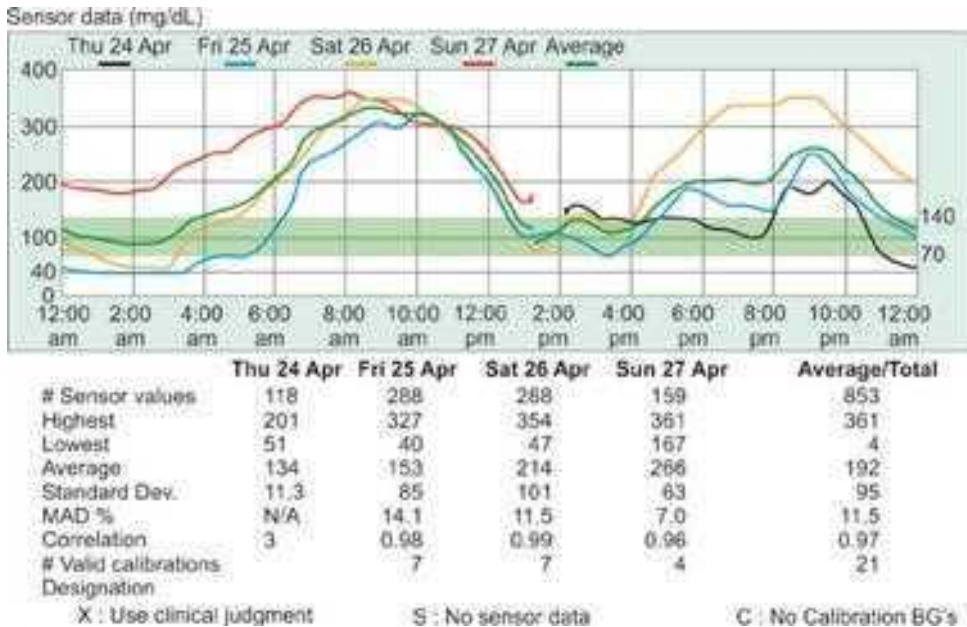
- (a) Dawn phenomenon
 - (b) Somogyi phenomenon
 - (c) Reactive hyperglycemia
 - (d) Reactive hypoglycemia
2. A 48-year-old gentleman known to have Type 2 diabetes for the past 2 years on Tab metformin 500 mg twice daily, has history of recurrent fasting hypoglycemia of 1 month duration. He presents to casualty with generalized tonic clonic seizures and has the following lab parameters:

Random Blood Sugar = 26 mg%,

Serum C peptide 3.5 ng/mL, urine ketones - Negative.

What is your diagnosis?

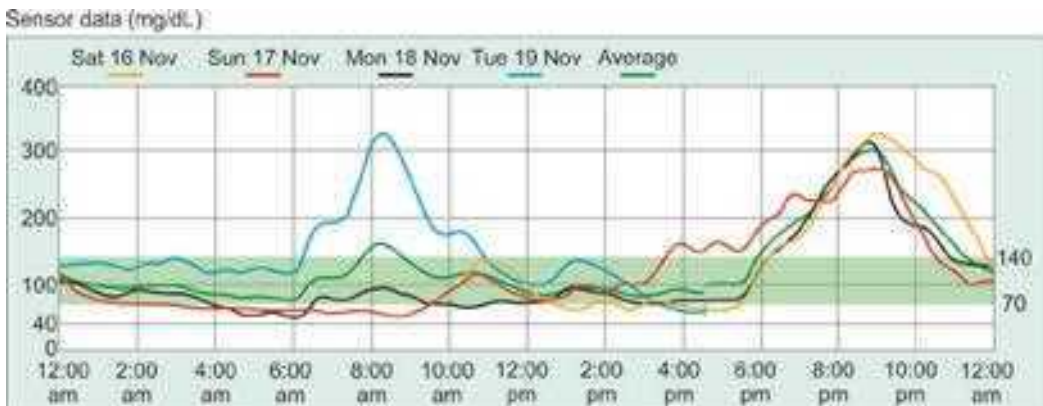
- (a) Metformin induced hypoglycemia
 - (b) Factious insulin intake
 - (c) Endogenous hyperinsulinemia
 - (d) Reactive hypoglycemia
3. A 62-year-old gentleman, known to have diabetes for 14 years on a stable dose of premixed insulin and metformin starts to experience recurrent hypoglycemia since the past 3 months. He also complains of facial puffiness of 1 month duration and underwent laser treatment for his diabetic retinopathy 2 weeks back. What would be the likely cause of hypoglycemia in this gentleman ?
 - (a) Ischemic heart disease
 - (b) Fatty liver
 - (c) Diabetic nephropathy
 - (d) Autonomic neuropathy
4. A 63-year-old lady is known to have type 1 diabetes mellitus and is on a basal bolus regime with three pre-meal short acting insulin and bed time glargine insulin. She has the following CGMS report, what suggestions will you gives with regards to her insulin dosage?



- Increase her glargine dose
- Reduce her morning short acting insulin dose
- Increase her afternoon short acting insulin dose
- Increase her after dinner short acting insulin dose

5. A nursing staff is known to have type 1 diabetes mellitus for 3 years duration. She has a meal at 10 am, sleeps and prior to her shift at 6 pm has a heavy meal then and goes to work. She has no complaints but her sugars are uncontrolled when monitored before 10.00 am.

Her CGMS shows the following pattern. What is your advice to her?



- To leave her job as her sugars can never be controlled with this job pattern.
- To ensure she has a snack during her night duty hours of work.
- To reduce her night short acting insulin to avoid 6 am hypoglycemia.
- To reduce her short acting insulin in morning as she has fasting hypoglycemia

CHAPTER

21

Pregnancy and Diabetes

Mahesh DM, Philip Finny, Kanakamani Jeyaraman, Senthil Vasan K, Mathew John

*“My sugars are high and I must worry,
Since, within my womb a child I carry,
Must reduce the sugars before it's too late,
Or baby will end up being high birth weight.”*

Although diabetes during pregnancy is often asymptomatic, the consequences are substantial. Metabolic derangements may present at the time of conception. During blastogenesis and organogenesis there is an increased risk of spontaneous abortions and congenital malformations. Placental vasculopathy in patients with diabetes may adversely affect the uteroplacental blood flow and nutrients to the fetus in pregnancy.

INTRODUCTION

With a prevalence of 9.09%, India currently harbors 65.1 of the 382 million people affected with diabetes. Along with the classical type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM), it includes gestational diabetes mellitus (GDM), monogenic forms of diabetes and secondary diabetes. “Gestational diabetes mellitus” has been defined as “carbohydrate intolerance of any degree of severity with onset or first recognition during pregnancy.” The age of onset of diabetes in women has shifted to the reproductive age group and an increasing number of pregnancies are being complicated by diabetes. Hyperglycemia during pregnancy not only places the mother at risk for future metabolic complications but also the fetus at risk for future diabetes. Thus, a diabetic pregnancy perpetuates the ongoing epidemic of T2DM. This should alert the medical fraternity to devote special attention to this segment of population.

In 2013, more than 21 million live births were affected by diabetes during pregnancy. Further, the prevalence of GDM corresponds to the prevalence of impaired glucose tolerance (IGT), in nonpregnant adults within that population. Around 7% of all pregnancies (1–14%, depending on the diagnostic tests employed and the population studied) are complicated by GDM, and hence resulting in approximately 200,000 cases annually. For example in one study from America, the prevalence of GDM in white women was 3.9% and in Asian women was 8.7%. Prevalence from Europe, China and Japan has been reported to be 0.6–3.6%, 2.3 and

2.9% respectively. In India, the prevalence of GDM has varied from 3.8% to 21% in different parts of the country. This variability is partly because of the different criteria and screening regimens used for diagnosing GDM in various countries.

TERMINOLOGY

Diabetes in a pregnant mother can either be a pre-existing diabetes or “*de novo*” GDM.

Gestational Diabetes Mellitus

By the Third International Gestational Diabetes Workshop, the definition of gestational diabetes had been broadened to include “glucose intolerance of variable severity with its onset or first recognition during pregnancy.” When this definition is applied to all women who are first diagnosed with diabetes during pregnancy, some overt cases of T2DM that predated pregnancy may be missed.

Pregestational Diabetes

If a lady, who is known to have diabetes and is undertreatment conceives, she is said to have pregestational diabetes. Since hyperglycemia is present throughout the pregnancy and not just in the second half as occurs in GDM, this group of patients are more prone for certain complications like congenital malformations of the fetus, worsening of diabetic complications in the mother, etc.

For many years, GDM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy, whether or not the condition persisted after pregnancy, and not excluding the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. This definition facilitated a uniform strategy for detection and classification of GDM, but its limitations were recognized for many years. As the ongoing epidemic of obesity and diabetes has led to more T2DM in women of child bearing age, the number of pregnant women with undiagnosed T2DM has increased. Because of this, it is reasonable to screen women with risk factors for T2DM at their initial prenatal visit, using standard diagnostic criteria. Women with diabetes in the first trimester should receive a diagnosis of overt, not gestational diabetes. In 2010, the International Association of Diabetes and Pregnancy Study Group (IADPSG), an international consensus group with representatives from multiple obstetrical and diabetes organizations, recommended a change to the above terminology. In this system, diabetes diagnosed during pregnancy is classified as overt or gestational.

Overt Diabetes

Women who meet any of the following criteria at their first antenatal visit:

- Fasting plasma glucose ≥ 126 mg/dL
- Glycated hemoglobin (HbA1c) $\geq 6.5\%$ using a standardized assay
- Random plasma glucose ≥ 200 mg/dL that is subsequently confirmed by elevated fasting plasma glucose or HbA1c, as noted earlier.

GDM carries risks for the mother and neonate. Not all adverse outcomes are of equal clinical importance. The hyperglycemia and adverse pregnancy outcome (HAPO) study, a large-scale (~25,000 pregnant women) multinational epidemiological study, demonstrated that risk of adverse maternal, fetal, and neonatal outcomes continuously increased as a function of maternal glycemia at 24–28 weeks, even within ranges previously considered normal for pregnancy. For most complications, there was no threshold for risk. These results have led to careful reconsideration of the diagnostic criteria for GDM. Different diagnostic criteria will identify different magnitudes of maternal hyperglycemia and maternal/fetal risk. In 2014, the American Diabetes Association (ADA) recommended that screening can be accomplished with either of two strategies:

1. “One-step” 2-hour 75-g oral glucose tolerance test (OGTT)
“One-step” (IADPSG consensus)

or

Perform a 75-g OGTT, with plasma glucose measurement fasting and at 1 and 2 hours, at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

The OGTT should be performed in the morning after an overnight fast of at least 8 hour.

The diagnosis of GDM is made when any of the following plasma glucose values are exceeded:

- Fasting: ≥ 92 mg/dL (5.1 mmol/L)
- 1 hour : ≥ 180 mg/dL (10.0 mmol/L)
- 2 hours ≥ 153 mg/dL (8.5 mmol/L)

2. “Two-step” (NIH consensus)

Perform a 50-g GLT (nonfasting), with plasma glucose measurement at 1 hour (Step 1), at 24–28 weeks of gestation in women not previously diagnosed with overt diabetes.

If the plasma glucose level measured 1 hour after the load is ≥ 140 mg/dL* (7.8 mmol/L), proceed to 100-g OGTT (Step 2). The 100-g OGTT should be performed when the patient is fasting.

The diagnosis of GDM is made when at least two of the following four plasma glucose levels measured fasting, 1 hour, 2 hours, 3 hours after the OGTT) are met or exceeded:

	Carpenter/Coustan	or	NDDG
• Fasting	95 mg/dL (5.3 mmol/L)		105 mg/dL (5.8 mmol/L)
• 1 hour	180 mg/dL (10.0 mmol/L)		190 mg/dL (10.6 mmol/L)
• 2 hours	155 mg/dL (8.6 mmol/L)		165 mg/dL (9.2 mmol/L)
• 3 hours	140 mg/dL (7.8 mmol/L)		145 mg/dL (8.0 mmol/L)

NDDG, National Diabetes Data Group. *The American College of Obstetricians and Gynecologists (ACOG) recommends a lower threshold of 135 mg/dL (7.5 mmol/L) in high-risk ethnic minorities with higher prevalence of GDM; some experts also recommend 130 mg/dL (7.2 mmol/L).

(*Source: American Diabetes Association. Standards of medical care in diabetes—2014. *Diabetes Care*. 2014;37(1): S14-80).

GESTATIONAL DIABETES MELLITUS

Most women with diabetes diagnosed during pregnancy have hyperglycemia that begins in pregnancy, but some may have T2DM that was unrecognized prior to pregnancy. Depending

on the ethnicity, the proportion of T2DM presenting as GDM may be as high as 35–40%. About 5–10% women with GDM have circulating islet-cell antibodies. Though they may have a “latent” form of T1DM, their risk of developing future T1DM is not known.

Pregnancy has been traditionally described as a transient excursion into the metabolic syndrome. During pregnancy, metabolic changes are necessary to ensure the growth and development of the fetus and in order to meet the demands of the pregnant mother. In addition, both are provided with adequate energy stores that are needed during labor and during the period of lactation. In general, during the latter half (end of second trimester) of the pregnancy, insulin sensitivity reduces and insulin secretion increases. Glucose seems to be the major substrate for the human fetus during pregnancy, and glucose metabolism has thus been the subject of most studies on metabolism in pregnancy. Pregnancy-related maternal insulin resistance benefits fetal growth, because a rise in postprandial glucose concentration aids glucose transfer to the fetus, a process termed “facilitated anabolism”. Maternal to fetal glucose transfer in the fasting state is enhanced by maternal lipolysis, which occurs in late pregnancy, with free fatty acids becoming the main maternal fuel substrate and diversion of glucose to the fetus. The ability of insulin to suppress lipolysis (via inhibition of hormone-sensitive lipase in adipose tissue) is severely impaired in late pregnancy, when maternal free fatty acid release and fatty acid oxidation are increased in parallel with reduced carbohydrate oxidation. This process of enhanced lipolysis has been termed “accelerated starvation” and is attributed to the actions of human placental growth hormone and other placental hormones. These metabolic changes facilitate the transfer of glucose and amino acids to the fetus. An increase in hepatic glucose output in late pregnancy, owing to hepatic insulin resistance, ensures that maternal glucose is available to the fetus between meals. Hence, the relative insulin resistance in pregnancy stabilizes glucose input to the fetus and the role of placental hormones seems to be crucial.

Pathophysiology

Pregnancy is characterized by progressive insulin resistance that begins near second half (20th week) and progresses through the third trimester (Fig. 21.1). In late pregnancy, insulin sensitivity falls by around 50%. Two main factors to insulin resistance are increased maternal adiposity and the insulin desensitizing effects of placental hormones. The fact that insulin resistance rapidly decreases after birth suggests that the main contributors are hormones secreted by the placental. Placental hormones such as progesterone, prolactin, cortisol and human placental lactogen (HPL) released in the second half, contribute to decreased insulin action in pregnancy. The placental human chorionic somatomammotropin (HCS, formerly called human placental lactogen) stimulates secretion of insulin by fetal pancreas and inhibits peripheral uptake of glucose in the mother. As the pregnancy progresses, the size of the placenta increases, so does the production of the hormones, leading to an increase in insulin-resistant state. In nondiabetic pregnant women, this is associated with β -cell hypertrophy and hyperplasia resulting in increased the first- and second phase insulin responses that compensate for the reduction in insulin sensitivity. It has been suggested that women who develop GDM may also have an underlying deficit in this additional insulin secretion (beta cell dysfunction). In pregnant women with abnormal glucose intolerance, the insulin resistance of pregnancy is not adequately compensated for, resulting in carbohydrate or glucose intolerance (Fig. 21.2).

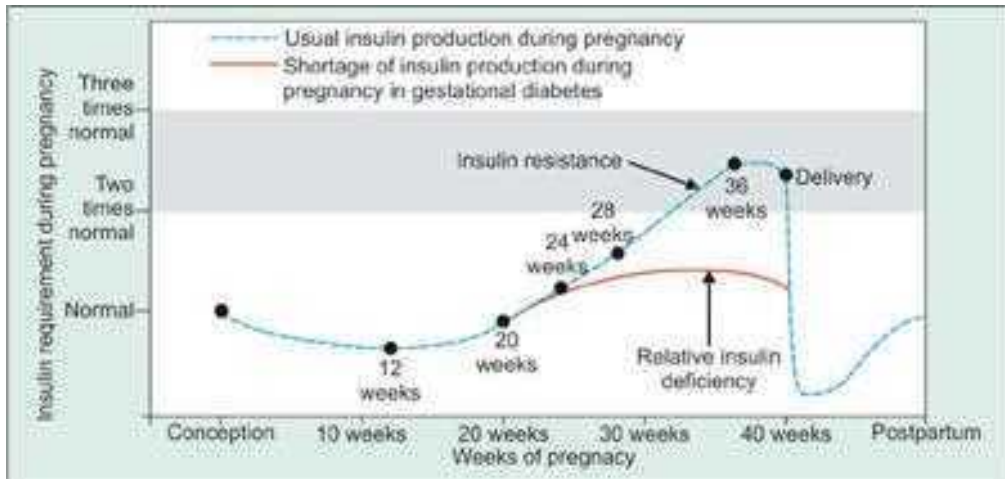


Fig. 21.1: The relative insulin deficiency in the presence of insulin resistance that sets in at around 20 weeks results in hyperglycemia in pregnancy.

Source: International Diabetes Center Publishing (2015). Gestational Diabetes. [online] Available from <http://www.idcpublishing.com/Gestational-Diabetes>. (Accessed April, 2015).

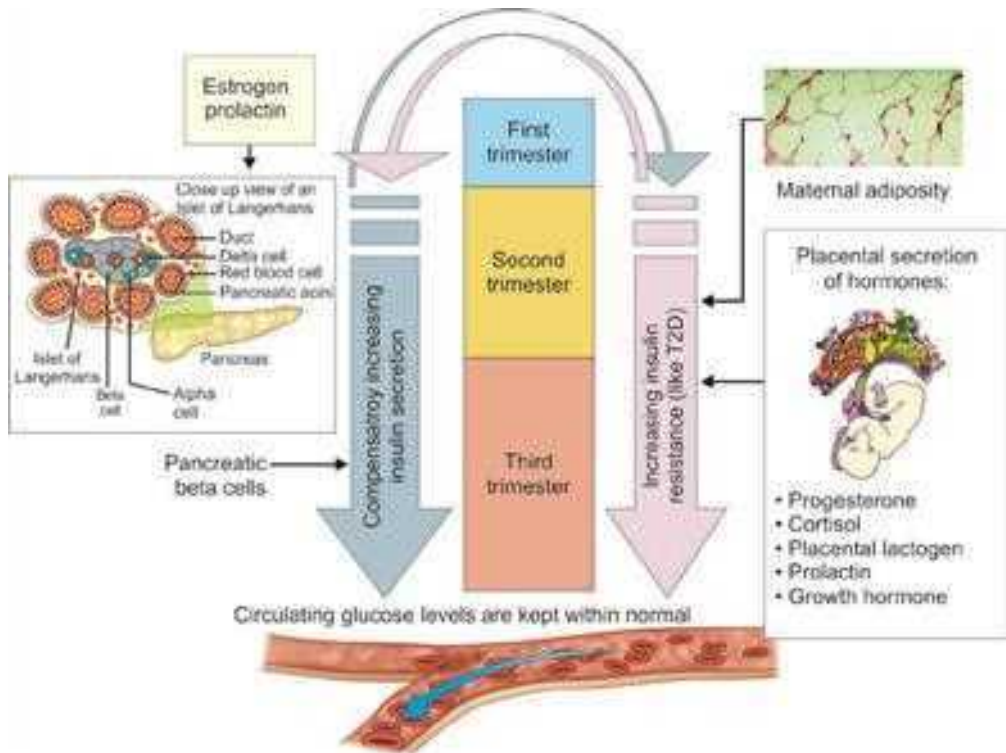


Fig. 21.2: Normal glucose regulation during pregnancy. (T2D: Type 2 diabetes mellitus).

Mechanisms of Insulin Resistance

The mechanisms related to the changes in insulin resistance during pregnancy are better characterized because of research in the past decade. The insulin resistance of pregnancy is almost completely reversed shortly after delivery consistent with the clinically marked decrease in insulin requirements. The placental mediators of insulin resistance in late pregnancy have been ascribed to alterations in maternal cortisol concentrations and placenta-derived hormones such as HPL, progesterone, and estrogen. Kirwan et al. reported that circulating tumor necrosis factor- α (TNF- α) concentrations had an inverse correlation with insulin sensitivity as estimated from clamp studies. Among leptin, HPL, cortisol, human chorionic gonadotropin, estradiol, progesterone, and prolactin, TNF- α was the only significant predictor of the changes in insulin sensitivity from the pregravid period through late gestation. TNF- α and other cytokines are produced by the placenta, and 95% of these molecules are transported to maternal rather than fetal circulations. Other factors, such as circulating free fatty acids, may contribute to the insulin resistance of pregnancy. Studies in human adipose tissue and skeletal muscle have demonstrated defects in the postreceptor insulin-signaling cascade during pregnancy. Friedman et al. showed that women in late pregnancy have reduced insulin receptor substrate-1 (IRS-1) concentrations compared with those of matched nonpregnant women. Downregulation of the IRS-1 protein closely parallels insulin's decreased ability to induce additional steps in the insulin-signaling cascade that result in the glucose transporter (GLUT-4) arriving at the cell surface to allow glucose to enter the cell. Downregulation of IRS-1 closely parallels the decreased ability of insulin to stimulate 2-deoxyglucose uptake *in vitro* in pregnant skeletal muscle. During late pregnancy in women with GDM, in addition to decreased IRS-1 concentrations, the insulin receptor- β (i.e. component of the insulin receptor within the cell rather than on the cell surface) has a decreased ability to undergo tyrosine phosphorylation. This is an important step in the action of insulin after it has bound to the insulin receptor on the cell surface. This additional defect in the insulin-signaling cascade is not found in pregnant or nonpregnant women with normal glucose tolerance and results in a 25% lower glucose transport activity. TNF- α also acts by means of a serine/threonine kinase, thereby inhibiting IRS-1 and tyrosine phosphorylation of the insulin receptor. These postreceptor defects may contribute in part to the pathogenesis of GDM and an increased risk for T2DM in later life.

Gestational Diabetes and MODY

Pregnancy, a state of increased insulin resistance is believed to catalyze the occurrence of GDM, especially in those with beta cell dysfunction. A proportion of these subjects with beta cell dysfunction may have *maturity onset diabetes of the young (MODY)*. Various genetic mutations predispose a pregnant woman to develop gestational diabetes. The importance of monogenic DM is due to the 50% risk of inheritance in offspring of affected subjects, the particular response of some types to sulfonylurea treatment, potential implications for treatment during pregnancy, comorbidities in specific types (HNF-1 β), and the insight provided for understanding gestational and T2DM.

Further, to determine the genetic profile of women with GDM in our population, utilizing the ion torrent next generation sequencing (NGS) based protocol, at our tertiary care center, we screened 50 pregnant women with diabetes for a comprehensive panel of ten MODY genes (HNF1A, HNF4A, GCK, PDX1, HNF1B, NEUROD1, KLF11, CEL, PAX4 and INS). Pathogenic variants were identified in 20% (10/50) of the subjects screened, the details of which are in the table below. This comprehensive MODY genetic testing in pregnant women with diabetes revealed a higher frequency of MODY mutations involving *PDX1* and *NEUROD1* genes.

Screening for Gestational Diabetes Mellitus

Whom to Screen?

Risk factors for gestational diabetes screening are:

- Ethnic group with a high prevalence of diabetes
- Women who have given birth to large infants (> 4 kg)
- History of recurrent fetal loss
- Persistent glycosuria
- Age > 25 years
- Past history of glucose intolerance/diabetes in previous pregnancy
- Obese/Overweight women (>15% of nonpregnant ideal body weight)
- Strong family history of diabetes
- History of stillbirth, unexplained neonatal death, congenital malformations, prematurity
- History of pre-eclampsia
- History of polyhydramnios
- History of traumatic delivery with an associated neurological disorder in the infant
- Chronic hypertension
- Recurrent severe moniliasis/urinary tract infection.

Recommended screening strategies range from selective screening of average-and high-risk individuals to universal diagnostic testing of the entire population dependent on the risk of diabetes in the population. Study groups from India, like Diabetes in Pregnancy Study group India (DIPSI), have made recommendations that universal screening is the best in Indian setting because of the very high prevalence of both GDM and background T2DM in Indian population.

When to Screen?

Universal screening has traditionally been performed at 24–28 weeks of gestation. However, it is wiser to screen as early as in the first prenatal visit if there is a high degree of suspicion of undiagnosed T2DM (e.g. marked obesity, personal history of GDM, glycosuria, previous congenital malformations in child or strong family history of diabetes). The IADPSG recommended that the time for screening for diabetes in pregnancy should be based upon the background frequency of abnormal glucose metabolism in the population and on local circumstances. Hence, it is rational to do early screening in the first trimester in Indian pregnant women, as recommended by DIPSI.

Table 21.1: Diagnostic criteria for gestational diabetes mellitus (GDM).

75 g 2 hour GTT#	IADPSG/ADA	WHO
0 hour	≥ 92	≥ 125
1 hour	≥ 180	OR
2 hour	≥ 153	≥ 140

*For NDDG and CC criteria, any two values should be abnormal to diagnose GDM.

#For IADPSG/ADA criteria, any one elevated value is considered a positive test.

(ADA: American Diabetes Association; WHO: World Health Organization; IADPSG: International Association of Diabetes and Pregnancy Study Group).

Diagnostic Testing

Glucose tolerance test commonly practiced in our clinical setting includes a simplified 75 g 2 hours GTT. The criteria for diagnosis of GDM are given in Table 21.1. The IADPSG recommends the 75 g 2 hour oral GTT because it is more convenient and better tolerated. The IADPSG defined thresholds are based on outcome data reported in the hyperglycemia and adverse pregnancy outcome (HAPO) study and a positive test needs only one elevated glucose and the cut-offs are slightly lower.

In India, a community based study—Diabetes in Pregnancy and Awareness Project (DIPAP) was done to validate the WHO criteria in Indian population. Depending on the results of this study and the observation that as high as 18–23% of women whose glucose challenge test (GCT) is positive in the first visit, fail to return for the confirmation GTT, the DIPSI has suggested “A one step procedure with a single glycemic value” for the diagnosis of GDM in Indian setup. Thus, DIPSI recommends a 2 hours plasma glucose more than or equal to 140 mg/dL after 75 g oral glucose load as the diagnostic criteria.

Other Methods of Diagnosing Diabetes in Pregnancy

For patients who cannot tolerate the hyperosmolar oral glucose, other oral methods like candies, predefined meal, commercial soft drinks, etc. have been suggested, but not validated in larger studies. In occasional patients intravenous (IV) GTT may be ordered. HbA1c does not differentiate between women with normal, borderline abnormal, and mildly abnormal blood glucose levels and is not suitable to detect mildly impaired glucose tolerance. However, an HbA1c more than or equal to 6.5% suggests overt diabetes in pregnancy as proposed by the IADPSG. An HbA1c below this level should not be taken as evidence against the diagnosis of diabetes. In fact, data are accumulating that an HbA1c level more than 2 SD above the normal mean during pregnancy (in most laboratories this level is approximately 5.3%), may identify those women at risk for delivering a large for gestational age infant (Fig. 21.3).

Maternal and Fetal Complications in Gestational Diabetes Mellitus

Several maternal and fetal adverse outcomes are associated with increasing levels of hyperglycemia. These are summarized in Table 21.2. Diabetic embryopathy is related to the degree of hyperglycemia in early part of pregnancy during organogenesis stage. This leads to



Fig. 21.3: On the right is a full term small for gestational age baby. The one in center is full term large for gestational age baby. On the left is a preterm baby.

Courtesy: Dr Niranjana Thomas, Department of Neonatology, Christian Medical College, Vellore, Tamil Nadu, India.)

increased rates of spontaneous abortions and major malformations because of yolk sac failure. Therefore, congenital malformations are more common in those with poorly controlled pregestational diabetes and in those with pre-existing diabetes first time diagnosed during pregnancy. These pregnant mothers are also more prone for worsening of diabetic micro- and macrovascular complications.

PREGESTATIONAL DIABETES

The successful outcome of the pregnancy for both the mother and the fetus is related to the degree of diabetes control and the intensity of any underlying maternal cardiovascular and renal disease.

The maternal effects include a high-risk for pre-eclampsia, recurrent abortions due to poor glycemic control in the first trimester and preterm delivery. Worsening of severe proliferative retinopathy and nephropathy (when associated with renal failure is common). In patients with coronary artery disease especially following myocardial infarction, there is a high risk of maternal death.

Fetal Effects

Major malformations are seen in 5–10% of babies of diabetic mothers and are 13–20 times more common when compared to normal pregnancies. Two-thirds of these anomalies involve either cardiovascular or central nervous system anomalies. Congenital malformations account

Table 21.2: Maternal and fetal complications in gestational diabetes mellitus (GDM).

Table 21.2: Maternal and fetal complications in gestational diabetes mellitus (GDM).	
	<i>Effects of diabetes on the mother</i>
Maternal complications	<ul style="list-style-type: none"> • First trimester—risk of recurrent abortions due to poor glycemic control → placental vasculopathy ↓ uteroplacental blood flow and nutrients to the fetus • Infection—high incidence of chorioamnionitis and postpartum endometritis • Higher risk of pre-eclampsia—affects 10–25% of all pregnant women with diabetes • Postpartum bleeding—high incidence caused by exaggerated uterine distension • Cesarean section—high incidence due to fetal macrosomia and cephalopelvic disproportion
	<i>Effects of pregnancy on diabetes</i>
	<p>In pregestational diabetes:</p> <ul style="list-style-type: none"> • More insulin is necessary to achieve metabolic control • Progression of diabetic retinopathy • Worsening of diabetic nephropathy • Increased risk of death for patients with diabetic cardiomyopathy and myocardial infarctions
Fetal complications	<ul style="list-style-type: none"> • Congenital abnormalities (5 to 10%)—due to metabolic derangements present at the time of conception, during blastogenesis and organogenesis • Hyperglycemia → Macrosomia → Traumatic delivery • Hypocalcemia • Intermittent hypoglycemia → risk of intrauterine growth restriction (IUGR) • Hyperviscosity syndrome • Hyaline membrane disease • Apnea and bradycardia • Unexplained fetal demise (during the last 4–8 weeks of gestation)
Neonatal complications	<ul style="list-style-type: none"> • Respiratory distress • Hypoglycemia • Hypocalcemia • Hyperbilirubinemia • Cardiac hypertrophy • Long-term effects on cognitive development

for half of the perinatal deaths in diabetic pregnancies. With lower HbA1c at conception, lower rates of malformations are seen. Intensive preconception glycemic management reduced fetal anomaly rate significantly (Box 21.1).

Unexplained Fetal Demise

As the name indicates, no obvious factors such as placental insufficiency, abruption, fetal restriction or oligohydramnios are apparent. These infants are large for age and die by 35 weeks or later. Polyhydramnios is seen quite often and is a consequence of fetal polyuria presenting secondary to hyperglycemia (Fig. 21.4).

Box 21.1: Common congenital malformations in fetus.

- *Cardiovascular system including great vessel:* Transposition of the great vessels with or without ventricular septal defects, coarctation of the aorta with or without ventricular septal defects or patent ductus arteriosus, atrial septal defects, single ventricle, hypoplastic left ventricle, pulmonic stenosis, pulmonary valve atresia, double outlet right ventricle, truncus arteriosus
- *Central nervous system:* Spina bifida, anencephaly with or without herniation of neural elements, arhinencephaly, microcephaly, holoprosencephaly, neural tube defects like meningomyelocele
- *Skeletal:* Cleft lip/palate, caudal regression syndrome (sacral agenesis), hemivertebrae
- *Genitourinary tract:* Ureteric duplication, hydronephrosis, renal agenesis
- *Gastrointestinal:* Anorectal atresia, imperforate anus, duodenal atresia, small left colon syndrome, situs inversus.

Source: Society of Obstetricians and Gynecologists. clinical practice guidelines approved by the executive council. 2007.



Fig. 21.4: Caudal regression syndrome in an infant of diabetic mother.

Courtesy: Dr Niranjan Thomas, Department of Neonatology, Christian Medical College, Vellore, Tamil Nadu, India.)

Preconceptional Counseling

All women of child bearing age with pre-existing type 1 or type 2 diabetes, when planning on pregnancy, should be educated about the importance of achieving near-normal blood glucose control before conception to reduce the risk of congenital malformations and spontaneous abortions.

Preconception counseling should include assessment of maternal and fetal risk and guidance to achieve target glycemic levels. It should be ensured that the mother learns self-administration of insulin and regular monitoring of blood glucose. HbA1c should be as

close to normal as possible without inducing undue hypoglycemia. Instructions should also emphasize on diet and regular exercises. Folic acid supplementation (5 mg/day) should be continued. Oral antidiabetic agents, angiotensin-converting-enzyme (ACE) inhibitors, beta-blockers and potentially teratogenic drugs should be avoided.

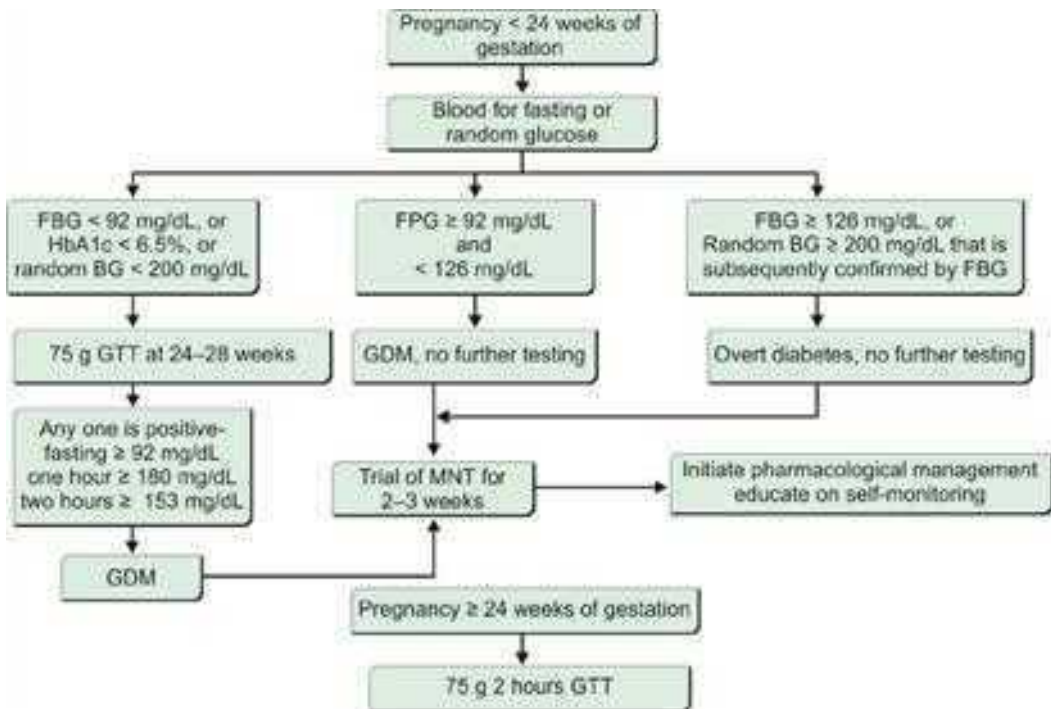
MANAGEMENT

Medical Management of Gestational Diabetes Mellitus (Flowchart 21.1)

The components of GDM management include:

- Medical Nutrition Therapy (MNT)
- Physical activity
- Pharmacological therapy
- Adequate monitoring of blood glucose.

Flowchart 21.1: Algorithm for management of diabetes in pregnancy.



Source: Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33:676.

(GTT: Glucose tolerance test; GDM: Gestational diabetes mellitus; MNT: Medical nutrition therapy; FBG: Fasting blood glucose; HbA1c: Glycated hemoglobin).

Table 21.3: Calorie allotment and weight gain in pregnancy.

Current weight (as % of ideal body weight)	Category	Recommended daily caloric intake (Kcal/kg)	Recommended total weight gain in all three trimesters of pregnancy (kg)
< 80-90	Underweight	36-40	12.5-18.0
0-120	Ideal	30	11.5-16.0
120-150	Overweight	24	7.0-11.5
> 150	Obese	12-18	At least 6

Medical Nutrition Therapy

The goals of MNT are to achieve normoglycemia, prevent ketosis, provide adequate weight gain and contribute to fetal well-being. The calorie allotment according to body weight is shown in Table 21.3.

Carbohydrates should be restricted to 40–45% of the total calories, the remaining divided between protein and fat. The calorie should be distributed into three meals and three snacks. A bedtime snack is insisted to prevent ketosis in fasting.

Physical Activity

Planned physical activity of 30 min/day is recommended for all who are capable of participating. Brisk walking or arm exercises while seated in a chair for at least 10 minutes after each meal accomplishes this goal. Exercises that use upper body muscles or those exercises which place little mechanical stress on the trunk are preferred.

Pharmacological Therapy

Pharmacological intervention in the form of insulin is done immediately if fasting plasma glucose (FPG) at diagnosis is more than or equal to 120 mg/dL. Otherwise, MNT can be tried for 2 weeks and if majority of the FPG (i.e. 4 out of 7 values in a week) more than 95 or 1 hour postprandial more than 120, then insulin can be started.

Insulin: Insulin therapy should be tailored to control the fasting and postprandial blood glucose. This can be achieved with either a basal bolus regime or premixed insulin. Target blood glucose levels are achieved by intensive management. Short acting insulin analogs like Lispro and Aspart can be used to achieve postprandial control. Long acting analogs like Glargine and Detemir are not licensed in pregnancy. Insulin requirements increase by 50% from 20 to 24 weeks to around 30 to 32 weeks of gestation at which time insulin needs often stabilize. The patient is taught self-administration of insulin and home glucose monitoring.

Oral antidiabetic agents: Most recent studies of metformin use in pregnancy have shown it to be safe for use in second and third trimesters. But at least one-third of women will need insulin to achieve glycemic targets. Metformin when used alone or with supplemental insulin was not associated with increased perinatal complications as compared to insulin. It was found

that those on combined treatment with both insulin and metformin required a lower dose of insulin and had lesser weight gain than those on insulin alone. The follow-up was available till early infancy and the APGAR scores were normal and there was no increase in neonatal acidosis. More follow-up data is required to establish long-term safety. Metformin is currently preferred over glibenclamide in pregnancy.

Tolbutamide diffuses across placenta most freely followed by Chlorpropamide and Glipizide. These oral antidiabetic drugs (OADs) are associated with fetal hyperinsulinemia and prolonged neonatal hypoglycemia and are not used in pregnancy. Glyburide crosses the placenta the least. Fetal concentration of Glibenclamide reached no more than 1-2% of maternal levels. Observational studies showed that Glibenclamide was not associated with any excess anomalies or hypoglycemia. The use of Glibenclamide was shown to be safe and equally effective as insulin in one randomized controlled trial of 404 mild GDM patients. More research is needed to determine: (1) if maternal and neonatal outcomes with glyburide are equivalent to those obtained with insulin therapy; (2) if glyburide has any effect on the postpartum progression of GDM to IGT/diabetes, or on recurrence; (3) whether glyburide affects the long-term well-being of offspring. Patients who are contemplating glyburide therapy should be counseled regarding the absence of information about these important questions.

Another study of women with polycystic ovarian syndrome who were treated with metformin and their infants followed-up till 18 months of age has provided no evidence of negative impact on growth or on motor and social development.

A systematic review done by John Hopkins University concluded that maternal glucose levels did not differ substantially between gravidae treated with insulin versus those treated with OADs. There was no consistent evidence of an increase in any adverse maternal or neonatal outcome with use of glyburide or metformin compared with use of insulin. However, till the time this chapter was written, the use of OADs in pregnancy was not approved by any of the major organizations like ADA and American College of Obstetricians and Gynecologists (ACOG). Nevertheless OADs are of practical necessity in rural India and metformin in early GDM could be used prior to insulin.

Blood glucose is ideally monitored at home using a glucometer, at least four times a day (fasting and three 1 hour postprandial). It is of interest to note that postprandial monitoring rather than premeal monitoring was associated with better glycemic control (HbA1c value 6.5 vs. 8.1%), a lower incidence of large-for-gestational age infants (12 vs. 42%) and a lower rate of cesarean delivery for cephalopelvic disproportion (12 vs. 36%). The glycemic goals are given in Box 21.2.

Box 21.2: Glycemic targets in pregnancy with diabetes.

ADA—capillary glucose

1. Premeal \leq 95 mg/dL
2. 1 hour postmeal \leq 140 mg/dL
3. 2 hours postmeal \leq 120 mg/dL

(ADA: American Diabetes Association).

Hypoglycemia in Pregnancy

Tight glycaemic control in GDM is associated with high incidence of hypoglycemia (<60 mg/dL) between 36% and 71%. Further, women with GDM on glyburide (28%) or insulin (63%) have masked hypoglycemia, defined as asymptomatic glucose levels less than 50 mg/dL for 30 minutes during continuous glucose monitoring.

At our center, we studied the prevalence of masked hypoglycemia in 30 women with GDM on insulin therapy and found that hypoglycemia was noted in 35% (7/20) of cases and 40% (4/10) of control, though the time spent at glucose levels less than 40 mg/dL for significantly higher in cases. Though the impact of this on maternal and fetal outcomes needs to be further studied in a larger population, in this group of pregnant women with masked hypoglycemia there was no adverse neonatal outcomes.

Obstetric Management of Gestational Diabetes Mellitus

Antepartum Management

The components include fetal monitoring, timing and mode of delivery, management of labor and immediate neonatal management. Fetal ultrasound is done at baseline to look for fetal size and, at 18–22 weeks ultrasound with fetal echocardiogram for major malformations. Later from 26 weeks onwards monitoring is done for growth and liquor volume. In late third trimester, frequent ultrasound is done to monitor abdominal: head circumference ratio as a marker of accelerated growth. Maternal monitoring of fetal activity is initiated in third trimester to reduce the risk of stillbirth (Table 21.4).

There is a small risk of late intrauterine death even with good glycaemic control. Hence, delivery is usually planned at 38 weeks so as to avoid late still birth and excess fetal growth leading to shoulder dystocia. The preferred mode is vaginal delivery and cesarean section is performed only for other obstetric indications. Cesarean delivery may reduce the likelihood of brachial plexus injury in the infant, if fetal weight of more than 4,500 g.

It is equally important to control maternal hyperglycemia in labor to prevent fetal hyperinsulinemia, fetal acidosis and neonatal hypoglycemia. Insulin requirements come

Table 21.4: Monitoring a patient with gestational diabetes at each visit.

<i>Clinical parameters to be monitored</i>	<i>Laboratory parameters to be monitored</i>
Medications	Hemoglobin
Pre-pregnancy weight	Blood sugars
Weight gain	HbA1c (in first trimester only)
Edema	Urine microscopy and albumin
Pallor	Thyroid functions (if goiter present)
Thyroid enlargement	
Blood pressure	
Fundal height	

(HbA1c: Glycated hemoglobin).

down during labor and the aim is to maintain blood glucose between 70 mg/dL to 90 mg/dL. The patient can be on routine GDM diet to maintain basal glucose requirements and blood glucose to be monitored at 1–4 hourly intervals during labor. Insulin is administered as infusion only if sugars more than 120 mg/dL. During later stages of labor dextrose should be started to maintain basal nutritional requirements (150–200 mL/hr of 5% dextrose) and continue hourly blood glucose monitoring. Postdelivery patients can be kept on dextrose-normal saline till oral intake is allowed. Insulin need not be given unless blood glucose is more than normal nonpregnant levels.

The immediate neonatal complication to be anticipated is hypoglycemia which occurs in as high as 50% of macrosomic infants and in 5–15% optimally controlled GDM. If blood glucose during labor and delivery exceeds 90 mg/dL, there is increased risk for hypoglycemia. Hypoglycemia in a neonate is defined as less than 40 mg/dL. If symptomatic, a bolus of 2–4 mL/kg of IV 10% dextrose is given and blood glucose is checked after 30 minutes. If hypoglycemia is persistent, IV dextrose can be infused at the rate of 6–8 mg/kg/min. Early breast-feeding should be encouraged. If there is seizure/irritability/respiratory distress, hypocalcemia should be ruled out. The infant should be examined for other congenital abnormalities.

If a woman is noninsulin requiring, early delivery is seldom indicated. Antepartum fetal monitoring may not be strictly required, as there is a low risk of fetal death. There is no special advantage in elective induction of labor. In insulin requiring subjects, fetal testing should be done and is managed as if they have overt diabetes.

Postpartum Management

Marked insulin sensitivity occurs immediately postpartum and insulin requirements drop to below preconception levels. To decrease the incidence of severe hypoglycemia, one-third to one-half of the preconception insulin dose is given in the first 24 hours. Insulin doses should be titrated regularly and eventually stopped when normoglycemia is achieved. Lifestyle modification continues to be the corner stone of good health in women at risk of developing overt diabetes in future. An OGTT at 6–12 weeks classifies a patient into normal/impaired glucose tolerance or diabetes.

FUTURE RISKS IN MOTHER

Recurrence of GDM is common and is seen in 30–60% of women. Older, multiparous women, those with weight gain in interpregnancy period and higher infant birth weight in index pregnancy are indicators of recurrence of GDM. These patients with GDM are at risk of developing IGT/T2DM in future. 20% of patients have IGT postpartum and 35–60% develop T2DM at the end of 10 years. The following are the risk factors that predict the risk of developing T2DM in long-term.

- Waist circumference and body mass index—strongest predictors
- Autoantibodies
- DM present at earlier gestational age
- Higher gestational requirement of insulin

Box 21.3: Salient features of International Diabetes Federation (IDF) 2009 guidelines for diabetes.

- A one-stage oral glucose tolerance test at 26–28 weeks of gestation is recommended to screen all pregnant women for gestational diabetes versus the ADA recommendation for selective screening in at-risk women only
- For women at high-risk for diabetes because of previous gestational diabetes, screening should be performed as soon as practical and should be repeated at 26–28 weeks of gestation
- For women with pre-existing diabetes, glycemic control should be optimized before planned pregnancy
- Angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers should be stopped and substituted with appropriate antihypertensive medications in pregnant women
- Statins, fibrates, and niacin should be stopped in pregnancy
- In women with existing diabetes or gestational diabetes, risks for glucose-lowering agents should be discussed, and use of insulin and the type of insulin should be assessed and discussed
- If possible, SMBG should be done frequently in pregnant women with diabetes
- Doses of glucose-lowering agents should be adjusted according to self-monitoring results, hemoglobin A1C level, and experience of hypoglycemia
- Eyes should be examined at the first prenatal visit and at each trimester
- Breast-feeding should be encouraged.

(ADA: American Diabetes Association; SMBG: Self-monitoring of blood glucose)

- Higher fasting and OGTT glucose levels
- Neonatal hypoglycemia
- Recurrent GDM.

CONCLUSION

The summary of the salient features of International Diabetes Federation (IDF) 2009 guidelines for diabetes is given in Box 21.3. These guidelines emphasize the universal screening and repetition for screening.

SUGGESTED READING

1. George A, Mathews JE, Sam D, et al. Comparison of neonatal outcomes in women with gestational diabetes with moderate hyperglycaemia on metformin or glibenclamide a randomised controlled trial *J Obstet and Gynaecol* 2015;55(1):47–52.
2. Thomas N, Grunnet LG, Poulsen P, et al. Born with low birth weight in rural southern India: what are the metabolic consequences 20 years later? *Eur J Endocrinol*. 2012;166(4):647–55.

SELF-ASSESSMENT

1. The ideal time to screen for gestational diabetes is:

- | | |
|------------------|-----------------|
| (a) 16–20 weeks | (b) 20–24 weeks |
| (c) 24–28 weeks | (d) 28–32 weeks |
| (e) 32–36 weeks. | |

2. The following is a contraindication for pregnancy:

- (a) Severe preproliferative retinopathy
- (b) Laser treated proliferative diabetic retinopathy
- (c) Microalbuminuria
- (d) Hypertension and diabetes complicating pregnancy
- (e) Mild nephropathy.

3. The OAD of proven efficiency in clinical trials in pregnancy and diabetes is:

- (a) Glimepiride
- (b) Glibenclamide
- (c) Gliclazide
- (d) Metformin

4. The period of improved insulin sensitivity in pregnancy is:

- (a) 12–14 weeks
- (b) 14–16 weeks
- (c) 16–18 weeks
- (d) 18–20 weeks
- (e) 4–6 weeks

5. The following are complications of DM in pregnancy *except*:

- (a) Pre-eclampsia
- (b) Polyhydramnios
- (c) Sudden death in 2nd trimester
- (d) Shoulder dystocia during delivery

6. The most common congenital anomaly in fetus with pregestational diabetes mellitus:

- (a) Renal agenesis
- (b) Club foot
- (c) Transposition of great vessels
- (d) Duodenal atresia
- (e) Cryptorchidism

7. The following are women with high-risk for GDM *except*:

- (a) Severe obesity
- (b) Bad obstetric history
- (c) Strong family history of type 2 DM
- (d) Past history of GDM
- (e) Age < 25 years

8. All of the following are common complications of *de novo* GDM *except*:

- (a) Macrosomia
- (b) Congenital anomalies
- (c) Polycythemia in newborn
- (d) Hypoglycemia in newborn
- (e) Hypocalcemia in newborn

9. Macrosomia affects all organs *except*:

- (a) Heart
- (b) Kidney
- (c) Lungs
- (d) Liver
- (e) Brain

10. Regarding metformin in pregnancy, which of the following are false?

- (a) Women with polycystic ovarian syndrome may conceive on metformin
- (b) It is known to cause lactic acidosis in pregnancy
- (c) It is not the standard drug combined with glibenclamide in pregnancy
- (d) It does not usually cause hypoglycemia in pregnancy
- (e) It may be started in persistent diabetes after pregnancy

CHAPTER

22

Diabetes in Childhood and Adolescence

Asha HS, Mathew John, Anna Simon, Veena V Nair

*"Like a steam engine breathing hard and fast,
With ketones in urine I was really aghast,
My glucose levels up and they're hitting the sky,
Beta cells are burnt out-please don't ask me why."*

INTRODUCTION

Childhood diabetes is a chronic disease with implications on the child's health and on the family as a whole. While it has been possible to treat type 1 diabetes mellitus (T1DM) since the discovery of insulin, optimal management to ensure a high quality of life while preventing late tissue damage demands a high degree of skill by both patients and their professional advisors. Children have characteristics and needs that dictate standards of care different from that of the adults. This short review deals with a practical approach to diagnosis and management of children with diabetes mellitus.

EPIDEMIOLOGY

Type 1 diabetes mellitus is the most common cause of diabetes in children. About 6–12% of individuals from India with diabetes below the age of 20 years have type 2 diabetes.

DIAGNOSIS

Most children and adolescents with type 1 diabetes present with history of polyuria, polydipsia, polyphagia and weight loss for several weeks, with hyperglycemia, glycosuria, ketonemia and ketonuria. The criteria for diagnosis of diabetes are similar to that of adults. Children with classical symptoms of diabetes mellitus with random plasma glucose more than 200 mg/dL or those with diabetic ketoacidosis (DKA) do not require any repeat testing. Oral glucose tolerance testing is seldom required in children.

Since the incidence of type 2 diabetes mellitus (T2DM) in children is increasing, it becomes increasingly difficult to distinguish a newly diagnosed patient with type 1 from type 2 diabetes.

The diagnosis of T1DM is clinically confirmed in a lean prepubertal child with DKA. However, in an overweight adolescent, differentiating T1DM from T2DM may be difficult. Antibody levels are useful for this differentiation. Irrespective of the type of diabetes, a child presenting with fasting hyperglycemia or DKA will require insulin.

CLASSIFICATION

Diabetes in the childhood and adolescence can be classified in various ways. The classification given in Table 22.1 outlines most of the types.

Childhood diabetes can be broadly divided as insulin requiring and noninsulin requiring forms. Among the insulin-requiring forms, T1DM due to autoimmune destruction of pancreas (Type 1A) is the most common type. Insulin requirement is also a feature of mitochondrial diabetes, genetic defects in insulin secretion or rarely from pancreatic agenesis (Table 22.2). Some forms of maturity onset diabetes of the young (MODY) associated with severe defects in

Table 22.1: Etiologic classification of diabetes mellitus in children.

I. Type 1 diabetes (beta cell destruction ultimately leading to complete insulin deficiency)
A. Immune mediated
B. Idiopathic
II. Type 2 diabetes (variable combinations of insulin resistance and insulin deficiency)
A. Typical
B. Atypical
III. Genetic defects of β -cell function
A. Maturity onset diabetes of the young (MODY) syndromes
1. MODY 1 chromosome 20, HNF-4 α
2. MODY 2 chromosome 7, glucokinase
3. MODY 3 chromosome 12, HNF-1 α , TCF-1
4. MODY 4 chromosome 13, IPF-1
5. MODY 5 chromosome 17, HNF-1 β , TCF-2
6. MODY 6 chromosome 2q32, neuro-D1/beta-2
7. MODY 7 chromosome 2q25, Kruppel like factor (KFL)11
8. MODY 8 chromosome 9q34, CEL (carboxyl ester lipase)
9. MODY 9 chromosome 7q32, Pax 4
10. MODY 10 chromosome 11p15.5, insulin gene
11. MODY 11 chromosome 8p23, BLK gene
12. MODY 12 chromosome 11p15, KCNJ 11
13. MODY 13 chromosome 11p15, ABCC8
14. MODY X mutation unidentified
B. Mitochondrial DNA mutations (includes one form of Wolfram syndrome; Pearson syndrome; Kearns-Sayre syndrome, diabetes mellitus with deafness)
C. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness): WFS1-Wolframin—chromosome 4p
1. Wolfram locus 2—chromosome 4q22-24
2. Wolfram mitochondrial
D. Thiamine responsive megaloblastic anemia (Roger's syndrome)

Contd...

Contd...

IV. Drug or chemical induced
<ul style="list-style-type: none"> A. Antirejection—cyclosporine B. Glucocorticoids (with impaired insulin secretion, e.g. cystic fibrosis) C. L-Asparaginase D. β-Adrenergic blockers E. Vacor (rodenticide) F. Phenytoin (Dilantin) G. Alpha-interferon H. Diazoxide I. Nicotinic acid J. Others
V. Diseases of exocrine pancreas
<ul style="list-style-type: none"> A. Immune mediated B. Cystic fibrosis-related diabetes C. Trauma—pancreatectomy D. Pancreatitis E. Others
VI. Infections
<ul style="list-style-type: none"> A. Congenital rubella B. Cytomegalovirus C. Hemolytic-uremic syndrome
VII. Variants of type 2 diabetes
<ul style="list-style-type: none"> A. Genetic defects of insulin action <ol style="list-style-type: none"> 1. Rabson-Mendenhall syndrome 2. Leprechaunism 3. Lipoatrophic diabetes syndromes 4. Type A insulin resistance—acanthosis B. Acquired defects of insulin action <ol style="list-style-type: none"> 1. Endocrine tumors <ul style="list-style-type: none"> Pheochromocytoma Cushing Others 2. Anti-insulin receptor antibodies
VIII. Genetic syndromes with diabetes and insulin resistance/insulin deficiency
<ul style="list-style-type: none"> A. Prader-Willi syndrome, chromosome 15 B. Down's syndrome, chromosome 21 C. Turner's syndrome D. Klinefelter syndrome E. Others <ol style="list-style-type: none"> 1. Bardet-Biedel syndrome 2. Alstrom syndrome 3. Werner syndrome
IX. Gestational diabetes
<ul style="list-style-type: none"> X. Neonatal diabetes <ul style="list-style-type: none"> A. Transient—chromosome 6q24, KCNJ11, ABCC8 B. Permanent—agenesis of pancreas—glucokinase deficiency (homozygous) and KCNJ11, ABCC8, FOXP3, EIF2AK3, IPF1 mutations

Source: American Diabetes Association Expert Committee classification of Diabetes Mellitus, 2007.

Table 22.2: Monogenic forms of diabetes causing defective beta cell function.

Type of diabetes	Gene mutation (Affected protein)	Mode of inheritance	Usual phenotype	Therapy
Permanent neonatal diabetes	KCNJ11 (<i>Kir 6.2</i>)	AD	Age of onset 3–6 months	Can be treated with sulfonylureas
	ABCC8 (<i>SUR1</i>)	AD	Age of onset 1–3 months	Can be treated with sulfonylureas
	GCK (<i>Glucokinase</i>)	AR	Age of onset 1 week	Insulin
	IPF-1 (<i>Insulin promoter factor 1</i>)	AR	Age of onset 1 week	Insulin; exocrine pancreatic replacement
	FOXP3 (<i>Forkhead box P3</i>)	X-linked	Sometimes at birth; presents as IPEX syndrome	Insulin
	EIF2AK3 (<i>Eukaryotic translation initiation factor2-alpha kinase3</i>)	AR	Age of onset 3 months; Wolcott-Rallison syndrome	Insulin and treatment of associated conditions
MODY 1	HNF4A (<i>Hepatocyte nuclear factor 4a</i>)	AD	Adolescence or early adulthood	Respond well to small doses of sulfonylurea
MODY 2	GCK (<i>Glucokinase</i>)	AD	Mild hyperglycemia in early childhood; may be present even at birth	Lifestyle measures; usually no drugs needed
MODY 3	TCF1 (<i>Hepatocyte nuclear factor 1a</i>)	AD	Adolescence or early adulthood	Respond well to small doses of sulfonylurea
MODY 4	IPF-1 (<i>Insulin promoter factor 1</i>)	AD	Early adulthood or later	Mostly sulfonylurea; some may need insulin
MODY 5	TCF2 (<i>Hepatocyte nuclear factor 1b</i>)	AD	Adolescence or early adulthood Renal anomalies and genital anomalies in females	Oral agents/Insulin
MODY 6	NeuroD1 (<i>Neurogenic differentiation factor 1</i>)	AD	Fourth decade of life Associated with obesity	Insulin
MODY 7	KFL11 (<i>Kruppel-like factor 11</i>)	AD	Early adulthood	Rare
MODY 8	CEL (<i>carboxy ester lipase</i>)	AD	Early adulthood	Rare
MODY 9	Pax4 (<i>paired box</i>)	AD	Early adulthood	Rare
MODY 10	INS (<i>Insulin</i>)		Early adulthood	Rare
MODY 11	BLK gene		Early adulthood	Rare

Contd...

Contd...

Type of diabetes	Gene mutation (Affected protein)	Mode of inheritance	Usual phenotype	Therapy
Wolfram syndrome	WSF1 (<i>Wolframin</i>)	AR	DM and optic atrophy in early childhood and diabetes insipidus in adolescence	Insulin
MIDD	tRNA	Mitochondrial	Onset at 30–40 years; associated cardiac conduction defects, deafness, neuropathy	Insulin secretagogues initially; high risk of lactic acidosis with Metformin

(AD: Autosomal dominant; AR: Autosomal recessive; IPEX syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; DM: Diabetes mellitus; MIDD: Maternally inherited diabetes mellitus and deafness).

insulin secretion may require insulin. Noninsulin dependent diabetes that occurs in childhood includes type 2 diabetes, MODY, milder mitochondrial defects and insulin receptor defects. Drugs like glucocorticoids can also give rise to a similar type of diabetes.

CLINICAL FEATURES

Type 1 Diabetes

Clinical presentation is with symptoms and signs of hyperglycemia—polyuria, polydipsia, polyphagia and weight loss. About 30–60% present with moderate to severe DKA at diagnosis. Younger children are more likely to present with DKA and nocturnal enuresis.

Type 2 Diabetes

It is more common in overweight adolescents, with signs of insulin resistance. They are usually detected on a medical checkup; a few may present with polyuria.

Pancreatic Diabetes Mellitus

Presentation is usually with symptoms of polyuria, polydipsia and weight loss. Fibrocalculous pancreatic diabetes and cystic fibrosis are seen in the younger age group. Preceding history of abdominal pain and steatorrhea are clues to the diagnosis.

Maturity Onset Diabetes of the Young

It is characterized by autosomal dominant inheritance, usually with a three generation family history of diabetes diagnosed before age 30–35 years. Acanthosis nigricans is not a feature, but may be present in obese children. They are usually diagnosed on evaluation for some other illness. Many of them respond to oral antidiabetic agents. Only a few with severe defects in insulin secretion require insulin therapy. Genetic testing in those with a strong family history helps to establish the diagnosis.

Lipodystrophic Diabetes

This is characterized by abnormal fat distribution. Several types of inherited and acquired lipodystrophies are known to be associated with diabetes.

Generalized Lipodystrophy

Berardinelli-Seip syndrome—characterized by diabetes mellitus requiring large doses of insulin due to severe insulin resistance, acanthosis nigricans, near total absence of body fat, prominent muscularity, hyperlipidemia, fatty liver, and hirsutism and polycystic ovary syndrome (PCOS) in females. They have to be treated with insulin sensitizers in addition to high doses of insulin.

Familial Partial Lipodystrophy

Dunnigan syndrome is characterized by loss of fat in the limbs during late childhood, puberty or later. The face, neck and intra-abdominal regions are spared giving a “cushingoid” appearance to the face. Acanthosis nigricans is usually mild. Girls may have hirsutism and PCOS. These patients usually require insulin and insulin sensitizers.

Acquired Lipodystrophy

Availability of highly active anti-retroviral therapy has helped prolong the longevity of individuals affected by HIV infection; but has also increased their risk of developing lipodystrophy and metabolic problems including diabetes mellitus and dyslipidemia. Diabetes in these individuals is due to increased insulin resistance and responds to oral anti-diabetic agents.

Mitochondrial Diabetes

It is characterized by inheritance from the mother, and associated deafness and myopathy.

Others

Diabetes associated with growth hormone excess and Cushing’s syndrome is described in the chapter on secondary diabetes.

APPROACH TO DIAGNOSIS

The diagnostic approach is based on the clinical presentation and whether or not the patient requires insulin for survival.

The investigations that would be helpful to make a diagnosis of the type of diabetes include

- *Urine ketones*: Positive in 30–60% of type 1 diabetes
- *Diabetes associated autoantibodies*: These include glutamic acid decarboxylase 65 (GAD 65), insulin autoantibody (IAA), islet antigen (IA-2) and zinc transporter isoform 8 (ZnT8) antibodies. The levels of one or more of these may be elevated in up to 80% of individuals

with type 1 diabetes at diagnosis. The sensitivity is different for the individual antibodies, varies with age, and antibody levels declining progressively over time.

- *GAD-65 antibody*: Positive in up to 80%, persists for more than 8–10 years from diagnosis
- *IA-2 antibody*: Positive in 32–75%, likelihood of detection is higher in younger children
- *IAA*: positive in 50–60% at diagnosis below age 10 years, about 10% below age 30 years
- *Islet-specific ZnT8 antibodies*: Positive in 50–60% at diagnosis, starts declining by 4 years from diagnosis.
- *Serum C-peptide* (fasting and 90 minutes after a standard mixed meal) provides an indirect measure of endogenous insulin secretion. This test has to be done after correction of hyperglycemia. Long acting insulin should be with-held from the previous day, and short acting insulin with-held on the morning of testing.
- *X-Ray/ultrasonography (USG) abdomen* help to make a diagnosis of fibrocalcific pancreatic diabetes mellitus
- *Genetic testing* for MODY and lipodystrophy syndromes.

Those presenting with acute hyperglycemia and DKA have T1DM and should be managed with insulin therapy.

In those presenting with acute hyperglycemia without ketoacidosis, insulin secretory reserve should be tested after metabolic stabilization with insulin therapy for a few weeks. In those with mild hyperglycemia and absence of ketoacidosis, it can be assessed at the time of diagnosis by measuring plasma glucose and serum C-peptide levels fasting and 90 minutes after a meal. C-peptide levels less than 0.75 ng/mL in fasting state or 1.8 µg/mL postmeal indicates marked insulin deficiency and hence should be managed as T1DM. Those with values above the cut-offs described earlier are likely to have T2DM, MODY or other types of diabetes. They should be given a trial of oral antidiabetic agents to assess response to therapy. Patients in early stages of pancreatic diabetes may have preserved C-peptide response.

X-Ray abdomen or ultrasound scan of abdomen are useful to look for pancreatic calculi and dilated ducts in those with fibrocalcific pancreatic diabetes.

Diabetes associated autoantibodies include GAD-65, IA-2, islet cell antibodies (ICA) and zinc transporter 8. Presence of high titers of one or more of these antibodies is seen in type 1 diabetes. GAD 65 antibodies persist for more than 8–10 years, while the other antibodies progressively disappear over time. This has to be kept in mind while interpreting the results of antibody tests (Table 22.3).

Lipodystrophic diabetes can be diagnosed with the demonstration of partial or total loss of subcutaneous fat in the different syndromes as described previously. Dual energy X-ray absorptiometry (DXA) scan helps in confirming decreased regional or total body fat. Genetic testing provides a definite diagnosis.

Noninsulin requiring diabetes with a strong three generation family history and absence of features of other forms of diabetes described above would favor a diagnosis of MODY.

Availability of high throughput next generation sequencing technology (NGS) has enabled simultaneous sequencing and analysis of a panel of genes. In a study conducted at our hospital we screened 80 subjects with young onset diabetes for a panel of 10 MODY genes (MODY 1–10) and identified mutations in 11 (19%) of 56 patients clinically diagnosed as MODY. We have also reported a family with partial lipodystrophy due to LMNA mutation.

Table 22.3: Characteristics of type 1 and type 2 diabetes in children and adolescents.

Characteristics	Type 1	Type 2	MODY
Age at onset	Throughout childhood	Pubertal/postpubertal	Pubertal/post-pubertal
Gender	Female = Male	Female > Male	Female = Male
Ethnicity	All (low incidence in Asians)	Native American African-American Hispanic	All
Onset	Acute Severe DKA common	Insidious Ketosis less common	Gradual
Obesity	As in the population	Common	Uncommon
Acanthosis nigricans	Absent	Present	Absent
Insulin secretion	Very low/absent	Variable	Variably decreased
Insulin sensitivity	Normal	Decreased	Normal
Insulin dependency	Permanent	Episodic	Infrequent
ICA (IA-2) Antibodies	70–80% ICA positive	ICA negative	ICA negative
GAD 65 Antibodies	40–70% GAD positive	GAD positivity ±	GAD negative
Family history	5–15%	75–90%	100%
Mode of inheritance	Non-Mendelian, sporadic	Non-Mendelian, familial	Autosomal dominant

(DKA: Diabetic ketoacidosis; ICA: Islet cell antibodies; GAD: Glutamic acid decarboxylase; MODY: Maturity onset diabetes of the young).

MANAGEMENT

The goals of ambulatory care include

- Maintains adequate glycemic control while avoiding hypoglycemia
- Permits normal growth and development with minimal effect on lifestyle
- Prevents ketoacidosis.

Diet

Nutritional recommendations for children and adolescents with type 1 diabetes should focus on achieving blood glucose targets without excessive hypoglycemia, lipid and blood pressure goals and normal growth and development. Caloric requirements are calculated based on the various methods. One easy to use method is given in Table 22.4. The initial weight loss at the time of diagnosis must be restored with adequate energy intake. The proportion of dietary constituents, i.e. calories, fats and protein should be adequate, although the height and weight gain form the most important basis of nutritional recommendations. Meal planning should be done either with carbohydrate counting or exchange system according to local expertise (Fig. 22.1).

Table 22.4: Calorie calculation.

Age	Boys*	Girls*
1st year	1,000 Kcal	1,000 Kcal
Up to 12 years	1,000 Kcal + (125 Kcal × age)	1,000 Kcal + (100 Kcal × age)
12 to 15 years	2,000–2,500 Kcal + (200 Kcal/year over the age 12 years)	1,000 Kcal + (100 Kcal/year over the age 12 years)

*Add up to 20% for pubertal needs.



Fig. 22.1: Management aspects in childhood diabetes.

Weight loss should be an essential goal in obese adolescents with type 2 diabetes. Children on insulin should have at least three major meals and 3–4 snacks. Total carbohydrate content and composition of meals and snacks is most important in determining the postprandial glucose response and thus in determining the premeal insulin dosage.

Exercise

Children and adolescents with type 1 diabetes should undertake a minimum of 30–60 minutes of moderate physical activity daily. Benefits of exercise in type 1 diabetes include a greater sense of well-being, weight control, improved physical fitness, improved cardiovascular fitness with lower pulse rate and blood pressure and improved lipid profile. Unaccustomed exercise which is generally of greater than usual intensity, duration or frequency increases the risk of hypoglycemia. This should be anticipated and prevented by frequent monitoring of blood glucose on those days.

The response of blood glucose levels to exercise varies between individuals and the type of exercise. Moderate sustained activity can cause hypoglycemia whereas bursts of high intensity exercise can cause hyperglycemia. The hypoglycemia is due to improved insulin sensitivity which may persist for several hours after stopping exercise. This effect is thought to be due to a relatively high rate of glucose uptake by the exercised muscles and lower hepatic glucose output as the glycogen stores are depleted. Hence, the risk of hypoglycemia persists for 6–12 hours following exercise which is called the lag effect. Also the risk of hypoglycemia is even greater if insulin is injected into the actively exercising limb. Hence, vigorous exercise

should be avoided for at least 1–1.5 hours after insulin injection and should not be administered in the actively exercising limbs.

Patients with good glycemic control can have hyperglycemia during and after vigorous exercise due to a surge of counter-regulatory hormones. Patients with poor control can have even marked hyperglycemia with or without ketosis.

Management of Exercise: Principles

1. *Anticipated exercise:* Reduce the dose of insulin (10–50%) before the meal especially that of the insulin having peak action during the period of exercise.
2. *Check blood glucose/urine ketones prior to exercise:* Patients with high blood glucose (>300 mg/dL) and/or ketonuria should refrain from exercise.
3. If blood glucose less than 100 mg/dL, feed 15 g carbohydrate (See Appendix—for food exchanges equivalent to 15 g carbohydrate).
4. Continue blood sugar monitoring hourly during moderate exercises. If blood glucose less than 100 mg/dL feed 15 g carbohydrate again.
5. For vigorous physical activity, more than 30 minutes, an additional 15 g carbohydrate may be necessary.
6. Check blood glucose in the postexercise period frequently during the next 12 hours and adjust insulin or supplement carbohydrate, accordingly.

Appropriate Management by Age

Glycemic targets and challenges in achieving them are different during each childhood stage. Furthermore, insulin requirement should be tailored for the individual child based on school timings, eating habits, cognitive abilities and emotional maturation.

Infants (< 1 Year)

In this age group, parents are solely responsible for management. Infants do not exhibit the classic catecholamine response to hypoglycemia and are unable to communicate the symptoms of hypoglycemia; seizures and coma are highest in this age group. Because the brain is still developing in infants, the adverse consequences of severe hypoglycemia may be greater than in older children.

1–3 Years

Between the ages of 1–3 years of age, hypoglycemia is a constant fear, especially when the child refuses to eat. It may be difficult to distinguish between a temper tantrum and hypoglycemic episode. Parents should be taught to measure blood glucose before ignoring a temper tantrum.

Preschoolers and Early School-Aged Children (3–7 Years)

Children at this stage of development need to gain confidence in their ability to accomplish tasks but often lack the fine motor control, cognitive development, and impulse control. Undetected hypoglycemia remains a concern because of the variations in activity and food intake characteristic of this age group.

School-aged Children (8–11 Years)

Children report mild depression and anxiety for a few weeks to months following the diagnosis, but these usually resolve by six months after diagnosis. School-aged children with diabetes can begin to assume the daily diabetes management tasks, such as insulin injections and blood glucose testing under supervision of their parents.

Several studies have shown that a child's early and independent participation in the diabetes management are significantly associated with poorer glycemic control. Current recommendations emphasize shared responsibilities between parents and children.

Adolescents

Many of the diabetes-related tasks can interfere with the adolescents' drive for independence and peer acceptance. While adolescents can fully take care of their diabetes management, they need help with decision-making about insulin adjustments. The challenge is to find the degree of parental involvement that is comfortable to the patient, without risking deterioration in glycemic control from over or under involvement.

Transitional Care of Childhood Diabetes: The Problems of the Emerging Adult

The transition of life stage from childhood to adolescence to adulthood is a complex process. Harboring a chronic illness like diabetes makes it more complicated. The major change involved in this transition is the shift from parentally supervised care to independent self-care by the patient. The adolescent period is characterized by physical, psychosocial and emotional changes which can hamper diabetes care. Family involvement and support is utmost important to prevent deterioration of glycemic control. In the post-adolescent period infrequent follow ups with the medical team and decrease in self-motivated care due to increasing responsibilities and stresses in personal and academic life results in poor glycemic control and risk for long-term complications. Hence, this period of emerging adulthood [defined by American Diabetes Association (ADA) as 18–30 years] is a critical period in diabetes care. With increasing prevalence of type 1 diabetes in children and increased occurrence of childhood type 2 diabetes paralleled with changing lifestyles and the obesity epidemic, more number of young patients pass through this delicate period.

A gradual smooth compassionate transition from pediatric to adult care is warranted to ensure effective diabetes self-management. Education about several pertinent issues like reproductive health, substance abuse, and acute and chronic complications will be useful. Studies have shown increased incidence of acute complications like hypoglycemia, ketoacidosis, eating disorders and psychiatric problems like anxiety and depression in young diabetics during the transition period. Moreover, careful assistance is required in this vulnerable group to prevent loss of follow-up resulting in adverse consequences.

ADA has suggested the following recommendations for transitional care of the emerging adults with diabetes:

1. Early and advanced preparation of the adolescent for the upcoming transitional care at least 1 year prior to transfer to adult healthcare.

2. Gradual transfer of diabetes self-management skills from the parents to the teens.
3. Inform about differences between pediatric and adult providers in their approaches to care.
4. Provision of a written summary by the pediatric provider to both the patient and the adult provider which includes an active problem list, compilation of medications, assessment of diabetic self-care skills, summary of past glycemic control and diabetes related co-morbidities as well as any mental health problems and referrals during pediatric care.
5. Provide support and links to resources which benefit the patient in adhering to diabetes management.
6. Care should be Individualized and developmentally appropriate.
7. Evaluation for underlying eating disorder and affective disorder by a psychiatrist who understands the fundamentals of working with a diabetic patient.
8. Ongoing visits, screening for microvascular and macrovascular complications and treatment of complications should be done as per the current pediatric and adult guidelines.
9. Issues like pregnancy planning and risks, birth control, prevention of sexually transmitted diseases, use of alcohol and drugs, smoking and driving should be discussed with the older teens and emerging adults by both pediatric and adult providers with emphasis on interplay of these issues with diabetes.
10. Accessible, patient centered, coordinated, comprehensive, compassionate and culturally acceptable health care should be ensured to every emerging adult by both pediatric and adult providers.

Establishment of special transition clinics jointly staffed by pediatric and adult health providers would be useful.

Insulin Management

A regimen comprising of multiple daily subcutaneous injections administered with a syringe or pen device is the most suitable regimen for majority of the patients. Regular human insulin or short acting analog (Aspart/Lispro/ Glulysine) is used as bolus insulin prior to meals and neutral protamine Hagedorn (NPH)/Detemir twice daily, or Glargine/Degludec once daily is used as basal insulin. Premixed insulin should not be used as it is difficult to maintain euglycemia with this regimen in type 1 diabetes. Although there is no single formula for calculating insulin doses, patients with newly diagnosed type 1 diabetes mellitus usually require an initial total daily dose of approximately 0.5–1.0 u/kg; comprised of 30–40% as basal insulin and the remaining as short acting insulin. In general, younger children require lower doses, while pubertal children require higher doses.

It is important to ensure rotation of injection sites to avoid lipoatrophy and lipohypertrophy. These lead to progressively higher insulin dose requirement due to reduced absorption of insulin from the sites of administration. This also leads to poor glycemic control due to insulin administration over lipohypertrophic and normal subcutaneous tissue areas on different days causing wide fluctuations of blood glucose levels. The health care provider should check the insulin injection sites at each visit of their patients to examine for lipoatrophy/lipohypertrophy.

The diabetes control and complications trial (DCCT) has shown that patients on multiple daily insulin injections achieved better metabolic control compared to those on traditional twice daily insulin dosing. Although a combination of short acting insulin analog (Lispro/Aspart) with a long acting analog (Glargine/Detemir/Degludec) seems to be the best option, the higher cost is a limitation. Insulin pump can be used if multiple daily injections fail to achieve glycemic control. However, this requires a motivated patient who is willing to monitor glucose levels more frequently and make appropriate insulin dose adjustments accordingly based on the meals and activity. Cost of the insulin pump as well as its consumables is another constraint.

Blood Glucose Monitoring

Self-monitoring of blood glucose (SMBG) is the corner stone of diabetes management. For children with type 1 diabetes, four or more tests per day are generally necessary. Preprandial blood glucose levels are important, but postprandial and overnight levels are also valuable in determining insulin dose adjustments. Safe management of younger children (<6 years) requires more frequent blood glucose testing. Additional testing is essential during periods of increased physical activity or illness.

Conventional self-monitoring of glucose in small children is confounded by the frequent eating schedule of toddlers. Many toddlers eat approximately every 2 hours except while they are asleep. Glycemic excursions may be dramatic, with reported blood glucose levels much higher than desired. Of note, however, because of the frequency of food ingestion, most blood glucose levels obtained are actually postprandial values.

Maintaining a log book with record of blood glucose values, quantity and type of food taken throughout the day, time and duration of exercise and insulin doses taken helps the patient, parents, nurses and doctors understand the glycemic patterns and reasons for glucose fluctuations. This understanding will lead to appropriate changes in diet, exercise and insulin doses resulting in better glycemic control.

Peer Support

This is an essential part of diabetes management. Interaction of patients with type 1 diabetes and their families with peers helps them get over the feeling of loneliness and enhances self-confidence. This form of psychological support to one another improves their acceptance of the disease and coping abilities. The end result would be enhanced self-care, which leads to better glycemic control. We have regular peer group meetings in our department at every clinic visit of our patients. We also have teleconferences of people with type 1 diabetes from different parts of the country as well as overseas once a month. This has significantly improved the confidence, coping abilities and self-care of our patients and has resulted in better glycemic control.

Glycemic Control

The glycemic goals should be individualized based on the risk of hypoglycemia-with or without symptoms and the risk of long term complications. Maintaining fasting glucose below

130 mg/dL, and postmeal below 180 mg/dL would be ideal. A glycated hemoglobin (HbA1C) goal of 7.5% is recommended across all pediatric age-groups, provided it can be achieved without significant risk of hypoglycemia. Targets should be relaxed in those with hypoglycemia unawareness and those with severe complications such as advanced chronic kidney disease or coronary artery disease where hypoglycemia is more harmful.

CHRONIC COMPLICATIONS

Growth Retardation

Long standing poor control of diabetes often leads to weight loss, inadequate height gain and delay in pubertal and skeletal maturation. Overtreatment with insulin on the other hand can lead to excessive weight gain. Impaired linear growth should raise suspicion of associated diseases like hypothyroidism or celiac disease.

Nephropathy

Annual screening for microalbuminuria should be initiated once the child is 10 years of age and has had diabetes for 5 years; more frequent testing is indicated if values are increasing. Albumin-to-creatinine ratio (ACR) in a spot urine sample can be used as a screening test. Values in the range between 30 mg/g and 299 mg/g creatinine are defined as microalbuminuria. Risk factors for nephropathy include poor glycemic control, smoking, and family history of hypertension or cardiovascular disease. Nondiabetic renal disease should be ruled out before considering the diagnosis of diabetic nephropathy in those with atypical features. Persistently elevated microalbumin levels should be treated with an angiotensin-converting-enzyme (ACE) inhibitor. If hypertension exists, rigorous attention to normalization of blood pressure is important to delay the progression of nephropathy. Tight glycemic control, avoidance of smoking and control of low-density lipoprotein (LDL) levels are other measures to prevent progression of diabetic nephropathy.

Hypertension

Blood pressure determination using an appropriately sized cuff and with the patient relaxed and seated should be part of every diabetes physical examination. Hypertension is defined as an average systolic or diastolic blood pressure more than 95th percentile for age, sex and height percentile, measured on at least three separate days. High-normal blood pressure is defined as an average systolic or diastolic blood pressure more than 90th but less than 95th percentile for age, sex, and height percentile measured on at least three separate days (Appendix). These children should be evaluated with serum creatinine and urinary albumin estimation.

Dietary intervention consists of a salt restricted diet and a reduction in foods high in sodium content. If target blood pressure is not reached within 3 months of lifestyle intervention, pharmacologic treatment of hypertension (systolic or diastolic blood pressure consistently above the 95th percentile for age, sex and height or consistently > 130/80 mm Hg,

if 95th percentile exceeds that value) should be initiated. ACE inhibitors should be considered for the initial treatment of hypertension, with dose titrated to achieve a blood pressure (both systolic and diastolic) consistently < 130/80 mm Hg or below the 90th percentile for age, sex and height, whichever is lower. A once daily formulation is recommended to ensure compliance. If target blood pressure is not reached with an ACE inhibitor alone, additional anti-hypertensive medication should be considered.

Dyslipidemia

There is unequivocal evidence that atherosclerosis is well established in some patients by adolescence and that dyslipidemia is a major risk factor for atherosclerosis. ADA guidelines recommend that a lipid profile be performed on prepubertal children with type 1 diabetes more than 2 years or at diagnosis if the family history for cardiovascular disease (CVD) is positive or unknown. If family history is negative, screening should begin at puberty. In either case, screening should be done after glucose control has been established.

If values fall within the accepted risk levels (LDL < 100 mg/dL), assessment should be repeated every 5 years based on CVD risk status. Medical nutrition therapy is aimed at a general decrease in the amount of total and saturated fat in the diet. The current recommendation for children with abnormal lipid levels restricts saturated fat to less than 7% of calories and cholesterol to less than 200 mg/day. Lifestyle changes are also recommended to optimize lipid levels. If diet therapy and lifestyle changes are not successful, pharmacotherapy is suggested if the LDL is more than or equal to 160 mg/dL. If the LDL is in the range of 130–159 mg/dL, medication should be considered based on the child's CVD risk profile.

The mainstay of drug therapy for the treatment of dyslipidemia in children has been bile acid sequestrants: cholestyramine and colestipol. Ezetimibe acts at the small intestine brush border to inhibit absorption of cholesterol and is approved for use in children more than 10 years of age. Aspirin therapy is not recommended for those less than 21 years of age due to the increased risk for Reye's syndrome.

Retinopathy

Although retinopathy is most commonly described after the onset of puberty, retinopathy can occur in prepubertal children. Hypertension, poor metabolic control, presence of albuminuria, hyperlipidemia, smoking, long duration of diabetes and pregnancy all confer increased risk of developing retinopathy. The first ophthalmologic examination should be obtained once the child is more than or equal to 10 years of age and has had diabetes for 3–5 years. After the initial examination, annual follow-up is generally recommended.

Foot Care

It is recommended that children with type 1 diabetes should have their feet examined at every visit and at least annually for protective sensation (with a 10 g monofilament), peripheral pulsations, skin integrity, and treatable nail problems such as ingrown toenails. The importance of use of appropriate footwear and proper monitoring of feet, including nail and skin care should be reviewed periodically, especially during adolescence.

Psychological Aspects

Diabetes is a risk factor for adolescent psychiatric illness. There is increased frequency of major depression, generalized anxiety disorders and suicidal ideation. Youth with difficulty in achieving treatment goals or recurrent diabetic ketoacidosis should be screened for psychiatric disorders.

Associated Autoimmune Conditions

The prevalence of autoimmune thyroid disorders in association with type 1 diabetes is about 17%. Hyperthyroidism alters glucose metabolism potentially with postprandial peaks and fasting hypos resulting in deterioration of metabolic control. Hypothyroidism is associated with an increased risk of symptomatic hypoglycemia and with reduced linear growth. Patients should be screened for autoimmune thyroid disease at diagnosis. Patients with previously normal thyroid-stimulating hormone (TSH) levels may be re-evaluated every 1–2 years, or at any time the growth rate is abnormal, or if an enlarged thyroid is evident. Celiac disease should be considered in children with poor growth velocity, inadequate weight gain, unpredictable blood glucose levels, unexplained hypoglycemia and deterioration in glycemic control.

ACUTE COMPLICATIONS

Hypoglycemia

Hypoglycemia is one of the major barriers in achieving normal glycemic control. Even mild hypoglycemia causes acute alterations in cognitive function, especially associative learning, attention and mental flexibility. Cognitive impairment can occur at blood glucose levels <60 mg/dL. The risk is higher in those with lower HbA1C, younger children, higher insulin doses and prior history of hypoglycemia. Frequent nocturnal hypoglycemia with hypoglycemia unawareness is associated with increased risk of seizures. The presence of hypoglycemia and hypoglycemia unawareness must be evaluated at every visit. Mild hypoglycemia (mild adrenergic and cholinergic symptoms with occasional neuroglycopenic symptoms) can be treated with 15 g of fast acting carbohydrate (10 g in a younger child). Moderate hypoglycemia requires 20–30 g of carbohydrate to be administered to the patient by a bystander (patient may not be able to take by self due to reduced level of comprehension at this stage). Severe hypoglycemia requires treatment with intravenous dextrose or glucagon (30 µg/kg subcutaneous injection). The blood glucose should be tested after 15 minutes and treatment should be repeated accordingly. Once blood glucose is >70 mg/dL, the patient should be advised to take a snack within 30 minutes to avoid recurrence of hypoglycemia. Patients on insulin should always carry glucose powder, glucose tablets or sugar along with a snack (few biscuits/groundnuts/almonds) and their glucometer to ensure that they recognize and manage hypoglycemia appropriately.

Diabetic Ketoacidosis

It is a consequence of absolute or relative insulin deficiency resulting in hyperglycemia and an accumulation of ketone bodies in the blood with subsequent metabolic acidosis.

Box 22.1: Food exchange for sick day management.

- Sick day food and fluids of 1 exchange = (15 g of carbohydrates)
 - Fluids: ½–¾ cup orange/apple/pineapple juice
 - ¾ cup of sweet soft drink
 - Tea/water with 1 table spoon of sugar
 - Food: A slice of bread
 - 1/3 cup of boiled rice
 - 1 small banana
 - 1 medium orange
 - 2 scoops ice cream
- 2–3 plain biscuits

Management of this potentially fatal condition is dealt with in detail in the chapter on emergencies in diabetes.

SICK DAY MANAGEMENT

The goals of sick day management are:

- Prevention and early treatment of hypoglycemia
- Prevention and early treatment of significant hyperglycemia and ketosis
- Prevention of DKA.

Decreased caloric intake whether due to decreased appetite during illness or nausea and vomiting may lead to a decrease in insulin requirement. On the other hand, the stress of illness may cause increased release of counter regulatory hormones, resulting in increased insulin needs. In very young children (< 6 years) in whom brisk counter-regulatory responses may not be well developed, decreased calories and excess insulin action may cause hypoglycemia. However, in older, especially pubertal children, a stressful illness is usually characterized by relative insulin deficiency and hyperglycemia. Frequent monitoring will help determine how to proceed. Ketones must be monitored no matter what the blood glucose level is, as acidosis can sometimes occur without elevated glucose levels, especially if oral intake is poor. Details of food exchanges that can be used on a sick day are provided in Box 22.1.

Principles of Sick-day Management:

- Frequent monitoring of blood glucose and urine ketone levels
- Monitoring food and fluid intake
- Adult supervision
- Treat the underlying disorder
- Symptomatic relief (of fever, headache, etc.)
- Rest and sugar free medication
- Never stop insulin
- Frequent contact with the diabetes health care team to review the clinical status.

Short and intermediate acting insulin have to be given at lesser than usual doses if the normal oral intake cannot be maintained. Further, insulin doses can be decided by following a simple algorithm based on blood glucose and urine ketone monitoring (Table 22.5).

Box 22.2: Criteria for screening for type 2 diabetes in children.

- Overweight (BMI > 85th percentile for age and sex, weight for height > 85th percentile, or weight > 120% of ideal for height)
Plus
- Any two of the following risk factors:
 - Family history of type 2 diabetes in first or second-degree relative
 - Race/ethnicity (American-Indian, African-American, Hispanic, Asian/Pacific Islander)
 - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, PCOS)

(PCOS: Polycystic ovary syndrome; BMI: Body mass index).

Table 22.5: Insulin management in sick-day care.

Blood glucose (mg/dL)	Urine ketones	Management
< 80	Negative/Positive	Consider omitting short acting insulin and decreasing intermediate/long acting insulin by 20–40%
80–250	Negative/Positive	No extra insulin Check after 2 hours
250–400	Negative	Give an extra 10% of TDD of short acting insulin Check after 2 hours
	Positive	Give an extra 20% of TDD of short acting insulin Check after 1 hour
> 400	Negative/Positive	Give an extra 20% of TDD of short acting insulin Check after 1 hour

Note: To calculate the total daily dose (TDD), add up all the insulin given on a usual day, i.e. the short acting and intermediate acting.

Home management should be abandoned and the patient should be shifted to hospital if there is persistent vomiting, patient becomes drowsy or develops severe or localized abdominal pain. Persistent ketonuria or increasing blood glucose levels despite extra insulin doses is an indication to shift to hospital. Children less than 2 years of age are preferably managed in a hospital set-up.

TYPE 2 DIABETES IN CHILDREN

Since there is a rapid increase in the prevalence of obesity, physical inactivity and unregulated food habits, there is an increase in prevalence of type 2 diabetes in the pediatric and adolescent age group. The risk is more in certain ethnic groups like Pima Indians, Hispanics and even Asians. ADA recommends screening for diabetes at the age more than 10 years or onset of puberty for children with the following criteria (Box 22.2). [This has been endorsed by the Indian Academy of Pediatrics (IAP) national task force for childhood prevention of adult diseases].

Both fasting and 2 hours post-glucose values must be used for diagnosis. Lifestyle measures like weight reduction through increased physical activity and dietary restriction with addition of Metformin should be emphasized. Target HbA1C of less than 7% can be achieved in most patients with the earlier measures. In symptomatic children with blood glucose more than 300mg/dL, or when ketoacidosis is present, insulin should be used in the initial stage of treatment, and later switch over to oral agents. Education and screening for diabetes in at risk groups can go a long way in containing this epidemic.

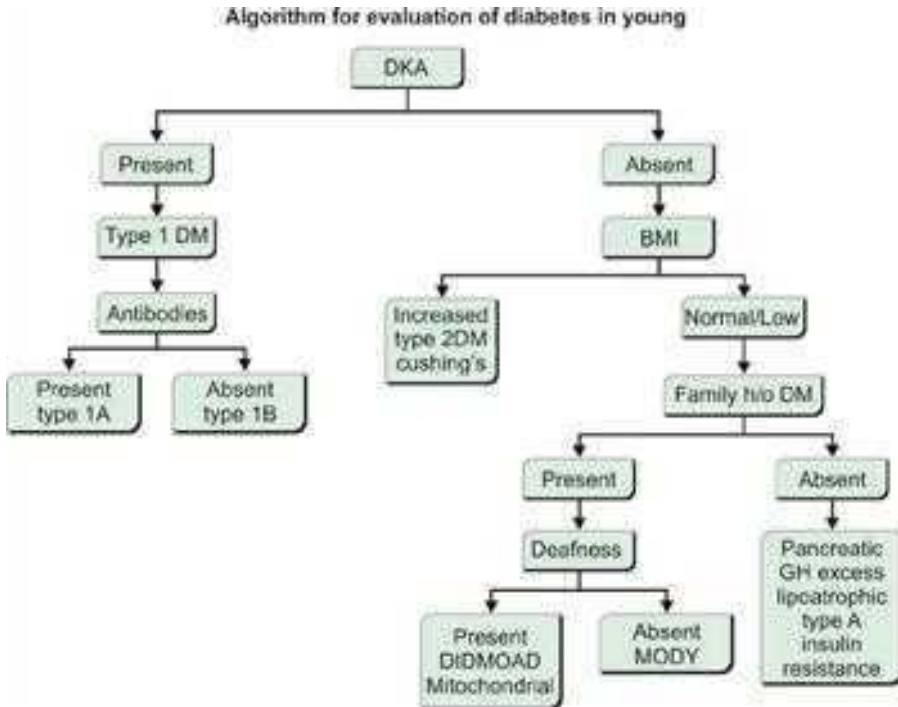
Prediction of Development of Type 1 Diabetes Mellitus

Type 1 diabetes develops from the interaction of genetic and environmental factors. The antibodies predictive for the development of disease are IA-2, IAA, GAD-65 and ZnT8. The presence of two or three antibodies has a predictive value of 50–80% for developing type 1 diabetes within 5 years (Table 22.6). Measurement of these antibodies are useful in

Table 22.6: Blood pressure ranges for height centiles.

		Boys						Girls					
		Systolic BP by height centile			Diastolic BP by height centile			Systolic BP by height centile			Diastolic BP by height centile		
	Height centile	5%	50%	95%	5%	50%	95%	5%	50%	95%	5%	50%	95%
Age (yrs)	BP centile												
1	90th	94	99	103	49	52	54	97	100	103	52	54	56
	95th	98	103	106	54	56	58	100	104	107	56	58	60
3	90th	100	105	109	59	61	63	100	103	106	61	63	65
	95th	104	109	113	63	65	67	104	107	110	65	67	69
5	90th	104	108	112	65	68	70	103	106	109	66	68	70
	95th	108	112	116	69	72	74	107	110	113	70	72	74
7	90th	106	111	115	70	72	74	106	109	113	69	71	73
	95th	110	115	119	74	76	78	110	113	116	73	75	77
9	90th	109	114	118	72	75	77	110	113	116	72	73	75
	95th	113	118	121	76	79	81	114	117	120	76	77	79
11	90th	113	117	121	74	76	78	114	117	120	74	75	77
	95th	117	121	125	78	80	82	118	121	124	78	79	81
13	90th	117	122	126	75	77	79	117	121	124	76	77	79
	95th	121	126	130	79	81	83	121	124	128	80	81	83
15	90th	122	127	131	76	79	81	120	123	127	78	79	81
	95th	126	131	135	81	83	85	124	127	131	82	83	85
17	90th	127	132	136	80	82	84	122	125	128	78	80	82
	95th	131	136	140	84	87	89	125	129	132	82	84	86

Source: Fourth report on high blood pressure in children and adolescents from national high blood pressure education program. NHBPEP working group on hypertension control in children and adolescents. Pediatrics. 2004;114:555-76.

Flowchart 22.1: Algorithm for the management of a child/adolescent with diabetes.

(DKA: Diabetic ketoacidosis; DM: Diabetes mellitus; BMI: Body mass index; MODY: Maturity onset diabetes of the young; DiDMOAD: Diabetes insipidus, diabetes mellitus, optic atrophy, deafness).

distinguishing these patients from early onset type 2 diabetes, maturity onset diabetes of the young (MODY) and pancreatic diabetes.

CONCLUSION

Managing diabetes in children requires a coordinated effort of the endocrinologist, the parents and the patients (Flowchart 22.1). Defining the targets of glycemic control and the frequency of glucose monitoring forms an essential step in the management, which needs to be periodically revised as the child grows older.

SUGGESTED READING

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2. Nair VV, Chapla A, Arulappan N, et al. Molecular diagnosis of maturity onset diabetes of the young in India. *Indian J Endocrinol Metab*. 2013;17(3):430–41.
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SELF-ASSESSMENT

- 1. The following are risk factors that necessitate screening for type 2 diabetes in children *except*:**
 - (a) BMI above the 85th percentile
 - (b) First or second-degree relative having diabetes
 - (c) Risk race/ethnic
 - (d) Hypertension
 - (e) Coeliac disease
- 2. IAP recommends screening for type 2 diabetes in children with:**
 - (a) FPG
 - (b) OGTT
 - (c) HbA1c
 - (d) PPG
- 3. All the following are true about sick day management of type 1 diabetes *except*:**
 - (a) Patients less than 2 years should be managed in a hospital set-up
 - (b) Patients who are refusing to feed should not be given insulin
 - (c) Ketones should be checked irrespective of the blood sugars
 - (d) Frequent monitoring of blood sugars and ketones is essential
- 4. Hypoglycemia is more common in all the following groups of type 1 patients *except*:**
 - (a) Lower HbA1c
 - (b) Adrenal insufficiency
 - (c) Thyrotoxicosis
 - (d) Those with hypoglycemia unawareness
 - (e) Younger children
- 5. Hypertension in children is defined as blood pressure above the:**
 - (a) 95th centile
 - (b) 90th centile
 - (c) 50th centile
 - (d) 4th quartile
- 6. The agent mostly used for management of dyslipidemia in children is:**
 - (a) Atorvastatin
 - (b) Bile acid resins
 - (c) Ezetimibe
 - (d) Torcetrapib
 - (e) *Ginkgo biloba*
- 7. The preferred method for diagnosing microalbumin in children with type 2 diabetes is:**
 - (a) Micral test strip
 - (b) 24 hours urine albumin
 - (c) Albumin/creatinine ratio
 - (d) Phenolphthalein test
- 8. The HbA1c target for an 8 years old child with reasonable self-help skills is:**
 - (a) < 8%
 - (b) < 7.5%
 - (c) 8.5–9.5%
 - (d) < 10%

9. Which of the following is currently not indicated for the use in patients with type 1 diabetes?

- (a) Lispro insulin
- (b) Pramlintide
- (c) Glimepiride
- (d) Insulin pumps

10. Type 2 diabetes in children can be:

- (a) Diagnosed on the basis of a high BMI with ease
- (b) Treated with pioglitazone
- (c) Treated with metformin
- (d) None of the above

CHAPTER

23

Diabetes in the Elderly

Rahul Baxi, Nihal Thomas

With improving life expectancy, better availability of health care, and increasing awareness about diabetes, the prevalence of diabetes in the elderly (age more than 70 years) is gradually increasing in India. The geriatric population now forms an important subset of our patients attending outpatient clinics for diabetes management. Even in the inpatient admissions, diabetes is a very common accompaniment in the elderly population. Guidelines published nationally and internationally may not always apply to the elderly population. Generally, diabetes management is not pursued comprehensively in the elderly, and treatment offered is often inadequate.

DIABETES IN THE OLDER ADULT: HOW IS IT DIFFERENT?

It is known that aging leads to decline in β -cell function and reduction in blood insulin levels. Aging may be associated with lack of physical activity and loss of muscle mass, which increases the risk of developing type 2 diabetes. With increasing age, most patients have a fasting plasma glucose of 125 mg/dL or less, whereas their postprandial glucose levels are often above 200 mg/dL. In the elderly patients, the classic symptoms of hyperglycemia may not be present. It is also known that the elderly have attenuated counter-regulatory response to hypoglycemia and have reduction in autonomic warning symptoms leading to “hypoglycemia unawareness”. Due to physiological changes, there are variations in drug absorption, metabolism and clearance, which must be taken into account while treating diabetes in the elderly patient.

Complications like major amputations of the lower limb, myocardial infarction, visual impairment and end-stage renal disease occur with a higher rate in the elderly patient with diabetes, compared to any age group. Those aged 75 years and above have higher rates of most complications than those aged 65–74 years. Hyperglycemic hyperosmolar state, a form of hyperglycemic crisis with a high mortality rate is also common in this age group. The elderly have a much higher rate of emergency department visits with hypoglycemia compared to the general population with diabetes.

Issues to be Considered in Management of Diabetes in the Older Adults

- *Cognitive dysfunction and depression:* Alzheimer’s disease and multi-infarct dementia are twice as likely to occur in those with diabetes, compared with age matched nondiabetic

control subjects. The presence of these disorders, along with functional impairment, affects the patient's ability to perform glucose monitoring, to titrate insulin doses and to be compliant with medications and diet.

- *Falls and fractures:* Normal aging and diabetes, along with associated complications like peripheral neuropathy and gait and postural problems are associated with higher risk of falls and fractures. Avoidance of severe hyperglycemia and hypoglycemia can decrease the risk of falls.
- *Polypharmacy:* It is common for elderly patients with diabetes to be prescribed more than six medications, which increase the risk of drug adverse effects and interactions, and also affect compliance. Effort should be made to reconcile medication and assess adherence and compliance on each visit.
- *Visual and hearing impairment:* They are known to occur more commonly in those with diabetes. Regular screening and management of impairment should be done to improve quality of life and self-care.
- *Other medical issues:* Urinary incontinence occurs commonly in the elderly, especially in females with diabetes. Apart from other causes, uncontrolled hyperglycemia can increase the amount and frequency of urine.

MANAGEMENT OF DIABETES IN THE ELDERLY

Recommendations for diabetes management in the older adults*

- Older adults who are functional and cognitively intact and have significant life expectancy should receive diabetes care with goals similar to those developed for younger adults.(E)
- Glycemic goals for some older adults might be relaxed, using individual criteria, but hyperglycemia leading to risk of acute hyperglycemic complications should be avoided.(E)
- Other cardiovascular risk factors should be treated in older adults with consideration of the time frame of benefit and the individual patient. Treatment of hypertension is indicated in virtually all older adults, and lipid-lowering and aspirin therapy may benefit those with life expectancy at least equal to the time frame of primary or secondary prevention trials.(E)
- Screening for diabetes complications should be individualized in older adults, but particular attention should be paid to complications that would lead to functional impairment.(E)
- Older adults with diabetes should be considered a high-priority population for depression screening and treatment.(B)

Goals for glycemic control in the older adults are different from that of the general adult population. They are mentioned in Table 23.1.

As seen in the recent guidelines, less stringent targets have been suggested in the elderly. Such emphasis should not lead to clinical inertia and withdrawal of antidiabetic agents from patients who are doing well, without any significant hypoglycemia. Such action may put the elderly at risk for sustained hyperglycemia and associated complications such as incontinence, hyperglycemic crisis, dehydration and cognitive disturbances. The goal for glycosylated hemoglobin (HbA1c) for the older adults should be decided after assessment of the risk from complications from diabetes, life expectancy, comorbidities and patient preferences.

*American Diabetes Association. Older adults. Sec.10. In standards of medical care in diabetes—2015. Diabetes Care. 2015;38(Suppl. 1):S67-9.

Table 23.1: Goals for glycemic control in the elderly.

<i>Patient characteristics</i>	<i>Rationale</i>	<i>Reasonable A1C goal*</i>	<i>Fasting or preprandial glucose (mg/dL)</i>	<i>Bedtime glucose (mg/dL)</i>
Healthy (few coexisting chronic illnesses, intact cognitive and functional status)	Longer remaining life expectancy	7.5%	90–130	90–150
Complex/intermediate (multiple coexisting chronic illnesses or 2 + instrumental ADL impairments or mild-to moderate cognitive impairment)	Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk	8.0%	90–150	100–180
Very complex/poor health (long-term care or end-stage chronic illnesses or moderate-to-severe cognitive impairment or 2 + ADL dependencies)	Limited remaining life expectancy makes benefit uncertain	8.5%**	100–180	110–200

*A lower A1C goal may be set for an individual if achievable without recurrent or severe hypoglycemia or undue treatment burden.

**A1C of 8.5% equates to an estimated average glucose of 200 mg/dL. Looser glycemic targets than this may expose patients to acute risks from glycosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing.

Source: American Diabetes Association. Older adults. Sec.10. In standards of medical care in diabetes—2015. Diabetes Care 2015;38(Suppl. 1):S67-9

Diabetes Education for the Patient and Family/Caregiver

The role of the diabetes educator is of prime importance in any patient with diabetes and even more so in an elderly. The consultation with the diabetes educator should be made upon the diagnosis or first contact with the patient and then followed up as needed. Issues to be discussed include:

- Symptoms of hyperglycemia and hypoglycemia and their immediate management and prevention
- Use of glucometer for self-monitoring of blood glucose (SMBG)
- Timing, technique and storage of insulin and other medications
- Education about risk factors for foot ulcers and foot care.

It is important to involve the primary caregiver and/or the family members involved in the care of the patient, so apart from ensuring day to day care, acute emergencies can be recognized early and treated in the elderly with cognitive impairment, hypoglycemia unawareness and those who cannot communicate. Use of information booklets and audio-visual aids should be considered. Regular diabetes group meetings in the community can be organized with the patients and the caregivers, where they get an opportunity to exchange ideas and learn from each other.

Nutrition in the Elderly with Diabetes

Older adults with diabetes are at risk for undernutrition due to anorexia, altered taste and smell, swallowing difficulties, dental problems and functional impairment. They are also at risk for micronutrient deficiency as they are unable to meet the micronutrient requirements due to lowered calorie intake. Over-restrictive dietary patterns may prove detrimental in this population as they may contribute to nutritional deficiencies. Addition of dietary fiber may improve glycemic response to a meal and also help in bowel movement which helps in relieving constipation, which is a common problem in this age group. When usual intake fails to meet the nutritional needs, interventions such as small frequent meals, fortifying usual foods and liquid nutritional supplements should be considered.

Physical Activity in the Elderly with Diabetes

There is evidence that progressive decrease in fitness and muscle mass and strength with aging is in part preventable by maintaining regular physical activity. The decrease in insulin sensitivity with aging is also partly due to lack of physical activity. Older adults with diabetes who are otherwise healthy and functional should be encouraged to exercise in moderation. Even patients with poorer health status benefit from modest increases in physical activity. Regular community events, walks and exercise programs can be organized for this group of patients. Balancing, posture and muscle strengthening exercises are imperative to maintain function and prevent falls.

Pharmacotherapy

Issues peculiar to the elderly are mentioned for each class of drug used in the management of diabetes.

- Oral Agents

- Biguanides

Metformin is considered as the first-line agent. When used as monotherapy, it has a very low risk of hypoglycemia. Metformin is known to cause gastrointestinal side effects and modest weight loss, which may be counterproductive in frail patients. Renal function should be monitored regularly and the dose should be reduced when estimated glomerular filtration rate (eGFR) is between 30 mL/minute/1.73 m² and 60 mL/minute/1.73 m² and metformin should be stopped when eGFR drops to below 30 mL/minute/1.73 m². It should be avoided in those with compromised hepatic function and decompensated cardiac failure. Lactic acidosis is rare but a potentially serious adverse effect.

- Sulfonylureas

Insulin secretagogues, which stimulate insulin release from pancreatic β -cells, have been popular for a longtime because of their good efficacy and relatively low cost. This group of drugs is considered as the second choice agents in most countries. Their major adverse effect is hypoglycemia, especially with the longer acting agents like glibenclamide and glimepiride. Glipizide and gliclazide are considered safer.

In patients with deranged renal function, high risk of hypoglycemia and in those with a tendency to miss meals, Sulfonylureas may not be the correct choice and other groups should be considered.

- Meglitinides

These belong to the non-sulfonylurea insulin secretagogue group. They are rapid acting and have a short half-life and hence a lower risk of hyperglycemia compared to sulfonylureas. They predominantly lower postprandial glucose.

- Thiazolidinediones

These drugs are effective in lowering fasting glucose level by increasing peripheral insulin sensitivity of muscle and adipocytes. They do not cause hypoglycemia as monotherapy but lead to moderate weight gain in most patients. In the elderly, side effects like fluid retention, propensity to cause or worsen cardiac failure and increased risk of fracture may preclude use of these drugs. They should also be avoided in patients with active liver disease.

- Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors are useful in lowering postprandial hyperglycemia, have very low risk of hypoglycemia, are weight neutral and have a favorable adverse effect profile. These factors make them a good choice for the elderly. Agents from this group can be added on to metformin in those patients who have suboptimal glycemic control and are also at significant risk of hypoglycemia. In a select group of patients with eGFR below 30 mL/minute/1.73 m², when metformin is contraindicated, DPP-4 inhibitors may be considered for monotherapy. However, their high cost limits their use in most countries.

- α -glucosidase inhibitors

These drugs are specifically used for control of postprandial hyperglycemia and are useful in patients who consume digestible complex carbohydrates in their meals. When used as monotherapy, they do not cause hypoglycemia. Flatulence and diarrhea are the limiting factors and frequent dosing required with these agents increase the pill burden and may not be suitable for the elderly.

- Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) inhibitors act by decreasing renal glucose absorption. They have a low risk of hyperglycemia as they act independent of insulin. They have also been shown to reduce blood pressure and body weight. On the other hand, they are known to increase the risk of urinary tract and genital infections and may cause hypotension due to intravascular volume contraction. Studies have shown that the elderly on these agents have a higher risk of adverse effects related to volume depletion and renal impairment. As the experience with this class of drugs in the elderly is still limited, the risks and benefits should be assessed in an individualized manner.

- Injectible Agents

- Insulin

Insulin therapy is indicated when oral combination therapy is insufficient to achieve glycemic targets and/ or to avoid hyperglycemic complications. It is also indicated in those with renal and hepatic insufficiency, when most of the oral agents are

Table 23.2: Features of insulin therapy in the elderly.

	<i>Indications</i>	<i>Advantages</i>	<i>Disadvantages</i>	<i>Hypoglycemia</i>
Basal insulin	Frail subjects Symptomatic control	Single daily dose Can be given by family or caregiver	May not achieve target	Common, especially with NPH
Twice daily insulin	Aiming for reasonable control	Easy to manage	Fixed meal timings Less flexibility	Lower risk
Basal-bolus insulin	Acute control in hospitalized patients Aiming for tight control	Achieve tight control Flexible meal timings	Requires frequent monitoring	Low risk

contraindicated. Patient's visual acuity, cognition, manual dexterity, social and financial support must be considered before initiating insulin therapy in the elderly patient.

In patients on appropriate doses of two or more antidiabetic agents, addition of a basal insulin once a day may be considered, if glucose targets are not met. NPH (Insulatard) has been traditionally used, but with the availability of long-acting analogues like glargine, degludec and detemir, more options are available, though their cost remains a barrier. Complex insulin regimens should be avoided in frail patients, those staying alone and those in elderly care facilities, and a longer acting insulin analogue once daily along with oral agents is a good option.

A variety of premixed preparations are available with different types of insulins combined in varying ratios to achieve different durations of action. They are generally used twice daily and are convenient to use, compared to basal bolus regimen, which may require four to five insulin injections daily, along with frequent glucose monitoring in the elderly. Premixed insulin is convenient to use, but they reduce the flexibility in diet and lifestyle and the risk of hypoglycemia may increase as age advances. Some of the features of insulin therapy are given in Table 23.2.

It has been shown that insulin pen devices are safer, more effective and find wider acceptance amongst the elderly, compared to the conventional syringe devices. Their higher cost restricts their usage in most countries.

- Glucagon-like peptide-1 analogues

This group of injectable drugs include exenatide and liraglutide. They improve glycemic control in the elderly, without increasing the risk of hypoglycemia. They also delay gastric emptying, increase satiety and promote weight loss in most patients. These drugs may particularly be useful in elderly obese patients with diabetes, especially if used early in the course of the disease. Their weight reduction property and gastrointestinal side effects may be detrimental in the elderly patients who have poor caloric intake, who are having unintentional weight loss and those who are at risk for malnutrition.

No overall difference in safety and effectiveness has been observed between the elderly and the young with these drugs. The experience with these drugs in cases of renal failure

Table 23.3: Risk factors for hypoglycemia in elderly patients.

Renal insufficiency
Autonomic neuropathy
Cognitive impairment
Hepatic dysfunction
Alcohol intake
Therapy with sulfonylureas or insulin
Sedative agents
Tight glycemic control

is limited. Exenatide is contraindicated in patients with creatinine clearance less than 30 mL/minute. No dose adjustment for liraglutide is suggested in patients with renal impairment. However, elderly patients are more likely to have impaired renal function and hence caution should be exercised while using these drugs in the elderly.

Hypoglycemia in the Elderly

This group of patients is particularly susceptible to hypoglycemia. Patients with hypoglycemia unawareness and cognitive impairment may not be able to recognize the symptoms of impending hypoglycemia and hence may not be able to treat it or communicate to their caregivers. The risk factors for hypoglycemia are mentioned in Table 23.3.

Severe hypoglycemia carries a worse prognosis and higher mortality in the elderly. Irreversible neurological damage may occur due to neuroglycopenia, partly contributed by the relatively compromised cerebral circulation in the elderly. In elderly patients with diabetes, who have limited life expectancy, preserving cognitive integrity and maintaining maximum possible independent function is more important than achieving HbA1c targets. Hypoglycemic events can lead to recurrent falls, decline in cognition, poor compliance, depression and possible cardiac events and arrhythmias. It has been found that raising the HbA1c targets may not be able to reduce the hypoglycemic events in this population. To achieve a reduction in hypoglycemia rates in the elderly, it is important to intensify the treatment gradually and safely, with appropriate selection of drugs with low glycemic variability, keeping into consideration the individual patient's characteristics.

Avoiding hypoglycemia, which may be iatrogenic, is one of the most important challenges in managing diabetes in the elderly.

SUGGESTED READING

1. Vasan SK, Pittard AE, Abraham J, et al. Cause-specific mortality in diabetes: retrospective hospital based data from south India. *J Diabetes*. 2012;4(1):47-54.

SELF-ASSESSMENT

1. Which of the following medications has the least risk of hypoglycemia in the elderly?

- | | |
|--------------------|-------------------|
| (a) Glipizide | (b) Glibenclamide |
| (c) Insulin lispro | (d) Sitagliptin |

- 2. The most important concern with SGLT2 inhibitors in the elderly is:**
 - (a) Pancreatitis
 - (b) Urinary tract and genital infection
 - (c) Thyroiditis
 - (d) Hypothyroidism
- 3. Risk factors for hypoglycemia in the elderly include all *except*:**
 - (a) Renal insufficiency
 - (b) Hepatic dysfunction
 - (c) Steroid therapy
 - (d) Cognitive impairment
- 4. According to ADA, the HbA1c goal for an older adult who is healthy has few coexisting chronic illnesses and intact cognitive and functional status is:**
 - (a) 6%
 - (b) 6.5%
 - (c) 7%
 - (d) 7.5%
- 5. Aging is associated with all *except*:**
 - (a) Decline in β -cell function
 - (b) Reduction in blood insulin levels
 - (c) Increase in muscle mass
 - (d) Lack of physical activity
- 6. Physical activity in the elderly with diabetes can:**
 - (a) Prevent progressive decrease in fitness and muscle mass
 - (b) Improve strength
 - (c) Help to improve balancing and posture
 - (d) All of the above
- 7. The following drug is considered to be the first-line agent in an elderly with type 2 diabetes mellitus:**
 - (a) Gliclazide
 - (b) Metformin
 - (c) Dapagliflozin
 - (d) Glargine
- 8. The following factors must be considered in an elderly before initiating insulin therapy:**
 - (a) Visual acuity
 - (b) Cognition
 - (c) Manual dexterity
 - (d) All of the above
- 9. All of the following statements about hypoglycemia in elderly are true *except*:**
 - (a) Severe hypoglycemia carries a worse prognosis and higher mortality in the elderly
 - (b) Hypoglycemic events can lead to recurrent falls
 - (c) Alcohol intake is protective against hypoglycemia
 - (d) Hypoglycemic events can lead to decline in cognition
- 10. Which of the following drugs is likely to promote weight loss?**
 - (a) Liraglutide
 - (b) Glimepiride
 - (c) Pioglitazone
 - (d) Detemir

CHAPTER

24

Secondary Diabetes and Other Specific Types

Kishore Kumar Behera, Dukhabandhu Naik, Nitin Kapoor, Nihal Thomas

*“My face it’s looking like the moon,
My sugars too are out of tune,
I cannot rise up or stand from the squat,
My steroid level’s high yes that is what.”*

Diabetes mellitus represents a set of disease states sharing hyperglycemia as the foremost common characteristic. In the latest classification of diabetes, four main categories have been proposed. The category “other specific types of diabetes” includes disorders other than those defined as type 1 or type 2 diabetes or gestational diabetes. Secondary diabetes is referred to here as hyperglycemia occurring secondary to non-diabetic conditions and therapies. Apart from nondiabetic conditions, this category also includes genetic defects causing diabetes, genetic syndromes which can have diabetes, infectious and immune mediated types of diabetes.

CLASSIFICATION OF SECONDARY DIABETES

The etiological relationship to diabetes is clearly understood—hyperglycemia resulting secondary to another pathological condition. The conditions include:

- Pancreatic disorders
- Diabetes secondary to overproduction of counter regulatory hormones
- Drugs or chemicals induced diabetes.

In some of the earlier conditions hyperglycemia develops in anyone who has the disease. In other conditions hyperglycemia gets unmasked in a genetically predisposed individual. Distinguishing between these two groups is not always possible.

Because of higher prevalence of type 2 diabetes in the general population, Secondary diabetes may clinically resemble type 1 or type 2 or impaired glucose tolerance (IGT). A complete destruction (or) removal of beta cells may manifest as type 1 diabetes in some, while in others, existing beta cell reserve usually avoids overt diabetes/ketoacidosis. Management varies from lifestyle modification alone or may require oral agents or even insulin.

Disorders of the Pancreas

This includes hyperglycemia occurring due to a primary pathology in the pancreas.

Table 24.1: Differences between tropical chronic pancreatitis and alcoholic chronic pancreatitis.

	<i>Tropical chronic pancreatitis</i>	<i>Alcoholic chronic pancreatitis</i>
Age and sex	Second and third decade; 70% male	Fourth and fifth decade; mostly male
Alcohol intake	Usually nonalcoholic	Usually chronic heavy alcoholics
Nature and incidence of diabetes	More aggressive; occurs in 90%	Slower; 50–60%
Pancreatic calculi	Large, discrete margins	Small, ill-defined margins
Nature and location	Large ducts and marked dilation	Small ducts and mild dilatation
Fibrosis of the gland	Marked	Less severe
Risk of pancreatic cancer	Very high	Higher than in the general population

Source: Holt RIG, Cockram C, Flyvbjerg A, Goldstein BJ. Textbook of Diabetes, 4th edition. UK: Wiley-Blackwell Publication; 2011.

Chronic Pancreatitis

In chronic pancreatitis due to various etiologies, calcification in the duct or parenchyma with irreversible acinar atrophy and fibrotic scarring of exocrine tissue produce progressive loss of beta cells. After 20 years, about 75% have glucose intolerance, of which 40–50% have frank diabetes while the remaining 25–30% have IGT. These patients have impaired response of glucagon and hence are prone for delayed recovery from severe hypoglycemia. Management of these patients requires careful monitoring of blood glucose and most of them require insulin therapy. Dietary modifications include small and frequent—low fat, high protein and carbohydrate diets. Antidiabetic agents are often ineffective and response depends on the residual beta cell function. Due to the abdominal symptoms, these patients do not tolerate metformin or alpha-glucosidase inhibitors.

Fibrocalculous Pancreatic Diabetes

Tropical chronic pancreatitis (TCP) is a juvenile form of chronic nonalcoholic calcific pancreatitis seen almost exclusively in developing countries of the tropical world (Table 24.1). When diabetes is present, the condition is called fibrocalculous pancreatic diabetes (FCPD), a later stage of TCP (Fig. 24.1). The classical triad consists of abdominal pain, steatorrhea, and diabetes. The etiopathogenesis is still debatable. The factors considered are:

- Malnutrition—not considered a major etiological factor
- Dietary toxins—cyanide in cassava. Theory not accepted
- Familial and genetic factors (most dominant factor). Some of the genes implicated are:
 - SPINK 1 (serine protease inhibitor, Kazal type 1) gene
 - Cationic and anionic trypsinogen genes
 - Cystic fibrosis transmembrane regulator (CFTR) factor
 - Cathepsin B
 - Calcium sensing receptor gene
- Oxidant stress hypothesis and trace element deficiency states.



Fig. 24.1: Fibrocalculous pancreatic diabetes.

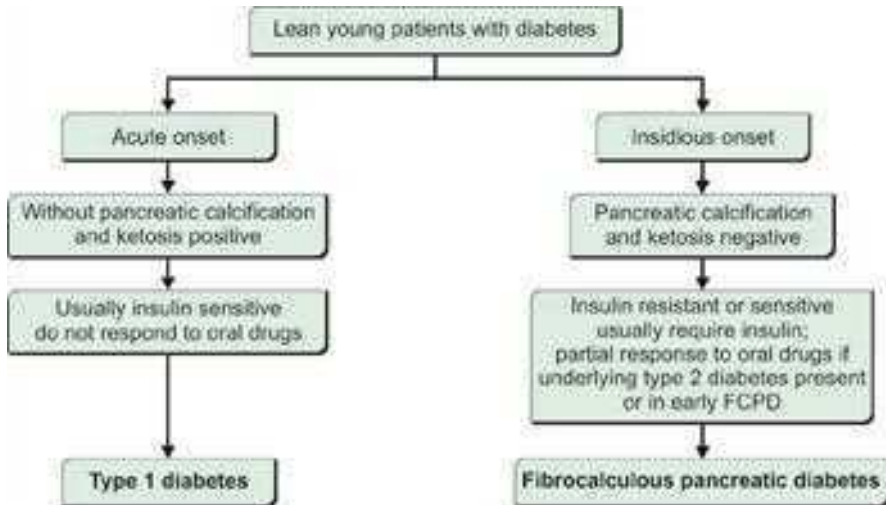
Massive ductal precipitations may produce exocrine and insulin deficiency. Higher insulin to glucagon ratio, absence/resistance of subcutaneous fat, carnitine deficiency and defective transport of fatty acids all contribute to the absence of ketosis. This condition should be suspected in very lean, young subjects with ketosis-negative diabetes. With increasing prevalence of obesity these patients need not be lean always. All young patients other than the typical type 1 diabetes and aged less than 30 years should undergo screening for pancreatic calculi with radiographic imaging of the abdomen.

In the classical presentation patients are malnourished and have low body mass index (BMI) ($<18 \text{ kg/m}^2$). However, requirement of insulin is usually high. Most patients require twice daily insulin injection but a small minority may respond for a variable period of time to oral drugs or once daily or premixed insulin or as in some cases twice daily short acting insulin. Metformin is not advisable in these patients as they have abdominal symptoms and a low body weight. Similarly, alpha-glucosidase inhibitors are not used in view of the associated gastric intolerance, bloating and diarrhea.

The prevalence of microvascular diabetic complications is similar to the common types of diabetes. Macrovascular complications are, however, rare in FCPD. This is believed to be due to young age, lean body and low lipid levels. However, ischemic heart disease, cerebrovascular accidents and peripheral vascular disease have been reported. The prevalence of pancreatic cancer is higher than in the general population which necessitates periodic screening. These patients particularly need investigations to rule out pancreatic malignancy when they present with unexplained weight loss and decreasing insulin requirement. The investigations for a suspected case of TCP without pancreatic calculi are:

Tests of pancreatic structure:

- Ultrasonography
- Computed tomography (CT) abdomen
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Endoscopic ultrasonography
- Magnetic resonance imaging cholangiopancreatography (MRCP).

Flowchart 24.1: A simple algorithm for approach to lean young patients.

ERCP is considered the gold standard when pancreatic stones are not found and usually reveals irregular dilatation of the pancreatic ducts with filling defects caused by stones.

Tests of pancreatic function: Tests of exocrine and endocrine pancreatic function.

Malnutrition Related Diabetes Mellitus

This as a separate entity has not been accepted. By description in this subset, there is no calcification in the pancreas. But patients are characteristically malnourished and are managed similarly as in FCPD (Flowchart 24.1).

Malabsorption can be effectively treated with a low fat diet and pancreatic enzyme supplementation. Diabetes control is often difficult to be achieved due to recurrent episodes of hypoglycemia. The glycemic control becomes all the more challenging when enzyme supplementation is started.

Acute Pancreatitis

About 50% have transient hyperglycemia of which less than 5% of patients continue to have hyperglycemia on long-term. During the acute phase these patients should be managed with insulin with regular monitoring.

Pancreatectomy

Pancreatectomy differs from type 1 diabetes in that these patients manifest with exocrine deficiency with malabsorption in addition to hyperglycemia. They may have ketosis but is of lesser severity and are prone for more frequent episodes of severe hypoglycemia with a sluggish recovery from hypoglycemic episodes. Glucose intolerance depends on the quantity of pancreas removed, the regeneration of beta cells, changes in nutritional status and concomitant exocrine and glucagon deficiency.

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive disorder caused by mutations in the CFTR gene, a multisystem disease characterized by recurrent airway infection leading to bronchiectasis, pancreatic insufficiency, abnormal sweat gland function and urogenital dysfunction. The incidence of diabetes in children with cystic fibrosis is 2–3% (about 20 times higher than in the general population). There is a steady increase in incidence of diabetes as age progresses. Up to 25% of patients in their twenties develop diabetes and a further 50% having glucose intolerance in addition. Pancreatic β -cell damage secondary to exocrine pancreatic degeneration is the key factor for pathogenesis of diabetes.

Patients initially respond to sulfonylureas, most need insulin in later stage for control of blood sugars.

Primary Hemochromatosis and Secondary Hemochromatosis

Iron gets deposited in the parenchyma of various organs including beta cells. The classical triad of hepatomegaly, diabetes and skin pigmentation (bronze diabetes) was first described by Trousseau in 1865 and called hemochromatosis by Von Recklinghausen in 1886 which occurs in lesser number of patients. About 80% have glucose intolerance, 50–60% have overt diabetes of which 50% may require insulin. There is response to iron depletion, which reduces progression of cirrhosis, improves diabetic control and reduces target organ damage (Fig. 24.2).

Thalassemia major is a condition causing secondary hemochromatosis. These patients require frequent blood transfusions and consequently have iron load causing insulin

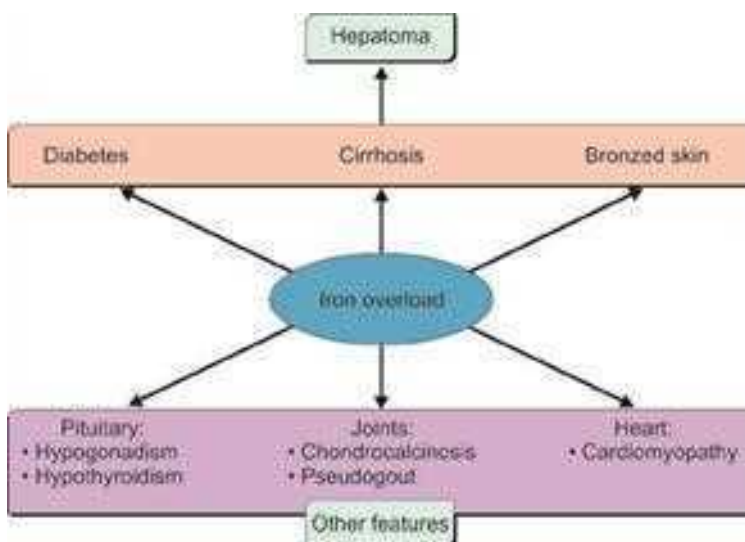


Fig. 24.2: Clinical features of secondary diabetes due to hemochromatosis.

Source: Holt RIG, Cockram C, Flyvbjerg A, Goldstein BJ. Textbook of Diabetes, 4th edition. UK: Wiley-Blackwell Publication; 2011.

resistance. It has been postulated that iron overload may induce autoimmune destruction of β -cells resulting in and glucose tolerance in 60% and frank diabetes in 15%.

Pancreatic Cancers

Beta cell loss as a consequence to pancreatic malignancy obviously leads to glucose intolerance. Also hyperglycemia or associated metabolic abnormalities are suspected to be causative for pancreatic malignancies where type 2 diabetes has been found to be more prevalent.

Endocrinopathies

The common feature here is that excess of proglycemic hormones produce a secondary hyperglycemic state. Apart from insulin, the other main hypoglycemic hormone in the body is glucagon like polypeptide-1 (GLP-1), an insulin secretagogue. Somatostatin, which inhibits both, glucagon and insulin, can behave either way. Growth hormone (GH) and control are hyperglycemic at supraphysiological levels. The stress hormones namely catecholamines, glucagon and glucocorticoids are both diabetogenic and ketogenic. If the primary pathology is corrected, euglycemia reverses unless there is an underlying genetic predisposition to diabetes.

Cushing's Syndrome

Cushing's syndrome is suspected in any patient with truncal obesity, purple colored striae, proximal muscles weakness, hyperpigmentation, hypertension, hypokalemia, hirsutism, osteoporosis and uncontrolled diabetes (Fig. 24.3A). Glucose intolerance occurs in both endogenous and exogenous Cushing's syndrome. The hypercortisolemia induced mechanisms include-reduced insulin postreceptor activity, inhibition of GLUT-4 activity, increased gluconeogenesis and increased production of glucagon. Glucocorticoid overproduction or exogenous therapy also unmasks underlying type 2 diabetes (Box 24.1).

Usually an insulin resistant state is predominant (Fig. 24.3B). Glucose intolerance occurs in 80–90% and; overt diabetes in 15–20% of these patients. Diet, physical exercise and insulin



Fig. 24.3A: A lady with Cushing's syndrome.



Fig. 24.3B: Classical abdominal striae in patient with Cushing's syndrome.

Box 24.1: Mechanistic overview in Cushing's syndrome.

- Reduced insulin postreceptor activity
- Inhibition of GLUT-4 activity
- Increased gluconeogenesis (by activation of PEPCK)
- Increased production of glucagon

(GLUT-4: Glucose transporter type-4; PEPCK: Phosphoenolpyruvate carboxykinase).

sensitizers play an important role in blood glucose management. There may be fluctuations in blood glucose levels of patients on exogenous steroids when they are on and off the steroids (for example, when on alternative day therapy). It requires careful monitoring of blood glucose on the days when due to endogenous hypercortisolism patients are on steroid therapy. Requirement of insulin may come down precipitously when the steroid dose is being withdrawn or tapered.

Growth Hormone Excess

Growth hormone excess (both endogenous and exogenous) induces receptor and postreceptor level resistance due to IGF-1 excess (Fig. 24.3C). Insulin resistance may also be exacerbated by the lipolytic action of GH, generating nonesterified fatty acids (NEFAs) which act on the liver to increase glucose production and in muscle to inhibit glucose utilization (via the "glucose-fatty acid" cycle). About 50–60% have glucose abnormalities of which only 10–15 percent patients require specific antidiabetic treatment as overt hyperglycemia with ketosis is relatively uncommon. Insulin sensitizers help in many, but those with severe resistance may require huge doses of insulin. Normalization of IGF-1 and GH levels improves glucose intolerance and reverses hyperinsulinemia (Box 24.2).



Fig. 24.3C: Classical signs in a patient with acromegaly.

Box 24.2: Mechanistic overview in acromegaly.

- Induces receptor and postreceptor level resistance due to IGF-1 excess
- Excessive lipolysis
- Increased gluconeogenesis (increased NEFA)

(IGF-1: Insulin-like growth factor-1; NEFA: Nonesterified fatty acids).

Box 24.3: Mechanistic overview in thyrotoxicosis.

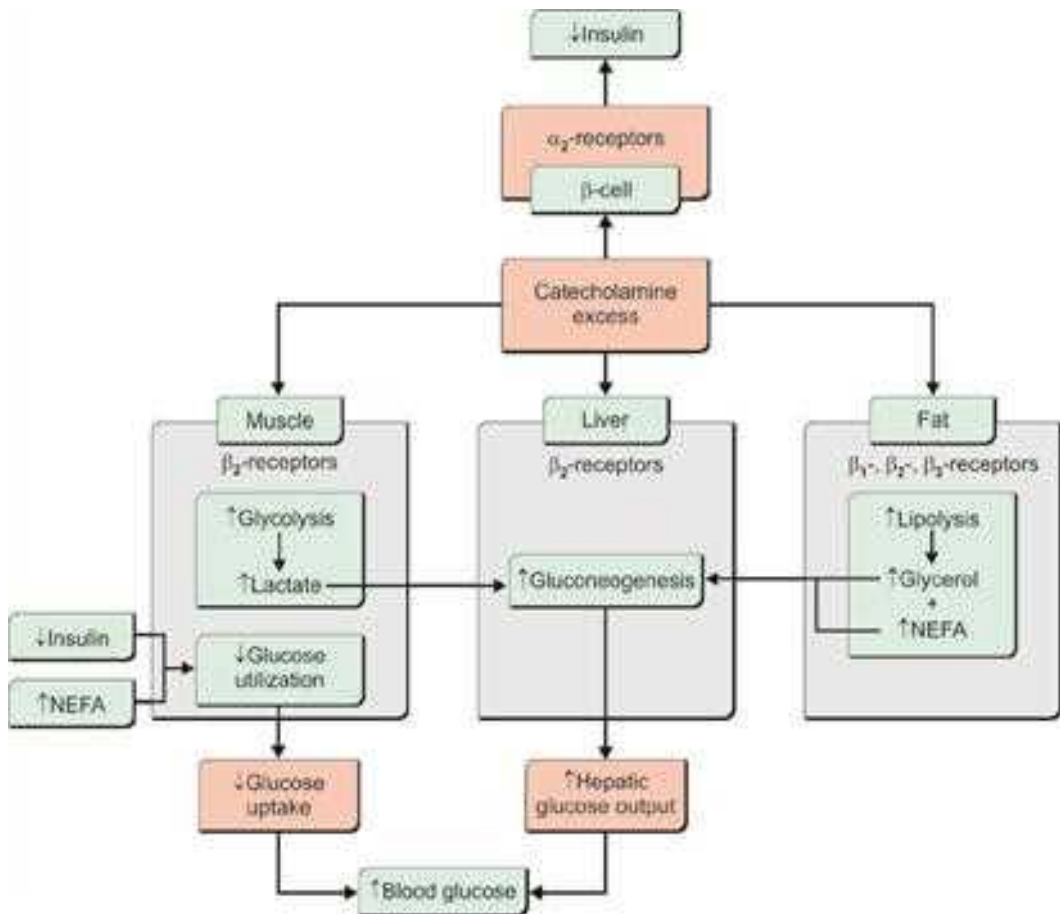
- More rapid postprandial absorption
- Increased glycogenolysis
- Increased gluconeogenesis

Hyperthyroidism

Increase in gastric emptying, high free fatty acid levels, enhanced proteolysis and accelerated metabolic clearance rate of insulin all potentially produce glucose intolerance. However, glycogen stores are markedly reduced. These patients may have fasting hypoglycemia with postprandial hyperglycemia. About 30–50% of these patients have mild glucose intolerance. These patients are prone for hypoglycemia when they are on treatment with thioamides (Carbimazole may have an affinity for the sulfonylureas receptor) and due to an autoimmune etiology (antibodies to the insulin receptor). Reversal of the hyperthyroid state is generally associated with a return to normoglycemia. Those associated with the polyglandular autoimmune syndrome may have coexisting type 1 diabetes, which requires long-term insulin therapy. Also those who have very low BMI due to the severity of the hyperthyroid state will benefit from insulin therapy (Box 24.3).

Pheochromocytoma

The predominant mechanism is catecholamine-mediated reduction in insulin sensitivity and insulin secretion, predominantly caused by epinephrine rather than norepinephrine
Flowchart 24.2.

Flowchart 24.2: Pathogenesis of hyperglycemia in pheochromocytoma.

Source: Holt RIG, Cockram C, Flyvbjerg A, Goldstein BJ. Textbook of Diabetes, 4th edition. UK: Wiley-Blackwell Publication; 2011.

NEFA: Nonesterified fatty acids).

This is characterized by catecholamine excess, which through various adrenergic receptors produces glucose intolerance. Thirty percent of these patients have glucose intolerance. Overt diabetes is unusual. Alpha-blocker therapy improves insulin secretion. Surgical removal of the tumor restores normoglycemia.

Primary Hyperparathyroidism

The prevalence of diabetes in primary hyperparathyroidism is approximately threefold higher than in the general population. Insulin resistance with hyperinsulinemia is generally held responsible, with raised intracellular calcium limiting cellular glucose uptake.

Primary Hyperaldosteronism (Conn's Syndrome)

The classical triad of hypertension, hypokalemia and glucose intolerance does not occur commonly. The blunted insulin secretion is due to hypokalemia. Removal of the primary tumor restores normoglycemia and correction of hypokalemia improves blood glucose levels.

Pancreatic Neuroendocrine Tumors

Glucagonoma and somatostatinomas are well known to produce glucose intolerance. The diagnosis of somatostatinoma is suggested by the triad of diabetes, steatorrhea and gallstones, associated with a tumor of the duodenum (Fig. 24.3D).

Vipoma (VIP) is associated with hypercalcemia glucose intolerance, but overt diabetes is unusual. Hyperglycemia is probably secondary to the glycogenolytic effect of VIP and/or to hypokalemia, which can impair both insulin secretion and insulin sensitivity. Multiple endocrine neoplasia (MEN) syndromes with pancreatic tumors have glucose intolerance.

Lipodystrophies

Lipodystrophies are a group of clinically heterogeneous disorders characterized by abnormal distribution of adipose tissue. Familial partial lipodystrophy (FPLD) is a rare autosomal dominant condition, caused by missense mutations in LMNA gene encoding lamin A/C, resulting in accumulation of fat in the neck and face, and atrophy of subcutaneous adipose tissue in the limbs and trunk. FPLD2 of the Dunnigan type is associated with a variety of metabolic disorders including dyslipidemia, insulin resistance, diabetes mellitus and hepatic steatosis. We have shown here two cases (patients and her mother) of lipodystrophy associated diabetes mellitus. Figure 24.4A showing clinical picture and Figures 24.4B and C showing lipoatrophy in the lower limbs with phlebomegaly. Insulin sensitizers or its combination insulin can help in achieving blood glucose levels depend upon severity of glycemic status.

Drug and Chemical Induced Diabetes

Drug induced hyperglycemia is an important cause of secondary hyperglycemia in view of the widespread use/abuse of some of these drugs. They may be causative in certain situations while in most situations these drugs unmask or worsen the hyperglycemia of the common types of diabetes (Table 24.2).

Protease inhibitors being used widespread in HIV patients induce lipodystrophy and insulin resistance. Atypical antipsychotic drugs like clozapine, olanzapine were associated with weight gain, hyperglycemia and hypertriglyceridemia in nonrandomized studies. Risperidone and quetiapine appear to have intermediate effects. Aripiprazole and ziprasidone, more recently introduced were not found to have these effects significantly. Alcohol in moderate consumption enhances insulin sensitivity. But excess intake is associated with 50% increase in incidence of diabetes.

While initiating therapy with these drugs, frequent monitoring is essential. The potential diabetogenic drug need not be withheld if indicated for the underlying illness, e.g. furosemide

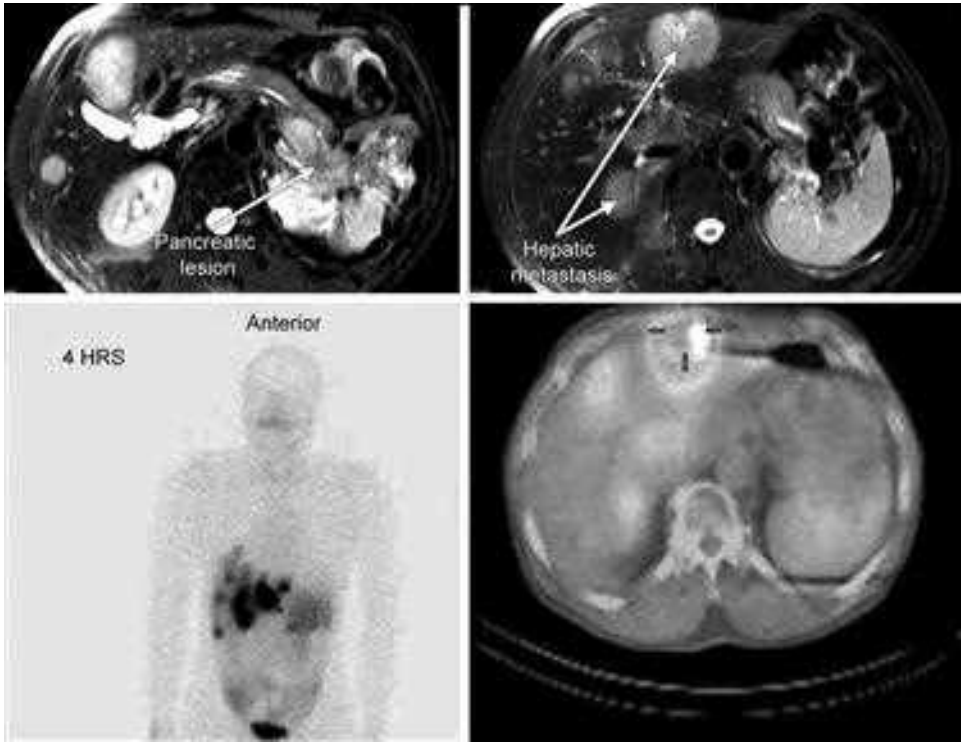


Fig. 24.3D: Magnetic resonance imaging (MRI) abdomen showing the pancreatic lesion (top left), hepatic metastasis (top right), Tc99m-octreotide scintigraphy (left lower) with single-photon emission computerized tomography (SPECT/CT) (right lower) showing multiple metastases in the liver, in a patient glycemia.



Figs. 24.4A to C: (A) Clinical photographs of the subject and her mother showing pseudo-cushingoid facies; (B and C) Lipoatrophy in the limbs with phlebomegaly.

in cardiac failure and glucocorticoids in immune mediated diseases. It needs closer monitoring of blood glucose taking into account the dosage, timing, frequency and change in dosage of these drugs as the glycemia fluctuates accordingly. Diuretics are not contraindicated in underlying diabetes. Drug therapy affects glycemia by their action on insulin secretion and/or action as given in Table 24.3.

Table 24.2: Drugs that causing diabetes mellitus.

<i>Drugs that cause diabetes by interfering with insulin-synthesis and secretion</i>
<i>Phenytoin L:</i> Asparaginase
<i>Pentamidine:</i> Tacrolimus
<i>β-blockers:</i> Didanosine
<i>Diazoxide:</i> Opiates
Calcium channel Blockers
<i>Drugs that cause diabetes by interfering insulin action</i>
<i>Glucocorticoids:</i> β-adrenoreceptor agonist
<i>Megasterol acetate:</i> Clonazepine, Olanzapine (antipsychotics)
<i>Oral contraceptives:</i> SSRI
<i>Growth hormone:</i> Protease inhibitors
<i>Drugs that causes diabetes by interfering with insulin secretion and insulin action</i>
<i>Thiazide diuretics:</i> Cyclosporine
<i>Diazoxide:</i> Atypical antipsychotic
<i>Drugs that cause diabetes independent of insulin</i>
Nicotinic acid
Statin
Aspirin
Total parenteral nutrition

(SSRI: Selective serotonin reuptake inhibitor).

Table 24.3: Effects of drugs on insulin secretion.

	<i>Insulin secretion defect</i>	<i>Insulin resistance</i>
Diuretics	+	?
Phenytoin	+	–
Nicotinic acid	–	+
Glucocorticoids, ACTH	–	+
Growth hormone, thyroxine	–	+
Cyclosporine, opiates	+	+
Protease inhibitors	–	+
Asparaginase	+	–
Atypical antipsychotics (Olanzapine)	?	+
Quinolones	+	?

CHRONIC COMPLICATIONS IN SECONDARY DIABETES

Exact data is not available when compared to primary diabetes because of a milder nature of diabetes, shorter duration of follow-up available and a lack of genetic markers.

Diabetic microvascular complications have a similar prevalence as in primary diabetes. There are some differences like presence of severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy which are less common in secondary diabetes most probably due to differences occurring in the survival of these patients because of the primary pathology when compared to the common types of diabetes. Alternatively, it may be due to differences in the growth factors.

Clinical Considerations—Why is Knowledge about Secondary Diabetes Important?

Identification of both the primary pathology and the resulting hyperglycemia becomes important due to the obvious potential for reversibility and also the need to manage the primary disease definitely. Also, additional unique management issues need to be remembered while dealing with these situations.

- In situations where lean, young individuals present with diabetes, pancreatic diabetes is an important differential diagnosis for type 1 diabetes. A history of recurrent abdominal pain, steatorrhea, a ketosis resistant state and radiological evidence of pancreatic calculi helps in diagnosis of pancreatic diabetes. Pancreatic enzyme supplementation and periodic screening for pancreatic cancer are required uniquely in this group
- Conversely, a history of recent weight loss in spite of increased appetite with hyperdefecation and predominant postprandial hyperglycemia, occurring more typically in females needs exclusion of hyperthyroidism. Hypoglycemia in the fasting state or while on thioamide therapy influences diabetes management
- Worsening hyperglycemia, uncontrolled hypertension, skin changes, aches and pains, multiple medication history for pain, in an otherwise apparently obese type 2 diabetic individual should arouse the suspicion of Cushing's syndrome. It has to be remembered that in those on chronic steroid use sudden withdrawal of steroids should never be attempted. Also glycemic fluctuations parallel the pharmacological properties of exogenous steroids
- Weight gain, dyslipidemia and hyperglycemia should be expected and looked for in any patients who are on long-term steroids or antipsychotic drugs. Therapy resistant hyperglycemia in patients on diuretics, anticonvulsants or protease inhibitors should be kept in mind by the treating physician during follow-up of such patients.

Management

- The management of any patient with secondary diabetes is not different from the more common types of diabetes. The general concepts to be borne in mind are:
- The presentation of the glucose intolerance varies grossly from IGT to over diabetes in patients with secondary diabetes
- Treatment of the primary cause or withdrawal of the causative agent usually reverses the intolerance. Permanent diabetes usually persists in those patients who have underlying genetic predisposition for diabetes or permanent pancreatic deficiencies
- In case of pancreatic disorders supplementation of pancreatic enzymes, close monitoring of glycemic fluctuations, screening for pancreatic malignancies and proper selection of

insulin regimens are vital. Pain can be intractable and requires measures like abstinence from alcohol, dietary modifications, supplementation of pancreatic enzymes, analgesics and somatostatin analogs. Oral pancreatic enzymes help in pain reduction and in attenuation of malabsorption

- In those patients with overt diabetes, weight reduction, diet control and drug therapy should be used with the aim of achieving near normal glucose levels. The target values for blood glucose are also the same as in type 1 or type 2 diabetes
- The decision regarding continuation or withdrawal of therapy can be logically arrived to by regular monitoring of the patients which is the case in any type of diabetes.

OTHER SPECIFIC TYPES OF DIABETES

Apart from the earlier mentioned secondary causes, other diabetic disorders are:

- Genetic defects of beta cell function by mutation
- Genetic defects in insulin action
- Infectious diseases
- Uncommon forms of immune mediated diabetes
- Other genetic syndromes with diabetes.

Identifying these conditions using clinical and laboratory clues makes a difference in management of these patients because they require attention to the associated comorbidities.

Genetic Defects of Beta-cell Function

Maturity-onset Diabetes of the Young

Mutations in islet cell transcription factors/glucokinase genes affect 2–3% of people with diabetes, although it often goes unrecognized. Its unique features are:

- Monogenic form of insulin secretion defect
- Autosomal dominant mode of inheritance with glucose intolerance found in at least three successive generations with only one of the parent affected
- The onset should have occurred before the age of 25 years in at least one, ideally two family members
- Presents as early onset of diabetes at third decade
- When compared to type 2 diabetes these patients lack acanthosis or any significant degree of insulin resistance and usually have a normal BMI. They are negative for antibodies.

There are different types of gene defects in maturity-onset diabetes of the young (MODY) with 11 types being well established. Those with unidentified mutations are labeled as MODY X. Novel candidate genes have been proposed and are likely to extend the list. The most appropriate treatment, progression in the future and counseling of family members about future diabetes can be made possible by finding out which type of MODY a person has.

The two main subtypes are:

1. Glucokinase gene defect—defective glucose sensor, usually present at birth.
2. Transcription factor defect—beta cell dysfunction occurring at adolescence/early adulthood.

In those with glucokinase defect the onset is at a much younger age, the glucose intolerance being mild and managed with diet, exercise and antidiabetic agents. In transcription factor defects (HNF-1alpha, HNF-1beta, HNF-4alpha) the onset is at adolescent age, progressively requiring oral antidiabetic drugs (OADs) and later insulin. MODY 3 (HNF-1 alpha defect) is the most common in adults while MODY 2 (glucokinase defect) is the most common variety among asymptomatic fasting hyperglycemia in children. The genetic aspects of MODY are discussed in Chapter 21.

Management: If obese, exercise should be prescribed to promote weight loss.

MODY 1, 3, 4: Respond very well to antidiabetic agents; insulin-replacement therapy in late stages particularly MODY 1 and 3.

MODY 2: Nonprogressive; can usually be managed with diet and exercise alone.

MODY 5: May require endocrine and exocrine replacements and therapy for other organ abnormalities.

In a study at CMC, Vellore (Tamil Nadu, India) we studied 50 patients with clinical suspicion of MODY and studied a comprehensive panel of 10 MODY genes consisting of HNF1A, HNF4A, GCK, HNF1 β , IPF1, NEUROD1, KLF11, CEL, PAX4, and INS, using a novel multiplex polymerase chain reaction (PCR) and further sequencing on Ion Torrent Personal Genome Machine. Mutations were found in seven patients, which include four with NEUROD1 mutation, one with HNF4A mutation, one with GCK mutation and one with HNF1B mutation.

Novel multiplex PCR coupled with Ion Torrent Next Generation sequencing is a useful, rapid and cost-effective way of performing comprehensive genetic screening. With this parallelized sequencing approach there was a higher frequency of NEUROD1 mutations, a pattern of MODY different from the Western population. This facility is currently available at CMC, Vellore.

Mitochondrial DNA Defects

These are maternally transmitted disorders. About 60% of the patients have deafness with phenotype more like type 2 than as type 1 diabetes. Maternally inherited diabetes mellitus and deafness (MIDD) syndrome is due to mutation in mitochondrial DNA (A3243G) characterized by a thin built and short stature, no history of ketoacidosis or evidence of islet cell antibodies. The diagnosis can be made by testing for the m.3243A > G mutation, usually in blood leukocytes.

Proinsulin/Insulin Conversion Defect and Aberrant Insulin Synthesis

There is secretion of incompletely cleaved and partially active insulin, inherited as an autosomal dominant disorder.

Defects in Insulin Action: Severe to Extreme Insulin Resistance

- *Type A syndrome—genetic defects in insulin receptor/postreceptor signaling:* Usually found in young women with hyperinsulinemia, obesity, oligomenorrhea, pseudoacromegaly features, hyperandrogenism and acanthosis. It requires stringent weight reduction, insulin sensitizers and antihyperglycemic agents.
- *Type B syndrome—circulating autoantibodies to the insulin receptor:* Subjects belonging to this category have other autoimmune conditions like systemic lupus erythematosus

(SLE), Sjögren's syndrome, etc. It is more common in middle aged females and is characterized by waxing and waning of glucose levels and at times hypoglycemia. Spontaneous remission may occur in some subjects in 2–3 years. The management of diabetes with autoantibodies is confounded by the cyclical nature of the autoimmune disease. It needs close monitoring of antibody titers and blood glucose. Glucocorticoids and immunosuppressants may be helpful.

- *Syndromes of extreme insulin resistance*
Leprechaunism and Rabson—Mendenhall syndromes are associated with severe mortality and morbidities with presentation of insulin resistance and other features occurring at birth or soon after.
- *Lipoatrophic diabetes*—they are congenital or acquired, complete or partial. Absence of subcutaneous fat, insulin resistance, dysmorphic features, liver and renal abnormalities are found in some types of this heterogeneous disorder.

Infectious Diseases

Congenital rubella, cytomegalovirus virus and Coxsackie viral infections in early childhood are associated with an increased risk of diabetes.

Other Uncommon Autoimmune Mediated Diabetes

For example, Stiff man syndrome— glutamic acid decarboxylase (GAD) antibody positive, generalized stiffness and diabetes.

Genetic Syndromes with a Higher Propensity to Develop Diabetes

- *Obesity related syndromes*: Prader-Willi syndrome, Lawrence Moon syndrome, Bardet Biedl syndrome and Alstrom syndrome
- *Hereditary neuromuscular syndromes*: Myotonic dystrophy—myotonia, diabetes, frontal baldness, distal muscle weakness; Huntington's chorea; Friedreich's ataxia
- *Chromosomal defects*: Down's syndrome, Klinefelter's syndrome, and Turner's syndrome
- *Progeroid syndromes*: Werner syndrome, Cockayne syndrome
- *Miscellaneous*: Wolfram's syndrome (DIDMOAD—diabetes insipidus, diabetes mellitus, optic atrophy and deafness). The DIDMOAD or Wolfram syndrome is inherited as an autosomal recessive trait. The syndrome is caused by a mutation in the gene responsible for the production of a protein called wolframin, a transmembrane protein located in the endoplasmic reticulum, which serves as a calcium channel, but is also associated with susceptibility to adult type 2 diabetes mellitus. The earliest manifestation of DIDMOAD is usually diabetes mellitus (average age of diagnosis approximately seven years), followed by optic atrophy, then diabetes insipidus and, lastly deafness.

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3. Dasgupta R, Naik D, Thomas N. Emerging concepts in the pathogenesis of diabetes in fibrocalculous pancreatic diabetes. *J Diabetes*. 2015 Feb 23.
4. Kapoor N, Job V, Jayaseelan L. Spot urine cortisol-creatinine ratio—A useful screening test in the diagnosis of Cushing's syndrome. *Indian J Endocrinol Metab*. 2012;16(Suppl 2): S376-7.
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SELF-ASSESSMENT

I.1. The following statements are true *except*:

- (a) The most prevalent form of chronic pancreatitis in the tropics is alcoholic pancreatitis
- (b) The unique feature distinguishing alcoholic chronic pancreatitis from TCP is that in TCP calculi are larger and invariably found in large ducts
- (c) The occurrence of microvascular complications in FCPD patients is very rare
- (d) The characteristic microscopic feature of TCP is the presence of diffuse and progressive fibrosis of the pancreas.

II. A 46-year-old lady came with a history of weight gain and hypertension of 2 years duration. She gave a history of treatment with various drugs including steroids for nearly 10 years. For the last 2 months she has been applying some green leaves for a non-healing ulcer over her left leg. She did not know about the diabetic status of her family members. On examination her BP was 140/100 mm Hg. She was obese and had severe proximal muscle weakness. An oral GTT showed her fasting and 2 hours glucose values as 189 mg/dL and 313 mg/dL, respectively.

2. The following statements are true *except*:

- (a) She has probably type 1 diabetes
- (b) She has secondary diabetes
- (c) The possibility of type 2 diabetes cannot be ruled out.

3. Regarding control of diabetes true is:

- (a) Metformin is a good choice to reduce insulin resistance in her
- (b) She may require insulin for control of diabetes
- (c) Both A and B are true
- (d) Sulfonylureas are contraindicated.

4. Pick up the correct statement in the following question:

- (a) Steroids should be withheld at once as they worsen the glycemic status
- (b) Insulin dose should be tapered down when the steroid dose is being reduced
- (c) Insulin dose should be increased when the steroid dose is being reduced
- (d) For her BMI, thiazolidinediones will be ideal insulin sensitizers.

III. A 29-year-old male presented with a history of fatigue and weight loss of 6 months duration. He does not have any other symptom. His grandfather had diabetes. His father who was the only child for his parents did not have diabetes. His BMI is 24.5 kg/m².

5. Pick up the correct statement in the following question:

- (a) He has pancreatic diabetes
- (b) The most probable type of diabetes is MODY
- (c) Genetic testing is mandatory for starting treatment
- (d) It's unlikely to be type 2 diabetes.

6. What features if present would have prompted a diagnosis of pancreatic diabetes?

- (a) A low BMI, lack of abdominal symptoms, presence of ketosis
- (b) *Acanthosis nigricans*, absence of family history, high BMI
- (c) A low BMI, strongly positive urine ketones and abdominal pain
- (d) Absence of ketosis, recurrent abdominal pain and low BMI

7. What are the preliminary investigations to be done in any young patient with diabetes?

- (a) Urine ketones, blood glucose, electrolytes
- (b) Ultrasound abdomen
- (c) Screening of family members
- (d) All of the above

8. If the above patient had seizure disorder:

- (a) Carbamazepine will be a better drug for his seizures
- (b) Phenytoin is the best drug for seizure
- (c) Both A and B are correct
- (d) Both A and B are wrong.

IV. A 26-year-old lady presents with a history of weight loss of 6 months duration with increased appetite and increased frequency of stools. Her BMI was 19.5 kg/m² and she had a heart rate of 110/min. Her blood glucose values were fasting—128 mg% and postprandial—260 mg%. She did not have previous history of diabetes.**9. With the above limited history what are the possibilities:**

- (a) Type 1 diabetes
- (b) Tropical pancreatitis
- (c) Thyrotoxicosis
- (d) All of the above

10. The urine ketone was negative and on closer examination she had hyperpigmentation of skin with fine tremors of the outstretched hand. What will be the most appropriate management?

- (a) Pancreatic enzyme supplement along with insulin
- (b) Insulin alone
- (c) Thyroid function tests and antithyroid drugs
- (d) Ultrasound abdomen and referral to surgeon

CHAPTER

25

Perioperative Care

Georgene Singh

*"Sugars go high and cause problems, like blackened feet and toes,
For a surgeon to slice through these tissues-with the sugar the higher it goes,
The problems are so complex, with the coronaries so tough,
So arrhythmias could happen, make the anesthetists' life rough."*

The prevalence of diabetes mellitus (DM) in both adults and children has been steadily rising throughout the world for the past 20–30 years. The American Diabetes Association conservatively estimates that 12–25% of hospitalized adult patients have diabetes. With the increasing prevalence of diabetic patients undergoing surgery and the increased risk of complications associated with DM, appropriate assessment and management in the perioperative period which includes all the three phases of surgery: preoperative, intraoperative and postoperative are imperative. Perioperative management of a diabetic patient affects surgical outcome.

An estimated 25% of diabetic patients will require surgery. Mortality rates in diabetic patients have been estimated to be up to five times greater than in nondiabetic patients, often related to the end-organ damage caused by the disease. Chronic complications resulting in microangiopathy (retinopathy, nephropathy and neuropathy) and macroangiopathy (atherosclerosis) directly increase the need for surgical intervention and the occurrence of surgical complications due to infections and vasculopathies. In a diabetic patient, undergoing surgery, the major risk factors are the end-organ diseases associated with diabetes such as cardiovascular dysfunction, renal insufficiency, joint collagen tissue abnormalities, inadequate granulocyte production and neuropathies. Infections account for approximately 66% of postoperative complications and nearly one quarter of perioperative deaths in patients with DM. Tight control of blood glucose is important to minimize infection.

METABOLISM AT REST

In the fasting state, glucose turnover in a 70 kg (154 lb) individual is approximately 2 mg/kg/minute (200 g/24 hours). The blood glucose concentration reflects the balance between intake (glucose absorption from the gut), tissue utilization (glycolysis, pentose phosphate

pathway, tricarboxylic acid (TCA) cycle and glycogen synthesis) and endogenous production (glycogenolysis and gluconeogenesis).

METABOLIC CHALLENGE OF SURGERY

The immediate perioperative problems facing the diabetic patient are:

- Surgical induction of the stress response with catabolic hormone secretion
- Interruption of food intake
- Altered consciousness, which marks the symptoms of hypoglycemia and necessitates frequent blood glucose estimations, and
- Circulatory disturbances associated with anesthesia and surgery, which may alter the absorption of subcutaneous insulin.

Surgery evokes the “stress response”, that is, the secretion of catecholamines, cortisol, growth hormone and in some cases, glucagon. These counter-regulatory hormones, as they have “anti-insulin” and hyperglycemic effects, gluconeogenesis is stimulated and peripheral glucose uptake decreased. Although diabetics need increased insulin during the perioperative period, requirements for glucose and insulin in this period are unpredictable and close monitoring is essential, especially in the unconscious or sedated patient. The Approach to a diabetes patient undergoing surgery is summarised in Figure 25.1.

PREOPERATIVE MANAGEMENT OF DIABETIC PATIENTS

Preoperative Assessment

- History about compliance with the medication
- Type 2 DM patients require higher insulin dose than type 1 DM
- Even if the glucose are high it doesn't warrant cancellation of the case
- Ask the patient to bring the insulin with the patient
- All the antidiabetic medication should be withheld on the day of surgery
- If the patient has episodes of nocturnal hypoglycemia reduce the previous night insulin dose by 20–30%
- Drugs belonging to sulphonylurea class have highest incidence of hypoglycemia, while biguanides and thiazolidinediones have lesser incidence.

Evaluation of End-organ Damage

A standard assessment is required with specific attention to the following details as mentioned in Table 25.1

LEVEL OF GLYCEMIC CONTROL

The goal for glycemic control in the perioperative period is to maintain blood sugar levels between 120 mg% and 180 mg%. Glycosuria begins at a blood glucose level of 180 mg/dL causing fluid shifts, dehydration and electrolyte abnormalities.

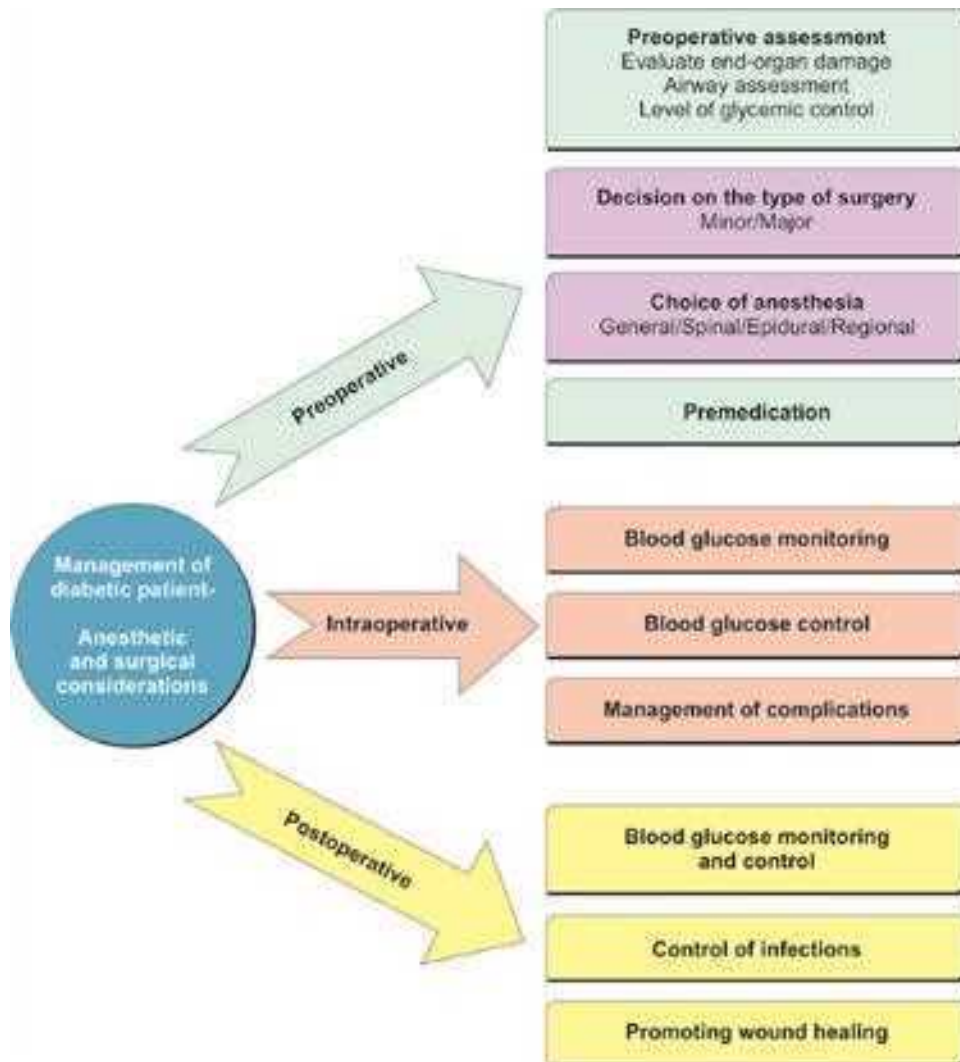






Fig. 25.1: Approach to a diabetic patient undergoing surgery.

Check fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) before admission and stabilize glycemia.


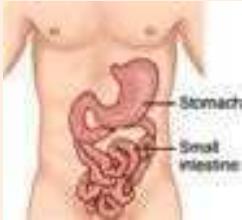


- Assess HbA1c levels as mentioned in the Table 25.2
- The best marker for recent control is the percentage of glycosylated hemoglobin (HbA1c)
- If HbA1c is unavailable, try to assess control by looking at the patient's own log of urine or blood glucose (home-monitoring results). If average value is less than 180 mg%, it indicates long-term good control
- Measure random blood glucose preoperatively
 - Four hourly for type 1 DM and type 2 DM on insulin
 - Eight hourly for type 2 DM on oral hypoglycemic agents (OHA).

Table 25.1: Preoperative assessment and anesthetic implications in a diabetic patient.

End-organ	End-organ damage evaluation	Anesthetic implications
<p>Autonomic Neuropathy</p> 	<p>Assess for other features of autonomic neuropathy, i.e. gastroparesis, gustatory sweating and nocturnal diarrhea</p>	<p>Adequate preloading with fluids to prevent hypotension Bradycardia and hypotension may not respond to the usual drugs (atropine, ephedrine) and may need early epinephrine Increased cardiovascular instability during anesthesia warrants careful monitoring Homeostatic reflexes are unable to compensate for effects of anesthetic agents on vascular tone and myocardial contractility Prone to arrhythmias and postoperative urinary retention</p>
<p>Peripheral neuropathy</p> 	<p>Most common—"Glove and stocking" type Also prone to mononeuritis multiplex and some particularly to painful sensory neuropathies</p>	<p>Patient positioning during anesthesia/surgery is important (Poor patient positioning results in pressure sores that heal poorly due to poor peripheral blood flow. This also predisposes for nerve injuries) Documentation of existing neuropathy is prudent, especially if considering a regional technique</p>
<p>Respiratory</p> 	<p>Diabetics, especially the obese and smokers are more prone to respiratory infections A chest X-ray, blood gases and spirometry are the gold standard investigations Careful repeated clinical assessment is also important</p>	<p>Chest physiotherapy, humidified oxygen and bronchodilators should be used aggressively to control the infection/bronchospasm before taking for surgery Nonemergency surgery should be delayed until chest is clear</p>
<p>Airway</p> 	<p>30–40% of type 1 diabetics have limited-joint mobility syndrome (stiff-joint syndrome). Chronic hyperglycemia causes glycosylation of tissue proteins which is the reason for restricted mobility. Temporomandibular joint and cervical (C)-spine (e.g. atlanto-occipital joint) are involved</p>	<p>Direct laryngoscopy may be difficult in 30% of type 1 diabetics Glycosylation of collagen in the cervical and temporomandibular joints can cause difficulty in intubation</p>

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End-organ	End-organ damage evaluation	Anesthetic implications
<p>Positive "prayer sign"</p> 	<p>Positive "prayer sign" (image at right): To test if a patient is at risk, ask them to bring their hands together, as if praying, and simultaneously hyperextend to 90° at the wrist joint. If the little fingers do not oppose, anticipate difficulty in intubation Thickening of soft-tissues occurs, e.g. ligaments around joints</p>	<p>If the neck is affected there may be difficulty extending the neck, making intubation difficult</p>
<p>Gastrointestinal</p> 	<p>A history should be sought of heartburn and acid reflux when lying flat Gastroparesis, lax gastroesophageal (GE) sphincter and delayed gastric emptying contributes to risk of aspiration Gastroparesis manifests as nausea, vomiting, early satiety and abdominal distension</p>	<p>Risk of aspiration at induction of anesthesia Should have a rapid sequence induction with cricoid pressure, even for elective procedures Use H₂ antagonist and metoclopramide (prokinetic) as a premedicant</p>
<p>Eyes</p> 	<p>Diabetics are prone to cataracts and retinopathy</p>	<p>Prevent surges in blood pressure, e.g. at induction, as this might cause rupture of the new retinal vessels</p>
<p>Cardiovascular</p> 	<p>Prone for: Ischemic heart disease (IHD)—silent myocardial ischemia/infarction (MI), hypertension, peripheral vascular disease, cardiomyopathy and perioperative MI Take detailed history Shortness of breath, palpitations, ankle swelling, fatigue, syncope and chest pain Examine carefully for Heart failure signs (distended neck veins, ankle swelling, tender swollen liver, crackles heard on listening to the chest) Routine electrocardiogram (ECG) should be performed Stress testing if inducible ischemia is suspected and echocardiography if left ventricular (LV) dysfunction is suspected</p>	<p>Watch for silent MI perioperatively Monitor 5 lead ECG whenever monitoring for MI is required Heart failure is a very serious risk factor and must be improved before surgery with diuretics</p>

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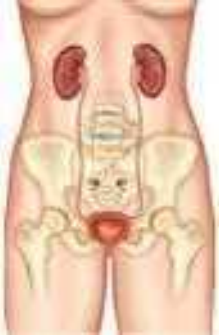
End-organ	End-organ damage evaluation	Anesthetic implications
Renal 	<p>Increased incidence of asymptomatic renal dysfunction</p> <p>End-stage renal failure can also be encountered</p> <p>Check urea, creatinine, electrolytes and proteinuria</p> <p>Specifically check the potassium levels in view of the possible need for suxamethonium as a result of gastroparesis</p>	<p>Ensure adequate hydration to reduce postoperative renal dysfunction</p> <p>Urine infections are common and should be treated aggressively with antibiotics</p> <p>The diabetic is at risk of acute renal failure and urinary retention postoperatively</p> <p>If the potassium is high (> 5 mmol/l) then specific measures should be taken to lower it before surgery</p> <p>Avoid nephrotoxic drugs like nonsteroidal anti-inflammatory drug (NSAIDs)</p>
Immune system	<p>Diabetics are prone to all types of infection. Indeed an infection might actually worsen diabetic control</p> <p>Inadequate granulocyte production, decreased chemotaxis and impaired phagocytic activity of granulocytes make a diabetic patient vulnerable to infection</p>	<p>Tight glycemic control will reduce the incidence and severity of infections postoperatively</p> <p>Perform all invasive procedures with full asepsis</p> <p>Appropriate antibiotics in the perioperative period</p>
Miscellaneous	<p>Diabetes may be caused or worsened by treatment with corticosteroids, thiazide diuretics and the contraceptive pill</p> <p>Autonomic neuropathy predisposes to hypothermia under anesthesia</p>	<p>Stop any such drug intake preoperatively</p> <p>Maintain temperature during surgery</p>

Table 25.2: Role of HbA1c in preoperative management of diabetic patients.

HbA1c	Glycemic control	Effect on surgery	Plan of action
<7%	Excellent control	<ul style="list-style-type: none"> • Low anesthetic risk • Good wound healing 	<ul style="list-style-type: none"> • Can be taken-up for surgery anytime • If current sugars out of control admit to 2-3 days, intensify control and then take up for surgery
7-10%	Reasonable control	Not much risk of impaired wound healing or serious infection	Manage sugars on outpatient basis and take up for surgery once controlled

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>10%	Poor control	<ul style="list-style-type: none"> • Impaired fibroblast function—poor wound healing • Impaired immune function predisposes to infection • Increased incidence of sudden cardiac death even under regional anesthesia 	<ul style="list-style-type: none"> • Patient needs optimization of control for several weeks before surgery • Then, admit preoperatively for correction of abnormalities in hydration, electrolytes, etc. and stabilization of blood sugar levels before the addition of surgical stressors
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CLASSIFICATION OF THE TYPE OF SURGERY

Minor: In general, if the patient can be expected to eat and drink within 4 hours of surgery, then it is classified as minor.

Major: All surgeries other than minor are classified as major. All emergency surgeries should be considered as major as shown in Flowchart 25.1.

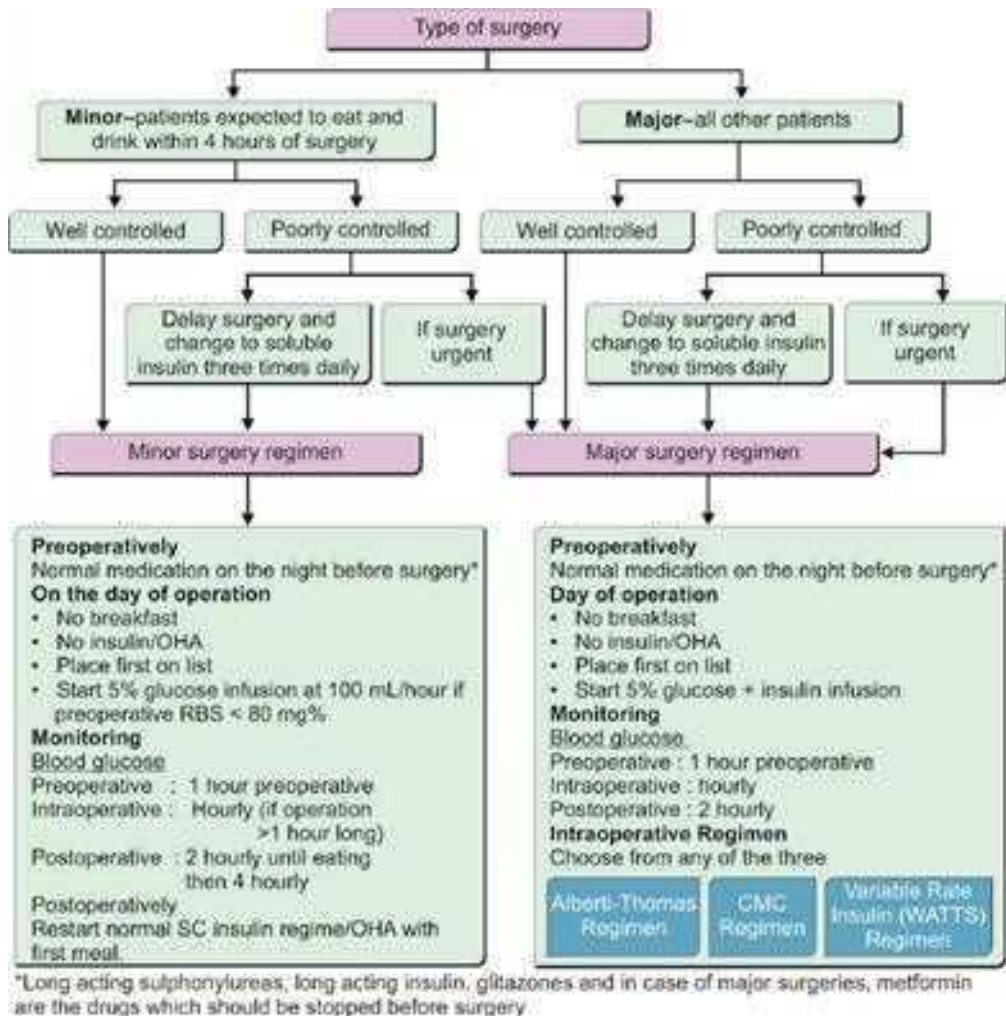
MANAGEMENT OF DIABETES DEPENDS ON

- Type 1 or type 2 disease—insulin dependence
- Preoperative control of blood glucose
- Associated end-organ dysfunction
- Magnitude of proposed surgery, likely period of postoperative fasting
- Presence of intercurrent major infection—anticipate fall in blood glucose levels in the postoperative period.

CHOICE OF ANESTHESIA

- The diabetic patient presents the anesthetist many challenges
- No specific guidelines for the choice of anesthesia but as dictated by the surgery
- Both general as well as regional anesthesia may be used in a diabetic
- Regional techniques are preferred always as they minimize the stress response and allow the patient to communicate symptoms of hypoglycemia and help avoid manipulation of a potentially difficult airway. Regional techniques though safer than general anesthesia, require the same amount of vigilance.

Diabetic patients undergoing surgery with neural blockade will usually resume oral intake earlier than after general anesthesia. It is now a common practice in cataract surgery to allow normal oral intake and hypoglycemic therapy throughout the perioperative period. In a series of 12,000 cataract extractions under local anesthesia, in which patients were not starved, only one patient's surgery was postponed because of persistent nausea. However, the possibility of converting to a regional technique to general anesthesia may militate against this practice in other forms of surgery. At present, there is no evidence that regional anesthesia alone, or in

Flowchart 25.1: Preoperative management of diabetic patients based on the type of surgery.

(OHA: Oral hypoglycemic agents; SC: Subcutaneous).

combination with general anesthesia, confers any benefit in the diabetic surgical patient, in terms of major complications and mortality.

PREMEDICATION

- Ranitidine 150 mg or cimetidine 400 mg plus metoclopramide 10 mg orally 2 hours preoperatively to reduce the acid volume in the stomach
- No insulin or OHA on the day of surgery
- Continue all diabetic medications until the night before surgery except:
 - Chlorpropamide (stop 3 days prior as it is long-acting and substitute with a shorter acting sulphonylurea)

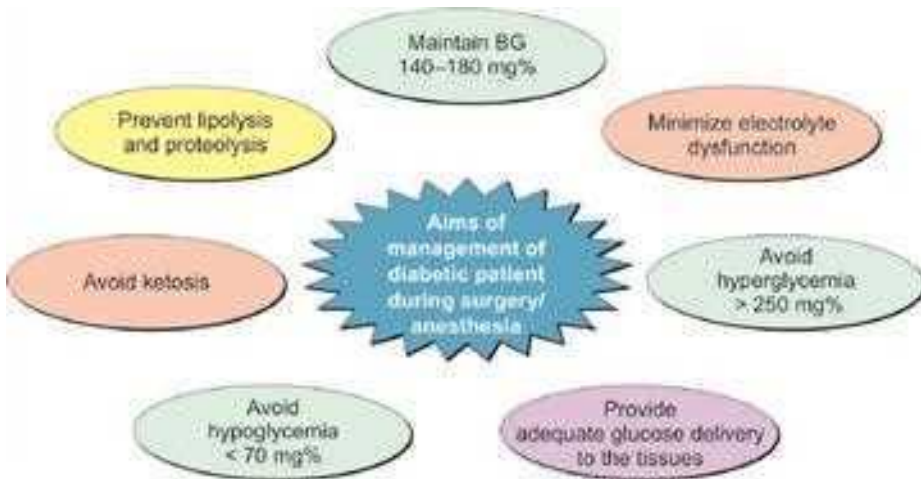


Fig. 25.2: Aims of intraoperative management of diabetic patients.

- Metformin, only if major surgery as there is a risk of lactic acidosis
- Glitazones
- Long-acting insulin—substitute with short/intermediate acting insulin.

INTRAOPERATIVE ANESTHETIC MANAGEMENT OF DIABETIC PATIENTS

Aims of Management

The aim of intraoperative glycemic control is to avoid hypoglycemia, hyperglycemia, ketoacidosis and electrolyte disturbances. Blood glucose between 120 mg% and 180 mg% is widely accepted. This requires the use of insulin, wise choice of intravenous fluids and close monitoring of glucose and electrolyte levels. Insulin is required for all diabetics who are taking insulin preoperatively and for those undergoing major surgery. One unit of insulin decreases blood glucose by to 50 mg/dL. Therefore, the actual blood glucose minus the desired level divided by approximately 50 provides the required dose of insulin in units. All algorithms are based on this principle as shown in Figure 25.2.

Monitoring under Anesthesia

The choice of monitoring depends on the nature of the proposed surgery and the hemodynamic status of the patient. However, it is mandatory for all diabetic patients under anesthesia to have oxygen saturation (SpO₂), Noninvasive blood pressure (NIBP) every 5 minutes and 3 lead electrocardiogram (ECG) monitoring.

- Oxygen saturation by pulseoximeter
- Noninvasive blood pressure every 5 minutes

- Continuous arterial blood pressure (ABP) monitoring is indicated if patient is hemodynamically unstable or if large fluid shifts are anticipated during the procedure
- 3 lead ECG
- 5 lead ECG if patient has evidence of myocardial ischemia
- End-tidal CO₂ for patients undergoing general anesthesia
- Random blood glucose monitoring every hour
- Urine output hourly
- Temperature monitoring.

General Principles of Management

Timing: diabetic patients should be placed first on the operating list. This shortens their preoperative fast and allows normal oral intake later that same day. Poorly controlled diabetics need to be admitted to hospital one or two days before surgery if possible to allow their treatment to be stabilized.

Glycemic control:

- Admission 2–3 days preoperatively for tighter control of blood sugars is required in those with poor glycemic control
- Patients planned for elective surgery must not be anesthetized unless their blood sugar is well controlled
- Diabetic patients should have random blood glucose checked hourly during surgery
- In the event of any neurological insult under anesthesia, hyperglycemia worsens the outcome. However, hypoglycemia under anesthesia is also potentially dangerous. Hence, both extremes are to be avoided.

Glycemic variability:

- Glycemic variability is as important as absolute glucose values
- Oxidative stress is precipitated by abrupt changes in blood glucose levels rather than by sustained hyperglycemia. Hence it is important to avoid fluctuations in blood glucose perioperatively.

Type of anesthesia: A regional technique, if suitable, is the first method of choice.

Positioning: Care with heels and other pressure areas. Positioning should be done gradually so that sudden drops in blood pressure can be avoided.

Anesthetic drug: Careful titration of induction agents with adequate preloading to avoid hypotension due to autonomic neuropathy is needed.

Hydration: Glucose in the urine (glycosuria) causes osmotic diuresis which makes the patient dehydrated and even more susceptible to hypotension. Check for dehydration and start an intravenous infusion.

Normally, normal saline (NS) is used as maintenance fluid. Dextrose containing solutions are avoided unless the patient is hypoglycemic. Ringer's lactate (RL) is to be avoided. If hypokalemia is suspected, potassium supplementation is required.

Table 25.3: Intraoperative insulin administration—CMC regimen.

<i>Blood glucose mg/dl (mmol/L)</i>	<i>Insulin infusion rate</i>
< 75 (4.1)	No insulin; 100 ml 5% glucose over 15 minutes
75–100 (4.1–5.5)	No insulin; 100 ml 5% glucose over 1 hour
100–150 (5.5–8.3)	1 unit actrapid in 100 ml 5% glucose over 1 hour
150–200 (8.3–11.1)	2 unit actrapid in 100 ml 5 % glucose over 1 hour
200–250 (11.1–13.8)	3 unit actrapid in 100 ml 5% glucose over 1 hour
250–300 (13.8–16.6)	4 unit actrapid in 100 ml 5% glucose over 1 hour
> 300 (16.6)	4 unit actrapid in 100 ml 0.9% normal saline over 1 hour

POINT OF CARE GLUCOSE MEASUREMENTS

Blood glucose is often estimated perioperatively by point-of-care (POC) techniques. POC results more often overestimated than underestimated glucose values compared with reference laboratory values. Patients with low perfusion index had the most substantial disagreements. However, POC glucose measurements in hemodynamically stable patients have correlated with lab reference.

MAJOR SURGERY REGIMEN

Various major surgery regimens for intraoperative management of diabetic patients have been tried under different settings. The often used regimens are (1) Alberti-Thomas regimen and (2) Variable rate insulin regimen (WATTS). An alternate simpler regimen (CMC regimen) is given below which combines the plus points of these two regimens, namely “safety” of the combined insulin-glucose infusion (Alberti-Thomas regimen) and the “economy” of the variable rate insulin infusion.

A burette set is connected to a 5% glucose (500 mL) bag, and 100 mL of glucose is filled into the burette at a time. Short-acting insulin (Actrapid) is added to the 100 mL of fluid in the burette according to the scale given below and this is infused over 1 hour.

Check blood glucose before infusion and then hourly. Adjust the amount of the insulin as mentioned in the Table 25.3.

MANAGEMENT OF DIABETIC PATIENTS UNDER DIFFERENT MODES OF ANESTHESIA

In General Anesthesia

- Anticipate difficulty in intubation and airway equipment like laryngeal mask airway (LMA), long blade, gum elastic bougie and experienced help should be available
- If gastroparesis is suspected, then a rapid sequence induction with cricoid pressure should be used. A nasogastric tube can be used to empty the stomach
- There are no contraindications to standard anesthetic induction or inhalational agents

- If the patient is dehydrated, then hypotension will occur and should be treated promptly with intravenous fluids. Hartmann's solution (Ringer's lactate) should not be used in diabetic patients as the lactate it contains may be converted to glucose by the liver and cause hyperglycemia
- Arrhythmias may occur:
 - Sudden bradycardia should respond to IV atropine 0.3 mg, repeated as necessary (maximum 2 mg).
 - Tachycardia may be due to light anesthesia or pain. If supraventricular tachycardia is present as seen on ECG, it may respond to gentle massage on one side of the neck over the carotid artery. If not then consider a β -blocker (Propranolol 1 mg increments: max 10 mg total or labetalol 5 mg increments: max 200 mg in total). But beware! β -blockers mask signs of hypoglycemia!!
- Intravenous induction agents normally cause hypotension on injection due to vasodilatation. If a patient has a damaged autonomic nervous system (and many diabetics do), then they cannot compensate by vasoconstricting, and the hypotension is worsened. Preloading the patient adequately and reduced doses of induction agents with slow injection of the drug will reduce hypotension.

In Regional Techniques

- These are useful because they get over the problem of regurgitation, possible aspiration and of course difficult intubation
- Regional techniques obtund stress response, decrease blood loss and reduces incidence of thromboembolic complications
- However, attention should be paid to avoiding hypotension by ensuring adequate hydration, preoperatively. With spinals and epidurals, patients with autonomic dysfunction may not be able to keep their blood pressure within the normal range. Early intervention with vasopressors such as ephedrine (6 mg boluses) should be initiated when the systolic pressure falls to 25% below normal
- Local anesthetic requirements are lower with regional anesthesia and addition of epinephrine poses greater risk of ischemic or edematous nerve injury in diabetics
- It is a wise precaution to chart any preexisting nerve damage before any regional anesthetic techniques are used.

PROBLEMS TO BE ANTICIPATED IN A DIABETIC PATIENT UNDER ANESTHESIA

Improved glycemic control has been shown to decrease perioperative morbidity and mortality in diabetic patients undergoing major surgery. Blood glucose usually falls during the preoperative fasting and rises during and after surgery. Achieving optimum glycemic control is truly a challenge.

A few minutes of serious hypoglycemia (< 40 mg/dL) can be harmful, potentially inducing arrhythmias or transient cognitive deficits. Hypoglycemia and subsequent neuroglucopenia can be difficult to detect in sedated patients postoperatively. Studies demonstrate that in

hospitalized patients the presence of hyperglycemia, with or without known diabetes, is associated with poor clinical outcomes.

Hypoglycemia

The main danger to diabetics is low blood glucose levels (blood glucose < 70 mg%):

- Anesthetized patients may not show any of the signs of hypoglycemia
- Therefore, monitor blood glucose regularly, and be very suspicious of any unexplained changes in the patient's condition. If in doubt, regard them as indicating hypoglycemia and treat
- Diabetic patients learn to recognize the early signs, and, if under regional anesthesia may be able to tell the anesthetist often. On the other hand, long standing diabetes with autonomic neuropathy may make patients unaware of hypoglycemic symptoms.

Treatment

- If conscious, as during the postoperative period, 15 g of glucose, if not available, an equivalent may be given
- If unconscious, 50 ml of 50% glucose (or any glucose solution available) given intravenously and repeated as necessary is the treatment of choice. 1mg of glucagon intramuscularly will help but it is neither freely available nor widely used in India.

Hyperglycemia

This is defined as a blood glucose level more than 200 mg%. Elevated levels are commonly found during and after routine major surgery and require vigorous treatment with insulin.

Treatment

It is usual to treat hyperglycemia in a diabetic patient undergoing surgery only if the level is above 180–200 mg%

Diabetic Ketoacidosis

The patient will become drowsy or even unconscious but in a patient under general anesthesia, it is difficult to identify but in either case, the patient may have fast, deep breathing due to acidosis. The ketones make their breath smell sweetly, like acetone. So close monitoring, and testing for ketones in urine and blood using strips are recommended.

Treatment

This is the same as treating ketoacidosis in a normal setting.

Rehydration:

- Give 1 L 0.9% saline over 30 minutes
- Give 1 L 0.9% saline over 1 hour
- Give 1 L 0.9% saline over 2 hours.

Table 25.4: Intraoperative potassium replacement.

Serum K ⁺ level (mEq/L)	< 3.5	3.5–4	4–5	> 5
K ⁺ (mEq/hour) replacement	40	30	20	0

Continue 2–4 hourly until blood glucose is controlled to less than 250 mg% then continue with 5% dextrose 1 liter 2–4 hourly.

Reduce blood sugar level:

- *Loading dose:* 0.1 unit/kg IV bolus (some consider this optional)
- *Maintenance dose:* Continuous IV insulin infusion (using an infusion pump, if available) at the rate of 0.1 unit/kg/hour. A mix of 24 units of regular insulin in 60 mL of isotonic sodium chloride solution usually is infused at a rate of 15 mL/hour (6 unit/hour) until the blood sugar drops to less than 250 mg/dL, then the rate of infusion decreases to 5–7.5 mL/hour (2–3 unit/hour or 0.05 unit/kg/hour) to maintain blood sugar at 200 mg/dL until the ketoacidotic state abates
- In the absence of an intravenous infusion pump 60 unit of insulin in 500 cc of isotonic sodium chloride solution is given at a rate of 50 mL/hour with a micro drip set. The infusion rate can be modified depending on the rate of decline of blood sugar values
- The optimal rate of glucose decline is 100 mg/dL/hour
- When patient has started taking orally, change to subcutaneous (SC) insulin.

Potassium supplementation:

- Potassium should be measured Q2 hourly
- Potassium corrections are not needed in the initial 2 hours of the surgery
- Start correcting potassium only after ensuring adequate urine output
- Guidelines as to the amount of K⁺ to be given in Table 25.4.

Other measures:

- *Correction of acidosis:* Blood gas estimation is done and only if pH less than 7.10, correction of acidosis should be attempted
- Dose of HCO₃ = 1 mEq/kg
- 50 mmol of 8.4% bicarbonate is usually given for an adult patient. Usually acidosis will correct itself slowly as the sugar comes down
- Give high flow oxygen therapy—100% O₂
- Endotracheal intubation—if patient is unconscious
- Urinary catheterization to assess urinary output
- Central venous pressure (CVP) line to estimate IV volume.

EMERGENCY SURGERY IN THE DIABETIC PATIENT

The most common emergency procedures performed in diabetic patients are trauma, appendectomy, incision and drainage procedures and lower extremity amputation for ischemia or infection. Very often, these diabetics may have significant metabolic decompensation, including ketoacidosis. Frequently, very little time is available for stabilization of the patient,

but even a few hours may be sufficient for correction of any fluid and electrolyte disturbance that are potentially life-threatening. It is futile to delay surgery in an attempt to eliminate ketoacidosis completely, if the underlying surgical condition will lead to further metabolic deterioration. The likelihood of intraoperative cardiac arrhythmias and hypotension resulting from ketoacidosis will be reduced if volume depletion and hypokalemia are at least partially treated.

SPECIAL CLINICAL SCENARIOS

- *In neurosurgery:* Hyperglycemia at the time of cerebral ischemic insults is associated with a poor outcome. It is thought that the extra glucose allows greater intracellular lactate accumulation and a more severe acidosis. Therefore, blood glucose should be very carefully kept within the normal range during neurosurgical procedures.
- *In cardiopulmonary bypass:* Both morbidity and mortality are higher in diabetics than nondiabetic patients. A dextrose-free pump prime is recommended; very high insulin requirements occur in the rewarming period. Hypothermia and stress reactions decrease the response to insulin and result in marked hyperglycemia.
- *Surgical removal of infected tissue* (i.e. amputation of gangrenous limb, incision of abscess, etc.) results in dramatic reductions in insulin requirement (and the danger of hypoglycemia) postoperatively.
- *The pregnant diabetic* requires very close monitoring and is normally induced early. Separate insulin and dextrose infusions are commonly used, with reduced insulin requirements after delivery.
- *Child with diabetes:*
Very short anesthesia—such as simple dental treatments, examination under anesthesia (EUA), etc.
 - During a short anesthesia, the greatest risk to the patient is that of hypoglycemia, and hence, careful adherence to protocol is needed to minimize this risk.
 - Longer operations or children with poorly controlled diabetes ($HbA1c \geq 10\%$)
 - Children with poorly controlled diabetes and those undergoing longer procedures, which are likely to be more physiologically stressful, are at higher risk of ketoacidosis. Admit the day before, arrange for child to be first on the list and diligently manage glucose levels with insulin infusions and prevent ketosis.

POSTOPERATIVE MANAGEMENT OF DIABETIC PATIENTS

Blood Glucose Monitoring and Control

- In diabetic patients undergoing minor surgeries,
 - Postoperative monitoring: 2 hourly until eating then 4 hourly
 - Restart normal SC insulin regime/OHA with first meal
- In diabetic patients undergoing major surgeries,
 - Postoperative monitoring: 2 hourly.

Control of infections: Prophylaxis with antibiotics in infected cases, good preoperative patient preparation, proficient and aseptic surgical technique and proper postoperative wound care with appropriate antibiotic coverage are recommended for diabetics subjected to surgery.

Surgical Wound Management

It has long been recognized that wound healing is impaired in diabetic patients. This observation has been repeated in animal models where it has been shown that pre- and postoperative glycemic control with insulin, not postoperative alone, can restore normal anastomotic healing. Recent work suggests that better glycemic control with insulin infusions may reduce the incidence of wound infections along with routine wound care methods in diabetic patients who have undergone surgery. This observation is supported by a study which demonstrated better preservation of neutrophil function with “aggressive” glycemic control using an insulin infusion, compared with intermittent therapy, in diabetic surgical patients.

SUMMARY

- It is well known that diabetic patients are at greater risk of perioperative mortality and morbidity after major surgery and have a higher incidence of coexisting disease
- A more aggressive approach to glycemic control in the perioperative period results in better wound healing, lower morbidity and shorter hospital stays. Tight metabolic control in the perioperative period is imperative and is a goal which is attainable in most patients
- Careful attention to clinical signs and rapid action to prevent even suspected hypoglycemia perioperatively should see them safely through their surgery
- Regional techniques are often safer than general anesthesia, but require the same vigilance
- It is important to avoid dosing errors.

As Jacober and Sowers have said, perioperative care of the patients with diabetes is more art than clinical science, but minimal disruption of the regimen tends to be the easiest course of managements.

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SELF-ASSESSMENT

1. The choice of anesthesia in a diabetic patient:

- (a) General anesthesia
- (b) Regional anesthesia
- (c) None of the above
- (d) Anesthesia is contraindicated

2. Preoperative management of a diabetic patient include:

- (i) Preoperative assessment
- (ii) Deciding on the type of surgery
- (iii) Premedication
 - (a) i and ii
 - (b) i and iii
 - (c) iii only
 - (d) All of the above

3. Identify the end-organ damage if the patient has the following:

- Gastroparesis
- Fall in systolic blood pressure on standing is more than 20 mm Hg
- Increase in heart rate in response to deep breathing is less than 10 bpm
 - (a) Autonomic neuropathy
 - (b) Peripheral neuropathy
 - (c) Acute gastroenteritis
 - (d) None of the above

4. Premedication in a diabetic patient going for surgery:

- (a) Metformin
- (b) Metoclopramide
- (c) Sulphonylureas
- (d) None of the above

5. Limited joint mobility syndrome is also called:

- (a) Stiff joint syndrome
- (b) Lax—joint syndrome
- (c) Arthritis syndrome
- (d) All of the above

6. Aims of management of diabetic patient during surgery/anesthesia are all of these *except*:

- (a) Avoid hyperglycemia more than 250 mg%
- (b) Avoid hypoglycemia less than 70 mg%
- (c) Avoid ketosis
- (d) Promote lipolysis and proteolysis

7. According to the intraoperative insulin administration—CMC regimen the amount of insulin to be given if the blood sugars are in the range of 250–300 is:

- (a) 1 unit actrapid in 100 ml 5% glucose over 1 hour
- (b) 2 unit actrapid in 100 ml 5% glucose over 1 hour
- (c) 3 unit actrapid in 100 ml 5% glucose over 1 hour
- (d) 4 unit actrapid in 100 ml 5% glucose over 1 hour

8. Drugs used in treating arrhythmias in a diabetic patient undergoing surgery are:

- (i) Atropine
 - (ii) Propranolol
 - (iii) Labetalol
- (a) i and ii
 - (b) i and iii
 - (c) All of the above
 - (d) None of the above

9. Choose the correct statement:

- (a) Patient positioning during anesthesia has no significance whatsoever in the operative management of a diabetic patient
- (b) Diabetic patients are prone for increased cardiovascular instability during anesthesia
- (c) Diabetic patients should always be placed last on the operating list
- (d) On the day of operation, the diabetic patient should take his/her morning dose of insulin

10. Monitoring of a diabetic patient intraoperatively includes:

- (a) SpO₂ monitoring
- (b) NIBP Monitoring
- (c) Hourly RBS estimation
- (d) All of the above.

CHAPTER

26

Obesity with Diabetes

Nitin Kapoor, Inian Samarasam, Nihal Thomas

*“Lack of Activity,
May lead to Obesity
While drug therapy seems inert
With surgery we like to flirt”*

The prevalence of obesity is increasing more rapidly than that of diabetes leading on to the combined pandemic called *diabesity*. This has not only overburdened the health care system of our country but also had a big impact on the quality of life of these individuals. Not unlike diabetes and hypertension, obesity is also indeed a chronic disease requiring patient specific, realistic and sustainable therapeutic strategies.

DEFINITION OF OBESITY

Obesity can be defined by different parameters as shown in Table 26.1, however the most commonly used methods are either body mass index (BMI) or waist circumference. The criterion for diagnosis of obesity in Asian adults is based on the guidelines published by the World Health Organization (WHO) in collaboration with the international association for the study of obesity and the international obesity task force in February 2000. For children the criteria are based on BMI percentiles which are summarized in Table 26.2. However with the understanding of the YY Paradox, more and more evidence is emerging against consideration of BMI as the single best measure of obesity.

Table 26.1: Parameters used to define obesity.

Parameter studied	Criteria for overweight/Obesity
Body mass index	> 23 kg/m ²
Waist circumference	> 90 cm in men, > 80 cm in women
Waist-hip ratio	0.9 in men and 0.8 in women
Body fat percentage*	> 25% in men; > 30% in women

*as measured by dual-energy X-ray absorptiometry (DXA)

Table 26.2: Criteria for using body mass index (BMI) as a measure of obesity in children and adults.²

Category	Children	Adults	
Underweight	BMI < 5th Percentile for age	<18.5 kg/m ²	
Normal weight	BMI ≥ 5th to 85th percentile for age	18.5–22.9 kg/m ²	
Overweight	BMI ≥ 85th to 95th percentile for age	23–24.9 kg/m ²	
Obesity	BMI ≥ 95th percentile for age	Obesity Grade 1	25–29.9 kg/m ²
		Obesity Grade 2	30–34.9 kg/m ²
		Obesity Grade 3	> 35 kg/m ²

Table 26.3: The prevalence of metabolic syndrome in parents and children from a semiurban population in Tamil Nadu, India (Unpublished data, Rahul Baxi, Nihal Thomas).

Variables	Father n = 107	Mother n = 151	Child n = 201
Waist	76 (71.03%)	127 (84.11%)	40 (19.90%)
AC Glucose	59 (55.14%)	66 (43.71%)	45 (22.39%)
Triglycerides	37 (34.58%)	28 (18.54%)	3 (1.49%)
Systolic BP	43 (41.19%)	25 (16.56%)	14 (6.97%)
Diastolic BP	44 (44.12%)	40 (26.49%)	17 (8.46%)
HDL	58 (54.21%)	110 (72.85%)	46 (22.89%)

(HDL: High-density lipoprotein; BP: Blood pressure).

*According to IDF definition for MetS in adults for fathers and mothers and IDF definition for MetS in adolescents for children.

In previously published data from our center, we explored body composition and metabolic parameters among rural adolescent school children around Vellore (Tamil Nadu, India). We identified a simple method of utilizing skin fold thickness as an important tool in predicting metabolic anomalies in these children. Hyperglycemia was also significantly associated with abdominal skin fold thickness in this cohort.¹

EPIDEMIOLOGY OF OBESITY AND ITS IMPACT ON DIABETES

Obesity is a common problem not only in the metropolitan cities but even data from a semiurban city like Vellore has revealed that 71% of men and 84% of women have an abnormal waist circumference and about 20% of their children also fall in the same category (Table 26.3).

Worldwide prevalence also seems to increase as estimated prevalence rates for India may amount to as high as a quarter of India's population being obese by 2015.

Also data from the Vellore birth cohort has shown marked increase in the incidence of obesity over a period of 12 years, more so in women where by the end of 2002 almost three-fourths of urban women were diagnosed to have obesity (Fig. 26.1).

ETIOPATHOGENESIS OF OBESITY

The pathophysiology of obesity is essentially due to the loss of balance between a higher energy intake and a lower energy expenditure in the background of genetic susceptibility as

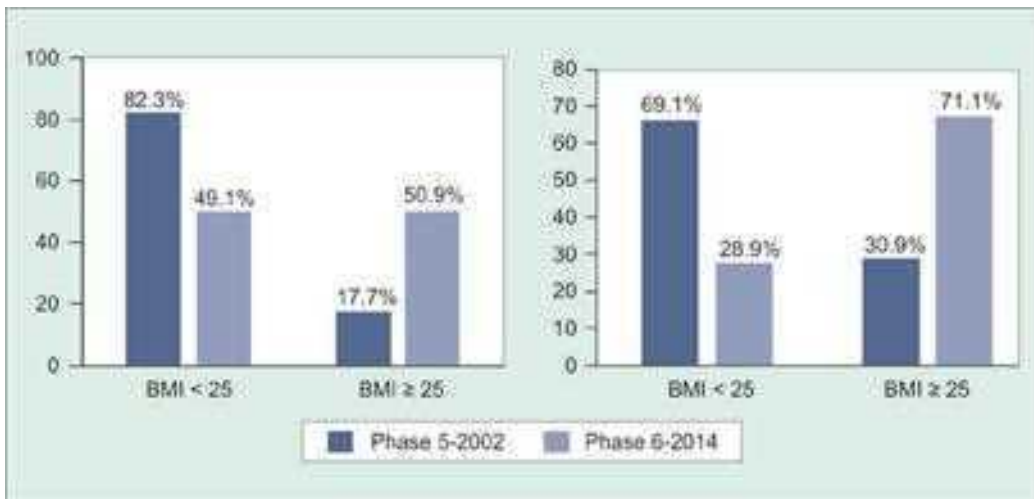


Fig. 26.1: Rise in prevalence of obesity in an urban population in Tamil Nadu, India (Data from the Vellore Birth Cohort; N = 553).

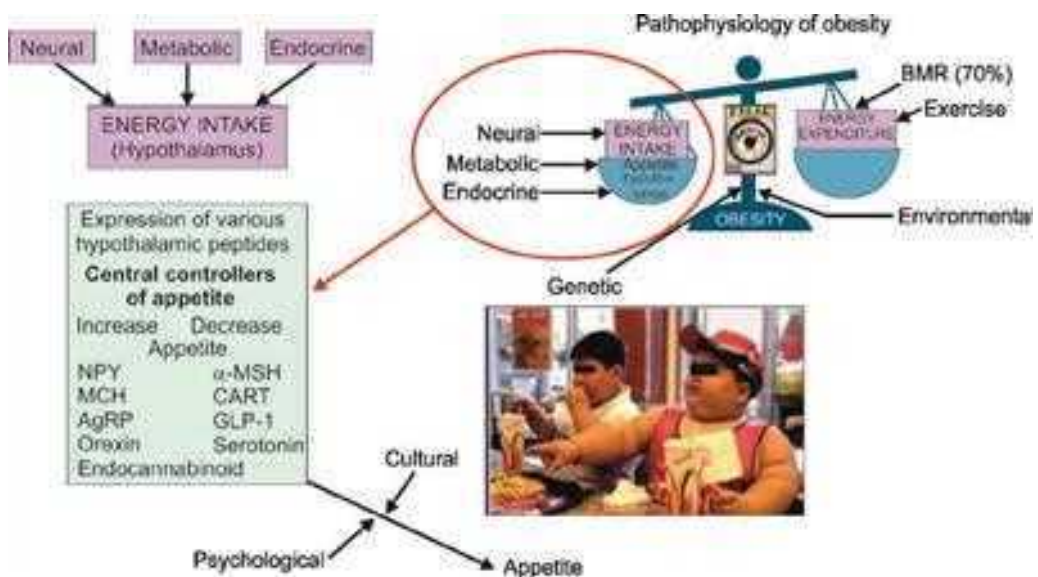


Fig. 26.2: Factors affecting energy intake.

(NPY: Neuropeptide Y; MCH: Melanin-concentrating hormone; AgRP: Agouti-related protein; MSH: Melanocyte stimulating hormone; GLP-1: Glucagon-like peptide-1; BMR: Basal metabolic rate).

summarized in Figures 26.2 and 26.3. Amongst the genetic susceptibility we have found an association between genetic variants in FTO (rs9939609) and near MC4R (rs17782313) with obesity- and type 2 diabetes mellitus (T2DM)-related traits. The FTO locus displayed significant associations with obesity-related anthropometric traits. There was a per allele increase of

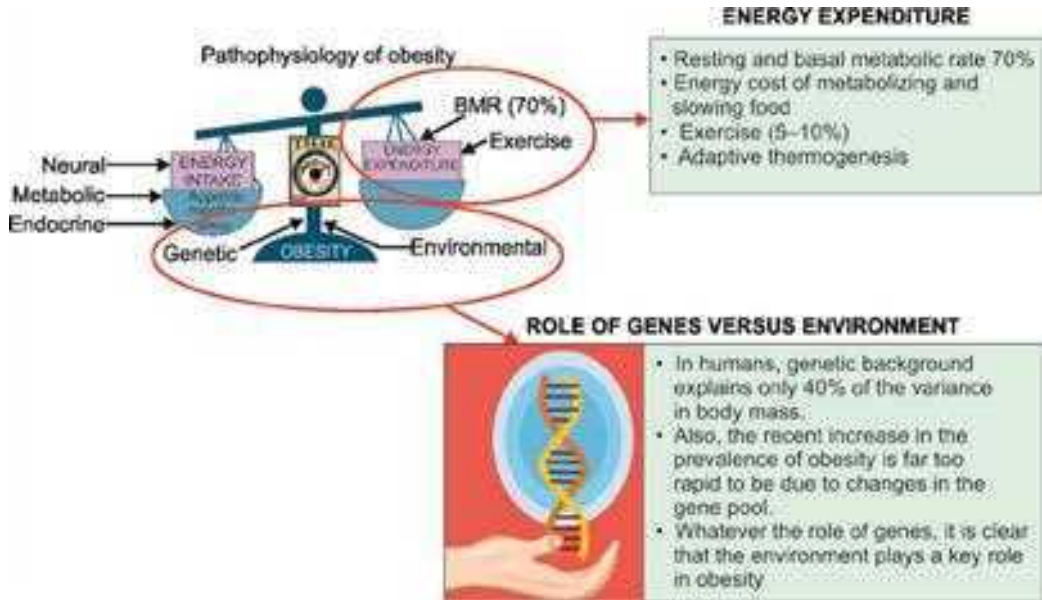


Fig. 26.3: Factors affecting energy expenditure. (BMR: Basal metabolic rate).

1% for BMI, waist circumference, hip circumference and waist-hip ratio. The effect on obesity-related traits for FTO was seen in adulthood, but not at younger ages.³

In another study in south India a high socioeconomic status, a non-Hindu religion, sedentary life style (>2 hour/day screen time), eating out more than once/month and eating frequent fast food (> once/week) emerged as significant ($p < 0.05$) factors affecting obesity/overweight in adolescents.⁴ In another study from South India, the role of inflammatory markers like high-sensitivity C-reactive protein (hsCRP) and nitrotyrosine was highlighted in the pathogenesis of increased body fat especially in women.⁵

EVALUATION OF OBESITY

As adopted from the Canadian obesity network guidelines, the 4M framework is useful in the assessment of obesity (Fig. 26.4). Also the root cause of obesity needs to be identified in each patient as only once it is assessed appropriately, will it become possible to target that particular aspect and thereby not only help weight loss but more importantly attain long-term weight maintenance. The 4M framework listed in Table 26.4 enables the treating physician to evaluate an obese patient as a whole with respect to all causes and complications of obesity.

Investigations to be done in a Patient of Obesity

- Fasting, postprandial blood glucose, glycated hemoglobin (HbA1c), creatinine, fasting lipid profile, thyroid-stimulating hormone (TSH), assessment of cortisol axis, liver function tests, serum electrolytes

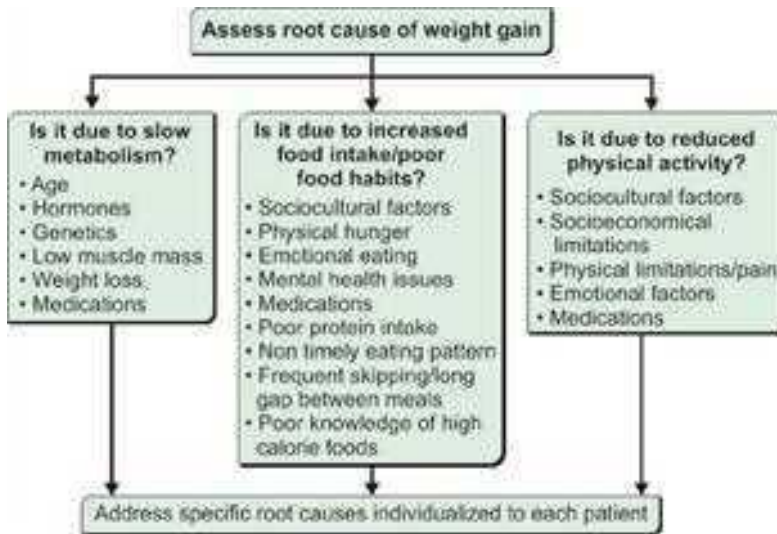


Fig. 26.4: Causes of weight gain.

Source: Modified from Sharma AM. M, M, M & M: a mnemonic for assessing obesity. *Obes Rev.* 2010;11(11):808-9.

Table 26.4: 4M framework in the assessment of the obesity.

4Ms in the assessment of Obesity			
Mental	Mechanical	Metabolic	Monetary
Cognition	Sleep Apnea	Type 2 diabetes mellitus	Education
Depression	Osteoarthritis	Dyslipidemia	Employment
Attention deficit	Chronic Pain	Hypertension	Income
Addiction	Reflux Disease	Gout	Disability
Psychosis	Incontinence	Fatty liver	Insurance
Eating disorder	Thrombosis	Gall Stones	Benefits
Trauma	Intertrigo	PCOS	Bariatric supplies
Insomnia	Plantar fasciitis	Malignancy	Weight loss programs

(PCOS: Polycystic ovarian syndrome).

Source: Modified from Sharma AM. M, M, M & M: a mnemonic for assessing obesity. *Obes Rev.* 2010;11(11):808-9.

- Uric acid
- Chest X-Ray, ECG
- Body composition analysis
- Ultrasound abdomen/upper GI endoscopy
- Sleep apnea assessment
- If diabetic, assessment of its complications.

MANAGEMENT

Management of *diabetes* begins with prevention of at risk people developing the disease followed by lifestyle modifications, medication and bariatric surgery.

Prevention

From both the diabetes prevention program and the Indian diabetes prevention program there is overwhelming evidence that lifestyle modification is very effective and even better than metformin in reducing weight and thereby reducing the risk of developing diabetes in people who are at risk. There is growing evidence that early detection and intervention by weight loss may ultimately help in the delaying the onset of diabetes if not preventing it totally.

Lifestyle Management

Though most dietary and physical activity related topics are covered in Chapter 3 and 4, another important concept to highlight in dietary advice given to obese patients with diabetes, especially in the Indian setting, is to maintain the normal recommended protein to carbohydrate ratios in each meal which they consume. This is very relevant in most Indian vegetarian diets wherein the consumption amounts to 20–30% of the recommended protein in the daily diets. The enhanced protein not only improves satiety and a reduced urge for snacking but also supports in glycemic control as shown in a previously published study.⁶

Drugs

Individuals who are obese and have diabetes may benefit for both glycemic control and weight loss with the following three available groups of antidiabetic drugs: (1) Biguanides-like metformin, (2) Incretin-based therapies (exenatide and liraglutide), and (3) Sodium-glucose co-transporter 2 (SGLT-2) inhibitors. The glucagon-like peptide-1 (GLP-1) analogs are the most potent of the lot, they need slow titration to have better tolerability. Pramlintide is another drug that has shown modest weight loss but is seldom used in the management of diabetes due to its weak antihyperglycemic effect. If these classes of drugs are unable to control blood sugars then addition of weight neutral drugs like DDP4 inhibitors alpha-glucosidase inhibitors, etc. should be considered.

Metformin in Obesity

Metformin, was originally developed to treat patients with type 2 diabetes, has also been used for management of obesity. A systematic review summarizing 14 randomized controlled trials (RCTs) has shown that metformin showed a net BMI reduction of 1.16 kg/m² (95% CI 1.6–0.73) attributable to the drug, which although small was statistically significant. Subgroup analysis showed a greater effect for those with a higher BMI at baseline (BMI >35 reduction of 1.23 vs. BMI <35 reduction of 1.05 kg/m²). Metformin dose made little difference, with 1 g daily being only marginally less effective than 2 g.⁷

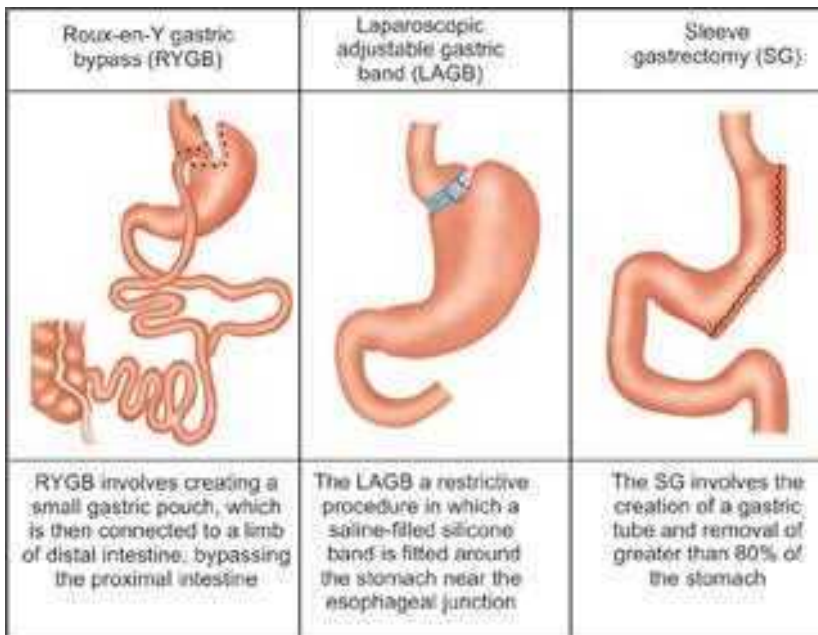


Fig. 26.5: Common bariatric surgical procedures.

Liraglutide in the Management of Obesity

The US Food and Drug Administration has approved liraglutide (3 mg/day, subcutaneous) as a treatment option for chronic weight management in addition to a reduced-calorie diet and physical activity.

This drug is approved for use in adults with a BMI of 30 or greater (obesity) or adults with a BMI of 27 or greater who have at least one weight-related condition such as hypertension, type 2 diabetes, or dyslipidemia. Results from a clinical trial that enrolled patients without diabetes showed that patients had an average weight loss of 4.5% from baseline compared to treatment with a placebo at 1 year. In this trial, 62% of patients treated with liraglutide (3 mg/day, subcutaneous) lost at least 5% of their body weight compared with 34% of patients treated with placebo.⁸

Bariatric and Metabolic Surgery

Bariatric surgery is derived from the Greek word “*Barios*” which means *weight or pressure*. Bariatric surgery has emerged as a highly effective treatment for obesity and is now increasingly recognized to have benefits in the treatment and prevention of diabetes. Bariatric surgery has become, in this way, the prototype of “metabolic surgery”.

The three most common bariatric surgical procedures are (Fig. 26.5):

1. Roux-en-Y gastric bypass (RYGB).
2. Laparoscopic adjustable gastric band (LAGB)
3. Laparoscopic sleeve gastrectomy (SG)

Table 26.5: Indications for bariatric surgery in patients with type 2 diabetes mellitus (T2DM).

Eligibility for bariatric surgery in patients with Type 2 Diabetes Mellitus				
	International diabetes Federation (IDF Criteria) 2011	American Diabetes Association (ADA Criteria) 2013	National Institute of Health & Clinical Excellence (NICE Criteria) 2006	International Federation for the Surgery of Obesity (IFSO-Asia Pacific) 2011
Recommended Priority for surgery	BMI > 40 kg/m ² BMI > 35 kg/m ² when type 2 DM and other comorbidities not controlled by medical management	No priority for any group	BMI > 50 kg/m ²	
Eligible BMI for surgery with Type 2 Diabetes Mellitus	BMI > 35 kg/m ² BMI > 30 kg/m ² when type 2 DM and other comorbidities not controlled by medical management	BMI > 35 kg/m ² when type 2 DM and other comorbidities not controlled by life style and pharmacological management	BMI > 35 kg/m ² with one weight loss responding comorbidity	BMI > 30 kg/m ² when type 2 DM and other comorbidities not controlled by medical management
Comments	To adjust BMI if of Asian ethnic origin	BMI < 35 kg/m ² only in research protocols		

Source: Ramos-Leví AM, Rubio Herrera MA. Metabolic surgery: quo vadis? *Endocrinol Nutr.* 2014;61(1): 35-46.

Roux-en-Y gastric bypass and SG result in similar magnitude of weight loss (average of excess weight lost 60–70% at 3 years), both superior to that seen with LAGB (average of excess weight lost 40–50% at 3 years).⁹

Bariatric surgical procedures also lead to improvements in glycemia in many patients with pre-existing T2DM. These surgical procedures promote greater improvements in diabetes than attributable to weight loss alone, suggesting additional physiologic mechanisms. The STAMPEDE trial (surgical treatment and medications potentially eradicate diabetes efficiently trial) compared the effects of RYGB, SG, and medical management for the treatment of type 2 diabetes in individuals with overweight or obesity. Rates of remission of type 2 diabetes were highest in the surgical groups.¹⁰

The 3-year follow-up results from the STAMPEDE trial, looking at the durability of the metabolic effects of surgery, long-term safety, quality of life and effects on diabetes related end organ disease has been recently published and the results favor the surgical group (Table 26.5).¹¹

Mechanisms by which Bariatric Procedures Help Glycemic Control

The physiologic mechanisms by which each type of surgery produces sustained weight loss and improvement in glycemia remain incompletely understood.

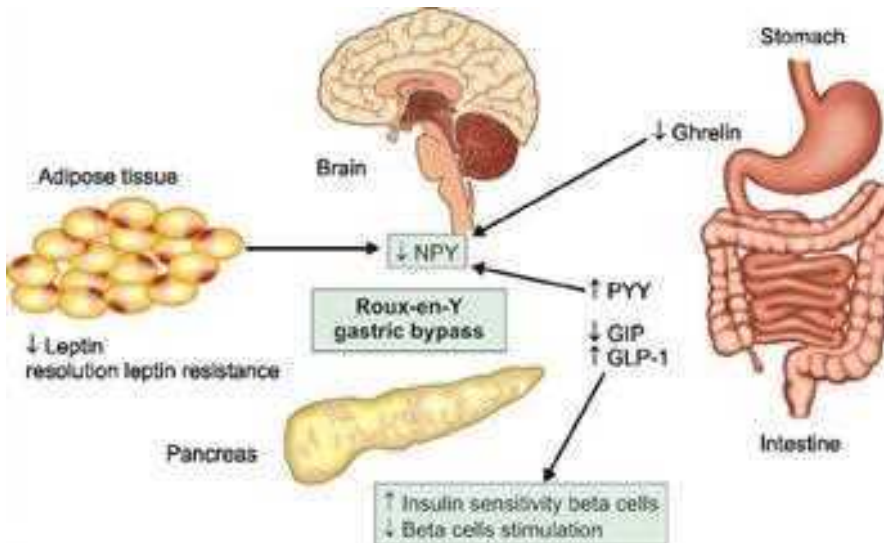


Fig. 26.6: Effects of Roux-en-Y gastric bypass bariatric surgery.

(NPY: Neuropeptide Y; GLP-1: Glucagon-like peptide-1; GIP: Gastric inhibitory polypeptide; PYY: Peptide YY).

LAGB is generally thought not to have weight-independent effects on metabolic control. Remission of diabetes after LAGB occurs gradually, in parallel with weight loss. In contrast, SG and RYGB results in very rapid improvement in sugar control and in fact this effect is seen prior to significant weight loss. Metabolic improvements are therefore greater than those predicted for the magnitude of weight lost.

The mechanisms by which RYGB improves sugar control have been most extensively studied. RYGB is a restrictive and a malabsorptive procedure. Two theories that have been put forth to explain the metabolic improvements after RYGB include the “foregut hypothesis” and the “hindgut hypothesis”. The “foregut hypothesis” refers to the metabolic effect of bypassing the duodenum and the “hindgut hypothesis” refers to the rapid delivery of the food in the terminal ileum due to the bypass effect.

The metabolic effects of SG occur without bypassing the duodenum and this is due to the substantial increase in gut peptides, comparable to that seen after RYGB. Changes that happen after these metabolic surgical procedures are also secondary to the changes in insulin secretion and insulin sensitivity. Incretins are gut peptides released following oral nutrient intake that potentiate pancreatic insulin secretion: these include GLP-1 secreted from jejunoileal L-cells and glucose-dependent insulinotropic peptide (GIP) secreted from duodenal K-cells. GLP-1 concentrations increase by a factor of 5–10 in response to nutrient challenges following RYGB.

RYGB also leads to improvements in insulin sensitivity. At 12 months, both peripheral and hepatic insulin sensitivity are improved in proportion to weight lost. However, early postoperative improvements are reported in some studies. In addition to the changes in incretin physiology, other factors such as ghrelin, peptide YY (PYY), adipokines such as leptin etc. contribute to the metabolic effects seen after these operations (Fig. 26.6).

Other mechanisms implicated in glycemic improvement after bariatric surgeries include changes in the microbiome, and in bile acid and lipid metabolism. Systemic bile acid concentrations increase after both RYGB and SG. Bile acids regulate hepatic lipid metabolism, activate nuclear transcription factors that regulate glucose metabolism.

An Approach to the Genetic Syndromes Associated with obesity is discussed in Flowchart 26.1.¹² Through these are rare causes of obesity they should be kept in mind of the classical phenotype is present (Figs. 26.7 and 26.8).

Flowchart 26.1: Approach to the genetic syndromes associated with obesity.

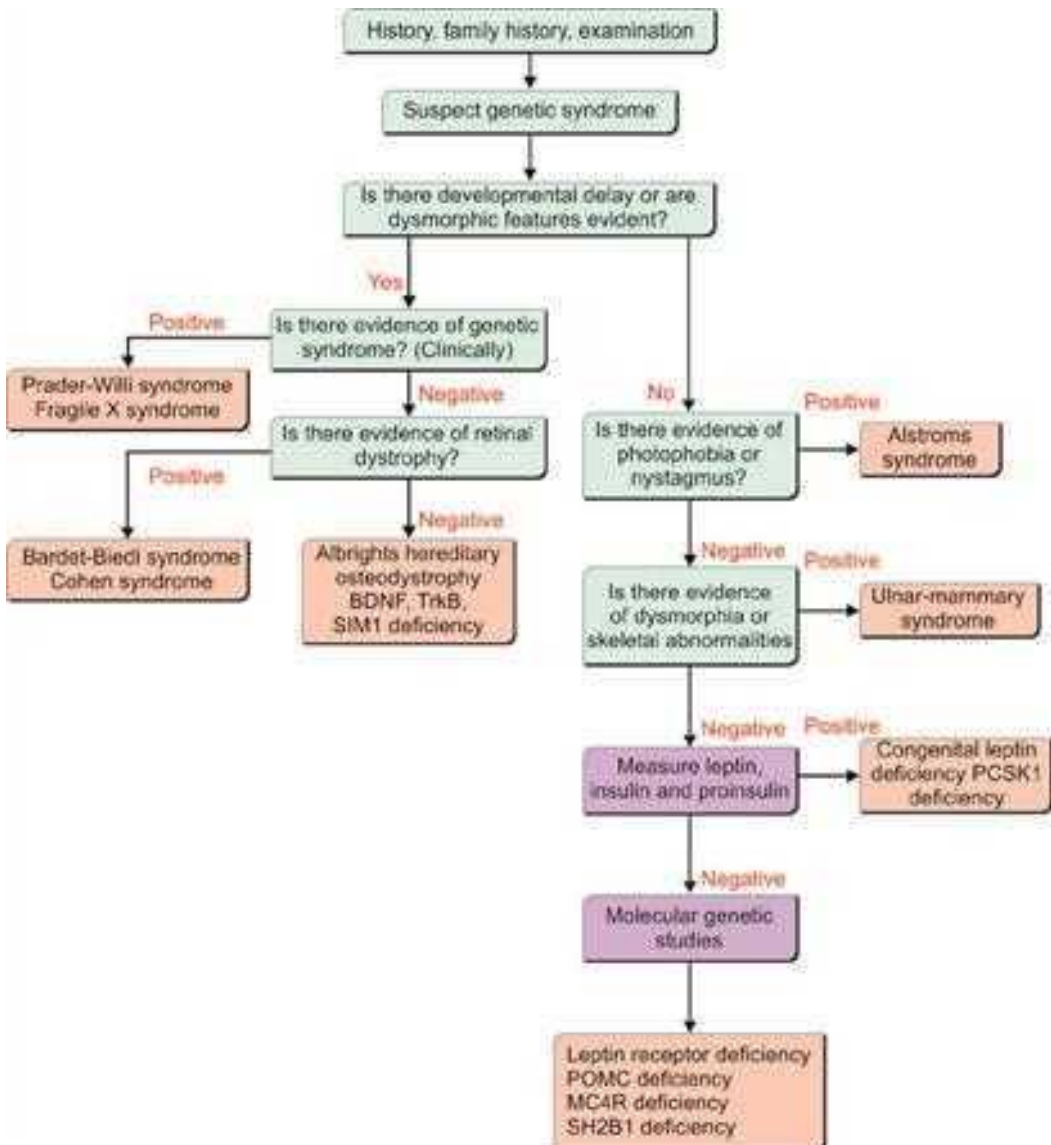
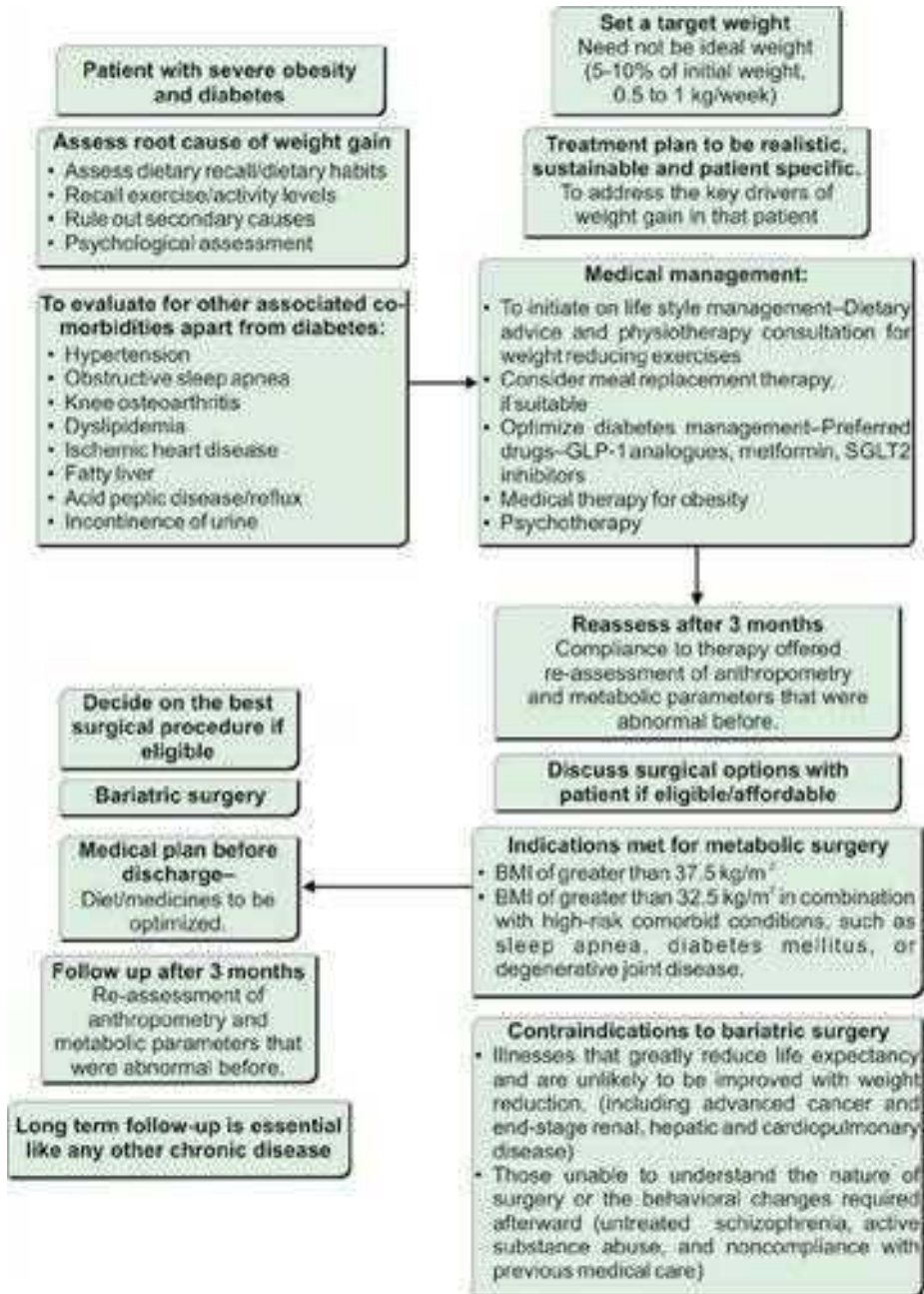




Fig. 26.7: Clinical picture of a 17-year-old boy who presented to the endocrine OPD, with complaints of progressive visual loss and new onset diabetes mellitus in the back ground of developmental delay and poor scholastic performance. He had a BMI of 30 kg/m² with signs of insulin resistance, polydactyly involving both the upper and lower limbs, hypogonadism and retinitis pigmentosa. He was diagnosed to have Bardet-Biedl syndrome.



Fig. 26.8: Clinical picture of a 12-year-old girl who presented with the history of progressive weight gain, breathlessness on exertion and nocturnal symptoms suggestive of obstructive sleep apnea. She had past history of delayed development of milestones with history of feeding difficulties initially followed by increased appetite and weight gain. Clinical pictures depict short stature with obesity associated with small hands and feet, a small mouth with a thin upper lip consistent with a diagnosis of Prader-Willi syndrome.

Flowchart 26.2: Algorithm for management of a patient with morbid obesity and diabetes.

CONCLUSION

There is a rapidly growing body of evidence to support the results of bariatric and metabolic surgery in *diabesity*. However, there are still quite a few unanswered questions in relation

to surgery. T2DM is a progressive disease, and we are yet to understand the long-term durability of postsurgical remission or the clinical benefit of a sustained period of remission. The following algorithm is a simple stepwise approach in a patient with morbid obesity and diabetes (Flowchart 26.2).

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SELF-ASSESSMENT

1. Obesity can be defined by all the following parameters *except*:

- | | |
|-------------------------|-------------------------|
| (a) Body mass index | (b) Body fat percentage |
| (c) Head circumference | (d) Skin fold thickness |
| (e) Waist circumference | |

2. The 4 Ms obesity include all *except*:

- | | |
|---------------|----------------|
| (a) Mental | (b) Mechanical |
| (c) Metabolic | (d) Mobile |

3. The three main reasons for weight gain include all *except*:

- | | |
|---------------------|-----------------------|
| (a) High metabolism | (b) Food habits |
| (c) Food intake | (d) Physical activity |

4. Following can be affected with obesity *except*:

- (a) Gout
- (b) Malignancy
- (c) Intertrigo
- (d) Psychosis
- (e) Hypersomnia

5. All of the following are types of bariatric surgery *except*:

- (a) RYGB
- (b) LAGB
- (c) SG
- (d) Liposuction

6. All of the following are genetic causes of obesity *except*:

- (a) POMC deficiency
- (b) MC4R deficiency
- (c) SH2B1 deficiency
- (d) SDH-B deficiency

7. All of the following are contraindications for bariatric surgery *except*:

- (a) Untreated schizophrenia
- (b) Active substance use
- (c) ESRD
- (d) Obstructive sleep apnea

8. All of the following investigations are to be done before bariatric surgery *except*:

- (a) Chest X-Ray
- (b) Upper GI endoscopy
- (c) ECG
- (d) DXA Scan

9. All of the following drugs are useful in obesity with diabetes

- (a) Biguanides
- (b) Pramlintide
- (c) Exenatide
- (d) Glipizide

10. All are features of Bardet-Biedl syndrome *except*:

- (a) Polydactyly
- (b) Hypogonadism
- (c) Retinal detachment
- (d) Good scholastic performance

CHAPTER

27

Laboratory and Analytical Methods

Geethanjali Arulappan, Charles Stephen

*“A fancy lab is not what you need,
With fancy gadgets that take the lead,
But what does play a major role,
Is discipline and quality control”*

The role of the clinical biochemistry laboratory is vital in both the diagnosis and management of diabetes mellitus. The main aim of this chapter is to give the readers a basic appreciation of the underlying principles and practical strategy of the analytical and preparative techniques that are fundamental in carrying out basic tests, which aid in the management of diabetes.

INTRODUCTION

Laboratories play an important role in the screening, diagnosis and management of diabetes. It is therefore necessary to know the basic functioning and the different quality procedures and measures that a good laboratory practices. Accuracy and precision are the two watchwords for a laboratory.

Accuracy refers to the closeness of a laboratory's result to the true value. It is expressed in percent bias. Lesser the bias better is the result. Accuracy is more important in the diagnosis of a disease. Precision refers to the reproducibility of a result. It is expressed in percent CV (coefficient of variation). Precision is very important in the monitoring the progression/regression of the disease.

A laboratory's prime aim should be to deliver quality results in time for the physicians to make decision. To achieve this goal a laboratory should follow standard operating procedures (SOP), identify errors and rectify them. Even the best laboratory is not error free, and identifying the errors is an important task of the laboratory. The clinician should have an insight into the common preanalytical errors that may confound the commonly done tests.

LABORATORY ERRORS

Laboratory errors are of three types:

- *Preanalytical*: All the errors that occur before the sample undergo actual analysis
- *Analytical errors*: Any error that occur at the time of analysis
- *Postanalytical error*: Errors that occur after the analysis till the final reporting. Mostly derived from inappropriate interpretation and utilization of laboratory results.

The most frequent are the preanalytical errors and are represented by an inappropriate choice of laboratory tests or panel of tests. Guidelines for sample collection, transportation, identification and pretreatment as well as rejection criteria should be drawn by each laboratory and followed strictly to minimize the preanalytical errors.

PREANALYTICAL, ANALYTICAL AND POSTANALYTICAL ERRORS

A study on the “Mistakes in a stat laboratory types and frequency” (Mario Plebania and Paolo Carraro, 1997) conducted in US identified that 68.2% of the errors are preanalytical, 13.3% analytical and 18.5% are of the postanalytical type. Although most of the mistakes did not affect patients’ outcomes, laboratory errors were associated with further inappropriate investigations, thus resulting in an unjustifiable increase in costs. In addition, laboratory errors were associated with inappropriate care and modification on therapy in some patients. The authors also concluded that “promotion of quality control and continuous improvement of the testing process, including preanalytical and postanalytical phases, seems to be a prerequisite for an effective laboratory service” (Table 27.1).

Control of Preanalytical and Postanalytical Errors

It is very difficult to establish effective methods for monitoring and controlling preanalytical variables because many of the variables are outside the laboratory areas and requires the coordinated effort of many individuals and hospital departments. These errors occur at different levels.

At the Test Selection

The highest frequency of errors occurs with the use of handwritten labels and request forms. While requesting for a test, the patient should be informed about the prerequisites for the test, such as fasting, time of collection, etc. To overcome these errors, double-checking should be carried out and the use of bar code technology would significantly reduce these errors. Delayed and lost test requisitions, specimens and reports can be major problems for laboratories.

At the Phlebotomy

Identification of the right patient, verifying the hospital identification number, recording the actual times of specimen collection, will minimize the errors.

While preparing the patient for the test, many factors such as, recent intake of food, alcohol, drugs, smoking, exercise, stress, sleep and posture during specimen collection should be considered. The laboratory must define the instructions and procedures and also ensure compliance with these instructions. Efforts should be made to correct non-compliance.

Table 27.1: Laboratory tests process and their potential errors.

<i>Process</i>	<i>Potential errors</i>
<i>Preanalytical phase</i>	
Test ordering	Inappropriate test
	Handwriting not legible
	Incorrect patient identification
	Special requirements not mentioned
Specimen acquisition	Incorrect tube or container
	Incorrect patient identification
	Inadequate volume of specimen
	Invalid specimen (hemolyzed or diluted with IV fluids)
	Specimen collected at wrong time
	Improper transport conditions
<i>Analytical phase</i>	
Analytical measurement	Instrument not calibrated correctly
	Specimens mix-up
	Incorrect volume of specimen
	Interfering substances present
	Instrument precision problem
	Conversion factors
Test reporting	Wrong patient identification
	Report not legible
	Report delayed
	Transcription error
<i>Postanalytical phase</i>	
Test interpretation	Interfering substance not recognized
	Precision limitations not recognized
	Delta check not available

During collection of the specimen, many errors could occur such as prolonged tourniquet application, collecting blood from an arm into which an intravenous infusion is fixed, transferring the blood into the container through the needle that will cause hemolysis and using wrong containers and incorrect preservatives. To monitor and control these problems, specially trained laboratory team should be assigned at specimen collection. The identification of the person collecting a specimen should be mentioned on the slip or in a register.

Sample rejection criteria should be well-defined.

At Transport

In big hospitals where the sample collection is away from the testing laboratory, the samples are transported by different ways. Some samples need to be sent in ice, some should reach the laboratory within a stipulated time period, some need to be protected from light, etc. These precautions should be followed correctly.

At the Laboratory

The samples received at the laboratory should be cross-checked with the request for the correct patient ID as well as the test requested. The time allowed for complete clotting, centrifuging steps, and storage conditions all play an important role in the final result. Falling short in any of the preanalytical procedure will interfere with the result.

At the Reporting (Postanalytical)

A substantial risk of transcription error exists from manual entry of data even with double-checking of the results; computerization will reduce this type of transcription error. When results are delivered through telephone, the receiving person should be asked to repeat the results/values to confirm.

Clinicians should be encouraged to report clinically inconsistent results as well as to cross check with the laboratory in case the results are prominently abnormal for the first time and are not in line with the clinical findings.

Control of Analytical Errors

There are many analytical variables such as the water quality, calibration of analytical balances, calibration of volumetric pipettes, stability of electrical power, temperature of heating baths, refrigerators, freezers and centrifuges—all must be carefully controlled. The analytical errors are of two types—random errors and systemic errors.

Random errors are of unknown origin and very difficult to identify or avoid. It is mostly identified by the clinicians since it may not correlate with their clinical findings.

Systemic errors can be easily identified by a good laboratory person since it will show a trend in the results. All the results in that batch of samples will be affected and the use of quality control sample will identify it.

Quality Control

Conformance to the requirements of user or customers is quality. Quality control gives reliability of the information about patients in the form of correct laboratory results. Quality control is intended to improve the reliability of laboratory results.

Quality control is primarily concerned with the study of errors and the procedures used to recognize and minimize them. It helps to reduce errors and to give both the laboratory and the clinician confidence in the results.

Specimens that are analyzed for quality control purposes are called “control materials/control samples”. These materials are required to be stable, available in aliquots or vials, and amenable to being analyzed periodically over a long time. There should be little vial-to-vial variation so that differences between repeated measurements are attributed to the analytical method alone.

The quality control systems are of two types: Internal quality control and external quality control/assurance.

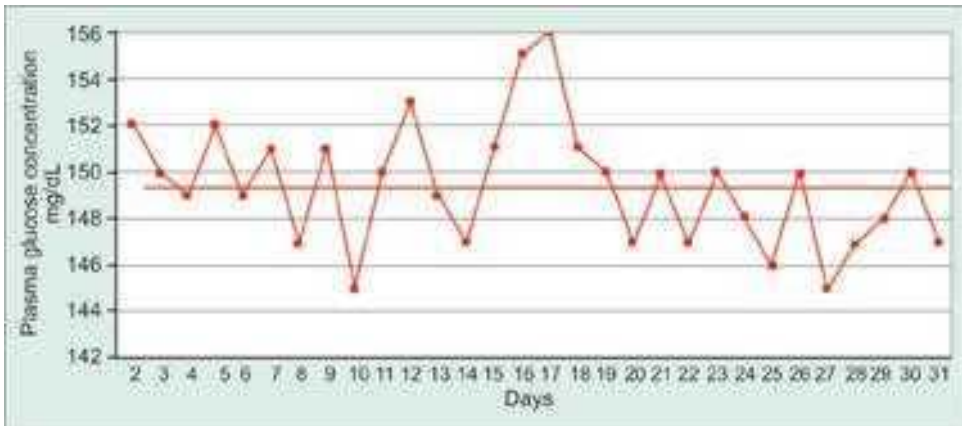


Fig. 27.1: Levey-Jennings chart for glucose (95% confidence limits 149 ± 7 mg%).

Internal Quality Control

The performance of analytical methods must be monitored by analyzing specimens (quality control samples) whose concentrations are known and then by comparing the observed values with known target values. The target values are usually represented by an interval of acceptable values, or upper and lower limits for control (control limits). The mean value is the target value; ± 2 SD are accepted control limits. When the observed values fall within the control limits, the analysis is working properly and when the observed values fall outside the control limits, the analysts should be alerted to the possibility of problems in the analysis. These data are plotted in a “Levey-Jennings” chart that displays the values in a graphical manner (Fig. 27.1).

External Quality Control/Assurance

The main aim of the external quality assurance scheme is to help the laboratory recognize where they stand in comparison with the other laboratories with in the country or internationally. There are many external quality assurance schemes that are commercially available for the clinical laboratories.

ROLE OF LABORATORY IN DIABETES MANAGEMENT

As mentioned earlier, the laboratory plays an important role in diabetes management. There are a set of test that are routinely done in most of the laboratories, and there are advanced tests done in tertiary care hospitals and are listed in Tables 27.2 and 27.3.

Acute Management: The parameters indicated in the Table 27.2 are frequently measured to guide clinicians in treatment to restore euglycemia and correct other metabolic disturbances.

Chronic Management: Measurement of plasma glucose and glycated proteins provides an index of short- and long-term glycemic control, respectively. The detection and monitoring

of complications are achieved by assaying urea, creatinine, urinary albumin excretion and serum lipids. Measuring C-peptide or insulin concentration can monitor the success of newer therapies, such as islet or pancreas transplantation.

Table 27.2: Tests recommended in diabetic patients.

<i>Routinely recommended tests</i>	<i>Advanced techniques for the assessment and control of diabetes</i>
<ul style="list-style-type: none"> • Fasting plasma glucose • Postprandial plasma glucose • Glycosylated hemoglobin (HbA1c) • Serum creatinine/urea • Fasting lipid profile 	Autoantibody standardization <ul style="list-style-type: none"> - Islet cell antibodies - GAD - IA2 - Insulin autoantibodies
<ul style="list-style-type: none"> • Fructosamine • Urine microalbumin • Urine ketones • Urine glucose 	Insulin levels C-peptide IV glucose load Clamp (euglycemic-hyperinsulinemic clamp)
<i>In pregnancy</i>	<i>In childhood and adolescents</i>
<ul style="list-style-type: none"> • Glucose challenge test • Oral glucose tolerance test 	Genetic testing MODY evaluation
<i>In management of acute complications of diabetes</i>	
<ul style="list-style-type: none"> • Blood and urine ketones • Acid-base status (pH, HCO₃) • Lactate • Other abnormalities related to cellular dehydration or therapy—sodium, potassium, phosphate and osmolarity 	

Table 27.3: Role of the laboratory in diabetes mellitus at tertiary care level.

IN DIAGNOSIS	
<i>Preclinical (screening)</i>	<i>Clinical</i>
1. Immunological markers	1. Plasma glucose
<ul style="list-style-type: none"> • ICA (Islet cell antibodies) • IAA (Insulin autoantibodies) • GAD autoantibodies • (Glutamic acid decarboxylase) • Protein tyrosine phosphatase antibodies (IA2) • Genetic markers (e.g. HLA) 	
2. Insulin secretion	2. Blood, urine ketones
<ul style="list-style-type: none"> • Fasting • Pulses • In response to glucose challenge 	3. Insulin
3. Plasma glucose	4. C-Peptide

Contd...

Contd...

IN MANAGEMENT	
<i>Acute</i>	<i>Chronic</i>
1. Plasma glucose	1. Plasma glucose
2. Blood and urine ketones	2. HbA1c
3. Acid-base status (pH, HCO ₃)	3. Fructosamine
4. Lactate	4. Urinary albumin excretion
5. Other abnormalities related to cellular dehydration or therapy—sodium, potassium, phosphate and osmolarity	5. Evaluation of complications creatinine, cholesterol, triglycerides
	6. Evaluation of pancreas transplant insulin, C-Peptide

AVAILABLE ASSAYS

Plasma Glucose

Preanalytical Considerations

Blood should be drawn in the morning after an overnight fast of minimum 8 hours. Glucose concentrations decrease with time after the sample is drawn because of glycolysis. This can be prevented by inhibiting the enzyme enolase with sodium fluoride. This can be used alone or more commonly with anticoagulants such as potassium oxalate, EDTA, citrate or lithium heparin. The glucose concentration is stable in whole blood for 72 hours at room temperature in the presence of fluoride. In separated, nonhemolyzed sterile serum without fluoride, the glucose concentration is stable for 8 hours at 25°C and 72 hours at 4°C.

Glucose can be measured in whole blood, serum, or plasma, but plasma is recommended for diagnosis. The molality of glucose in plasma and whole blood are identical. Glucose concentration in heparinized plasma is reported to be 5% lower than the serum value.

Methods and Analytical Considerations

In the past, glucose analysis was often performed with relatively non-specific methods based on reduction properties of glucose resulting in falsely increased values.

Folin-Wu and Ferricyanide methods based on this reduction property of glucose are the oldest but affected by the presence of number of other reducing substances like glutathione, ascorbic acid and uric acid to produce falsely high values. These methods are no more in use.

Orthotolidine method uses acetic acid, and the chemical itself is carcinogenic and hence it is not recommended for routine use. This method is still used by some laboratories in India.

The enzymatic reference method for glucose is the hexokinase/glucose-6-phosphate-dehydrogenase. But, since the reagents are very expensive, the other enzymatic GOD-POD method is widely used.

GOD-POD method uses glucose oxidase and peroxidase with phenol and para-amino antipyrine as chromogens. The red color produced is measured with a photometer/spectrophotometer. The reaction catalyzed by GOD is highly specific whereas the POD catalyzed

reaction is less specific. High concentration of uric acid, ascorbic acid, bilirubin, hemoglobin, tetracycline and glutathione inhibit the reaction causing a negative error in the result. Urine contains high concentrations of substances that interfere with the peroxidase reaction (such as uric acid), producing falsely low results. GOD method should therefore not be used for urine. Glucose dehydrogenase method, which uses the enzyme glucose dehydrogenase and NAD is highly specific for glucose and shows no interference from substances normally found in plasma.

Recommended Results

Glucose is most often measured in venous serum/plasma.

Normal range for a fasting adult is around 70–100 mg/dL.

Whole blood glucose is around 5–10% lower than serum glucose. This is because glucose passes freely in and out of the red blood cells, which have a lower content of water than plasma does.

Capillary blood (as from a fingerprick, essentially arterial blood) usually has around 5 mg/dL more glucose than venous blood.

After carbohydrate loading (as during a glucose tolerance test), this difference may increase to 20–70 mg/dL because of increased glucose utilization by peripheral tissues.

Oral Glucose Tolerance Test

It is a provocation test to check the ability of the body to metabolize a known load of glucose. OGTT helps in the differential diagnosis of people with impaired glucose tolerance and with diabetes or latent diabetes. OGTT is more sensitive than fasting plasma glucose in the diagnosis of diabetes.

The recommended load of glucose is 75 g for adults and 1.75 g/kg body weight up to a maximum of 75 g for children.

The person undergoing this test should have normal diet for the previous three days and then have a 12-hour fast before the test. After the collection of the fasting sample, the person is asked to drink the glucose solution with 10–15 minutes time period. The second sample is collected after 120 minutes. OGTT can be affected in conditions like surgery, infection, malabsorption, smoking, certain drugs like steroids, estrogens, thyroxine, phenytoin, etc.

Glycated Hemoglobin (GHb, HbA1c)

Preanalytical Considerations

Blood can be obtained by venipuncture or by fingerprick capillary sampling. Blood tubes should contain anticoagulant as specified by the manufacturer of the HbA1c assay. (EDTA can be used unless otherwise specified). Sample stability is assay specific. It is recommended that the HbA1c assays that are used, should have an inter-assay CV less than 5%. At least two control materials with different mean values should be analyzed as an independent measure of assay performance. The patients need not be fasting to give a specimen for HbA1c.

Methods and Analytical Considerations

Hemoglobin A1c concentration represents the integrated values for glucose over the preceding 6–8 weeks. This provides an additional criterion for assessing glucose fluctuations and are unaffected by recent exercise or food ingestion.

There are more than 30 different methods for the determination of HbA1c. These methods separate HbA1c from hemoglobin using techniques based on charge difference (ion exchange chromatography, HPLC, electrophoresis or isoelectric focusing), structural difference (affinity chromatography or immunoassay) or chemical analysis (photometry, or spectrophotometry). All methods express the HbA1c as a percentage of total hemoglobin.

Based on several studies, a consensus suggests a reference range of 4–6% of HbA1c for apparently healthy subjects. The treatment goal in adult with diabetes should be near normal with HbA1c value less than 7%. The interpretation of HbA1c depends on the lifespan of red blood cells. Patients with hemolytic disease or conditions with shortened red blood cells survival exhibit a substantial reduction in HbA1c. Similarly, individuals with recent sufficient blood loss have falsely low values owing to higher fraction of young erythrocytes. High HbA1c concentrations have been reported in iron deficiency anemia, probably because of the high proportion of old erythrocytes. Depending on the particular hemoglobinopathy and assay method, results may be spuriously increased or decreased. Another source of error is carbamylated hemoglobin. This is formed by attachment of urea that is present in large amounts in renal failure. Pre HbA1c (labile intermediates) may be increased, especially in the electrophoresis and ion exchange methods and produce misleading high values. The labile fraction changes rapidly with acute change in blood glucose concentration and thus is not an indicator of long-term glycemic control.

Recommended Results

Normal ranges often vary among laboratories. The usual range is 4–6%.

Serum Creatinine

Methods and Analytical Considerations

In Jaffe method, creatinine forms a complex with picric acid in alkaline medium to form an orange color product. A significant negative error is noted when bilirubin is present in the specimen above the concentration of 10 mg/dL. Hence, a sample blank correction should be made to correct for this interference, which produces a false negative value. Reports on acetoacetate interference vary from negligible to an increase of 3.0 mg/dL in the apparent creatinine value at an acetoacetate concentration of 8 mmol/L.

Recommended Results

The normal ranges are:

- Women: 0.7–1.2 mg/dL
- Men: 0.9–1.4 mg/dL.

Lipid Profile

Preanalytical: Lipid profile should be done in the fasting state because LDL and especially triglyceride concentrations are dramatically affected by food intake.

Serum Cholesterol

Methods and analytical considerations: The older methods, such as Carr-Dreker based on chemical oxidation of cholesterol, are completely replaced by newer method based on enzymatic oxidation of cholesterol. The CHOD-PAP (cholesterol oxidase—para-amino antipyrine) photometric method uses cholesterol oxidase and peroxidase enzymes. This method is accurate, precise and easy to use, but in the presence of high concentrations of bilirubin and ascorbic acid, this method can give inaccurate results.

Serum Triglycerides

Methods and analytical considerations: The enzymatic method uses lipase, glycerokinase and peroxidase. Since endogenous glycerol interferes with this method, blanking of the glycerol present in the specimen should be achieved.

High-Density Lipoprotein Cholesterol

Methods and analytical considerations: A major breakthrough in HDL cholesterol assay was reported with the introduction of homogeneous immunoassay methods, replacing earlier precipitation methods requiring manual pretreatment steps. These methods basically block the chylomicrons, VLDL and LDL particles leaving only the HDL particles to react with the reaction enzymes. Evaluation studies have demonstrated better precision, with coefficients of variation about half those of conventional pretreatment methods.

Low-Density Lipoprotein Cholesterol

Methods and analytical considerations: Following the approach similar to those used with the homogeneous methods for HDL cholesterol, homogeneous assays have been developed to measure LDL cholesterol also. The potential advantage of the homogeneous assays over the Friedewald calculation is to use it for those patients with elevated triglycerides.

Recommended results:

Optimal levels are:

- *Cholesterol:* 150–200 mg/dL
- *LDL:* Less than 100 mg/dL
- *HDL:* Greater than 40 mg/dL for men or greater than 50 mg/dL for women
- *Triglycerides:* Less than 150 mg/dL.

Urinary Albumin Excretion

Preanalytical Considerations

Acceptable samples for urinary protein excretion are timed samples for 24 hours. Untimed spot samples are used for measurement of urinary microalbumin and measurement of

albumin-creatinine ratio. For screening, a random sample for albumin measurement may be considered. Albumin is stable in untreated urine stored at 4°C or 20°C for at least 1 week.

Methods and Analytical Considerations

The microquantity of albumin in urine is measured by immunoturbidimetric assay using monoclonal antibody. The highly specific antibody complexes with albumin and forms a precipitate and the resultant turbidity is measured photometrically. Increased urinary albumin excretion is considered when the albumin concentration is above 30 mg/g creatinine in a random collection or 30 mg in a 24 hours collection. Care must be taken that the sample should not be collected after exertion, in the presence of urinary tract infection, during acute illness, immediately after surgery or after an acute fluid load. Diagnosis requires the demonstration of increased urinary albumin excretion in at least two of three tests measured within a 6-months period. Semi-quantitative assays have been recommended only for screening purposes; however, because of the low sensitivity (67–91%), their use is limited even for screening. Dye-binding and protein precipitation assays are insensitive and non-specific and should not be used. Radial immunodiffusion method requires long incubation and a high level of technical skill. Radioimmunoassay methods involve radioactive reagents with short shelf life.

Nonanalytical sources of variation: Transient increase in urinary microalbumin has been reported with short-term hyperglycemia, exercise, UTI, marked hypertension, heart failure and acute febrile illness.

Recommended Results

Results of the urine microalbumin test are measured as milligrams per day in a 24-hour-collection or as mg/g of creatinine in a random spot sample.

- Less than 30 mg is normal
- 30–299 mg defines microalbuminuria
- 300 mg or more indicates macroalbuminuria
- Without appropriate treatment, the kidneys are likely to fail within a few years of developing macroalbuminuria.

OTHER TESTS OF RELEVANCE

Ketone Bodies in Urine

Ketones are not present in the urine of normal healthy individuals eating a mixed diet. They are present in the urine of those with uncontrolled diabetes, prolonged fasting or those consuming high fat and low carbohydrate diet.

The most common method of detecting ketones in urine uses a reaction between sodium nitroprusside and acetoacetate or acetone under alkaline conditions. A lavender color is produced if the urine is positive for ketone bodies. However, this method cannot detect β -hydroxybutyrate.

Fructosamine

Many proteins are glycosylated when exposed to glucose in the blood. As albumin is the most abundant plasma protein, glycosylated albumin is the major contributor of serum fructosamine.

Assay Method

Fructosamine reduces NBT (nitroblue tetrazolium salt) to produce a purple pigment that can be measured colorimetrically. This procedure can be easily automated on chemistry analyzers.

Insulin and C-Peptide

Insulin assays are essential in various dynamic tests, such as OGTT or intravenous glucose tolerance tests, to determine the insulin response of the pancreas and the degree of insulin resistance.

Human C-peptide is a 31 amino acid chain with a molecular mass of approximately 3,020 Daltons. Metabolically inert, it originates in the pancreatic β -cells as a byproduct of the enzymatic cleavage of proinsulin to insulin.

Within limits, C-peptide levels can serve as a valuable index to insulin secretion.

Insulin and C-peptide levels can be measured by many techniques—RIA, ELISA and chemiluminescence immunoassay. The chemiluminescent immunoassay is the most popular.

It is a solid phase, two-site chemiluminescent immunometric assay (Fig. 27.2). The solid phase (bead) is coated with anti-insulin antibody that reacts with insulin (antigen) in the serum sample. Then the liquid phase that consists alkaline phosphatase conjugated to monoclonal anti-insulin antibody is added, which binds to the antigen-antibody complexes. A chemiluminescent substrate is finally added to generate a signal that is proportional to the bound enzyme conjugated to the antibody.

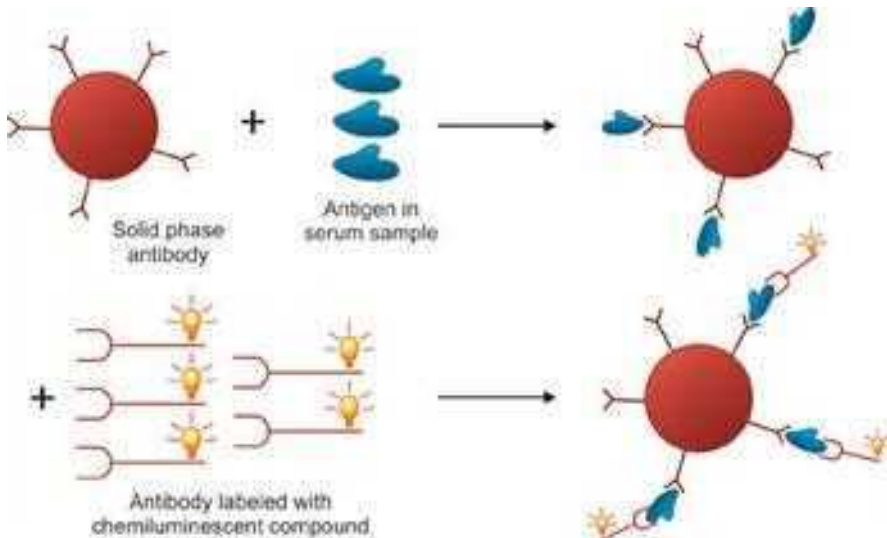


Fig. 27.2: Solid phase two-site chemiluminescence immunometric assay.

The patient sample and the reagent are incubated together with the coated bead and insulin/C-peptide in the sample that forms the antibody sandwich complex with monoclonal anti-insulin/C-peptide antibody on the bead and enzyme-conjugated monoclonal anti-insulin/C-peptide antibody in the reagent. Unbound patient sample and enzyme conjugate are then removed by centrifugal washes. Finally, chemiluminescent substrate is added to the reaction tube containing the bead, and the signal is generated in proportion to the bound enzyme.

Normal Range

- Insulin 0–30 mU/mL
- C-peptide 1.1–5.0 ng/mL.

Islet Cell Antibodies

Type 1 diabetes (T1DM) is an organ specific autoimmune disease in which the antibodies destroy the islet cell of pancreas. These antibodies will be present years before the onset of the disease. They are a heterogeneous group of antibodies known as islet cell antibodies (ICA) which include

- Insulin autoantibodies (IAA)
- Tyrosine phosphatase-like protein (IA2Ab)
- Glutamic acid decarboxylase antibodies (GAD Ab)
- Zinc transporter 8 antibodies (ZnT8Ab).

These antibodies do not appear all at once, but at different times in different patients. ICA is found in 80% of the newly detected T1DM patients (when detected by immune fluorescence technique of the frozen sections). Patients with latent autoimmune diabetes of adults (LADA) are positive for these ICA whereas the type 2 diabetes are not. These antibodies are used in the screening of the first-degree relatives of T1DM patients.

Insulin autoantibodies is the first antibody to appear during the asymptomatic period and is detected in majority of the children who are prone to develop this disease. They can be used to diagnose LADA or type 1.5 diabetes. It is estimated that 20% of the type 2 diabetes may have actually LADA. The serological marker IAA is used for the differential diagnosis of type 2 diabetes and LADA.

Islet cell antigen ICA 512, also known as IA2, has a tyrosine phosphatase domain, and its antibodies are detected in the T1DM patients. Glutamic acid decarboxylase 65 was discovered as a major islet cell antigen and its antibodies in serum is found to be a good marker for the autoimmune disease T1DM. The combination of antibodies to GAD and IA2 is found to be a better serological marker for the differential diagnosis of T1DM.

Zinc is an essential trace element in the mammals, and its concentration is highest in the pancreas. It is considered to be an essential component for the storage and secretion of insulin inside the secretory granules of the islet cells. Recently a new protein is identified on the membrane of the insulin secreting granules called the zinc transporter 8 (ZnT8). Autoantibodies to this protein are found in nearly 70% of those children, and adolescents affected by T1DM and hence considered to be one among the ICA.

Assay

Most of the ICA in serum are detected by ELISA technique, using specific antigen coated on to the wells. In most of the ELISAs, during the first incubation the antibodies in the sera are bound to the specific antigen on the plate. The unbound excess sera are washed off and the second incubation is with the antibody—biotin conjugate. The conjugate forms a divalent linkage with the already immobilized antibody (from the patient's sera) on the plate. The excess unbound conjugate is washed off, and the third incubation is with streptavidin peroxidase conjugate. Streptavidin specifically binds to biotin. The unbound conjugate is washed off, and the final reaction is with a peroxidase substrate TMB (3,3',5,5'-Tetramethylbenzidine). The enzyme peroxidase reacts with TMB to give blue color product. The reaction is stopped with the addition of acid, forming a yellow color whose absorbance can be measured in an ELISA plate reader.

SUGGESTED READING

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SELF-ASSESSMENT

1. **In the normal resting state of humans, most of the blood glucose burned as “fuel” is consumed by:**
 - (a) Liver
 - (b) Brain
 - (c) Kidneys
 - (d) Adipose tissue
 - (e) Muscles
2. **Whole blood glucose concentration is lower than plasma glucose concentration by:**
 - (a) 5–7%
 - (b) 7–9%
 - (c) 9–12%
 - (d) 12–15%
 - (e) 15–17%
3. **The common source of error in the measurement of HbA1c may be due to the presence of:**
 - (a) Carbamylated Hb
 - (b) Carboxy Hb
 - (c) Methylated Hb
 - (d) Oxygenated Hb
 - (e) Reduced Hb
4. **The possible error that could occur during the process of ordering a test is:**
 - (a) Incorrect tube or container
 - (b) Improper transport conditions
 - (c) Inadequate volume of sample
 - (d) All of the above
5. **The quality of the results can be monitored by:**
 - (a) Autoanalyzers
 - (b) Stable control materials
 - (c) Commercial kits
 - (d) Skilled technologists

- 6. A liver biopsy from an infant with hepatomegaly, stunted growth, hypoglycemia, lactic acidosis, and hyperlipidemia revealed accumulation of glycogen having normal structure. A possible diagnosis would be:**
- (a) Branching enzyme deficiency (b) Acid maltase deficiency
(c) Liver phosphorylase deficiency (d) Debranching enzyme deficiency
(e) Glucose 6 phosphatase deficiency
- 7. The preservative added to the sample collection tube for glucose estimation is:**
- (a) Na-EDTA (b) K-EDTA
(c) Na-F (d) Gentamycin
(e) Heparin
- 8. The hydrolysis of glucose 6 phosphate is catalyzed by a phosphatase, which is not found in which of the following:**
- (a) Liver (b) Kidney
(c) Muscle (d) Small intestine
(e) None of the above
- 9. The interfering substance in creatinine estimation by Jaffe's method is, increased levels of:**
- (a) Glucose (b) Ascorbic acid
(c) Bilirubin (d) Pyruvate
(e) Uric acid
- 10. The following metabolic abnormalities occur in diabetes mellitus *except*:**
- (a) Increased plasma FFA
(b) Increased pyruvate carboxylase activity
(c) Decreased lipogenesis
(d) Decreased gluconeogenesis
(e) Increased PEP—Carboxykinase activity

CHAPTER

28

Recent Advances

Mahesh DM, Ron Thomas Varghese, Nihal Thomas

*“Things move fast, I must confide,
With Chloroquine and Dulaglutide,
With stem cells being the latest fad
And many more they could be had.”*

Though several treatment modalities are defined in glycemic control in diabetes, newer insights into the pathophysiological mechanisms and better understanding of the disease extends the scope of emerging newer therapeutic approaches in diabetes management (Table 28.1).

DRUGS WHICH POTENTIATE INSULIN SECRETION

Newer Glucagon-Like Peptide-1 Analogs

Beyond the existing glucagon-like peptide-1 (GLP-1) analogs such as exenatide and liraglutide, newer agents with a longer duration of action are being researched upon. Extended release exenatide [exenatide long-acting release (LAR)] is currently available in Europe and the United States. A study comparing 2 mg preparation of exenatide-LAR given once weekly with conventional exenatide 10 µg given twice daily showed a greater reduction in HbA1c levels with exenatide-LAR. The adverse effects of this exenatide-LAR are not different from that of the twice daily formulation. However, nausea has been reported less frequently with once weekly than with twice daily administration (26% vs 50%).

Albiglutide

Albiglutide (tanzeum) is an agonist of the albumin-based GLP-1 fusion protein. It augments glucose-dependent insulin secretion and slows gastric emptying. The human GLP-1 fragment sequence 7–36 has been modified with a glycine substituted for the naturally-occurring alanine at position 8 in order to confer resistance to dipeptidylpeptidase-4 (DPP-4) mediated proteolysis. The human albumin moiety of the recombinant fusion protein, together with the DPP-4 resistance, extends the half-life to 5 days allowing once-weekly dosing. Albiglutide

Table 28.1: Examples of newer drug mechanisms in management of type 2 diabetes.

Type of agent	Action	Example
New GLP-1 analogue	Enhance insulin secretion	Dulaglutide
Insulin action potentiators	Enhance actions of insulin	Newer selective PPAR Modulators
Counter-regulatory hormone inhibitors	Suppress secretion/action of counter-regulatory hormones	Glucagon receptor antagonists, cellular glucocorticoid inhibitors
Direct glucose regulators	Increase glucose metabolism	GK activators, F16Pase inhibitors
Lipid regulators	Inhibit oxidation of fatty acids	CPT-1 inhibitors
Insulin mimetics	Insulin-like effects on glucose metabolism	IGF-1

(GLP-1: Glucagon-like peptide-1; PPAR: Peroxisome proliferator-activated receptor; GK: glucokinase; CPT: Carnitine palmitoyl transferase; IGF: Insulin-like growth factor 1; F16Pase: Fructose-1,6-diphosphatase).

is supplied as a solution for subcutaneous injection. The recommended dose is 30 mg once weekly given as a subcutaneous injection in the abdomen, thigh, or upper arm region. The dosage may be increased to 50 mg once weekly if the glycemic response is inadequate. Albiglutide may be administered at any time of day without regard to meals. In April 2014, the U.S. Food and Drug Administration (FDA) approved this drug. The FDA approval of albiglutide was based on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. A total of 296 subjects with type 2 diabetes inadequately controlled on diet and exercise were randomized compared with placebo, treatment with tanzeum 30 mg or 50 mg resulted in statistically significant reductions in HbA1c from baseline at week 52. The adjusted mean change in weight from baseline did not differ significantly between tanzeum (-0.4 to -0.9 kg) and placebo (- 0.7 kg) at week 52.

Dulaglutide

Dulaglutide (Trulicity) is a human GLP-1 receptor agonist with 90% amino acid sequence homology to endogenous human GLP-1 (7-37). Dulaglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase in pancreatic β -cells. Dulaglutide increases intracellular cyclic adenosine monophosphate (cAMP) in β -cells leading to glucose-dependent insulin release. Dulaglutide also decreases glucagon secretion and slows gastric emptying. The recommended initiating dose is 0.75 mg once weekly. The dose may be increased to 1.5 mg once weekly for additional glycemic control. In September 2014, the U.S. FDA has approved dulaglutide (Trulicity), a once-weekly subcutaneous injection to improve glycemic control (blood sugar levels), along with diet and exercise, in adults with type 2 diabetes. The FDA approval of trulicity was based on a 52-week double-blind study (26-week primary end point). The study enrolled 807 patients inadequately treated with

diet and exercise, and one antidiabetic agent used at submaximal dose. The subjects were randomized to trulicity 0.75 mg once weekly, trulicity 1.5 mg once weekly, or metformin 1,500–2,000 mg/day following a 2-week washout. Treatment with trulicity 0.75 mg and 1.5 mg once weekly resulted in reduction in HbA1c from baseline at the 26-week primary time point. The difference in observed effect size between trulicity 0.75 mg and 1.5 mg, respectively, and metformin excluded the prespecified noninferiority margin of 0.4%. It should not be used in patients with a personal or family history of medullary thyroid cancer (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (a disease in which patients have tumors in more than one gland in their body, which predisposes them to MTC).

Taspoglutide

This is another extended release molecule which works on a once-weekly basis and has shown promising results in phase 2 studies. Taspoglutide has a 93% homology to endogenous GLP-1. The development of taspoglutide was recently discontinued because of hypersensitivity concerns, an effect that has not been seen with any of the other approved or experimental GLP-1 mimetics.

Lixisenatide

A GLP-1 agonist, it is being tried as a once-daily monotherapy in latest phase 3 trials. It has been demonstrated to improve glycemic control and promote weight loss in phase 3 multicentric trials.

Newer Dipeptidyl Peptidase 4 Inhibitors

The sixth line of established oral antidiabetic drugs (OADs) has achieved reasonable success in the management of diabetes mellitus. There are a number of DPP-4 inhibitors in the pipeline, undergoing phase 3 trials. Their adverse effects and potency are generally comparable to that of sitagliptin, vildagliptin and saxagliptin. However, they are structurally unique in their origins and only long-term usage may tell us more of the profile of the adverse effects that they cause.

The medications involved in this group include:

Alogliptin (a quinazoline derivative) administered in doses of 12.5 or 25 mg/day, dutogliptin and melogliptin.

INSULIN RECEPTOR ACTIVATORS

L-783281, an active nonpeptide molecule has been shown to initiate phosphorylation and tyrosine kinase activity of the β -subunit of insulin receptor in Chinese hamster ovary cell models. It can thus activate downstream regulators and decrease blood glucose levels. Oral administration of the same also led to lowering of blood glucose in insulin resistant obese db/db mice.

Insulin-like growth factor-1 (IGF-1) also binds to insulin receptor, and can activate downstream mediators and lower blood glucose. This is of potential value especially in insulin resistant subjects. The potential proliferative and unwanted side effects of IGF-1 are a cause of concern.

Studies are now underway, wherein recombinant IGF-1 and IGF-binding protein-3 (IGFBP-3) is being simultaneously administered in an effort to minimize the adverse effects of IGF-1.

TLK-16998, another nonpeptide molecule was seen to increase phosphorylation at the β -subunit without binding to the α -subunit. Intraperitoneal injection of the same also led to lowering of blood glucose levels in insulin resistant obese db/db mice.

C-peptide is secreted in equimolar concentrations as insulin in the human body. It is seen that C-peptide causes activation of phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK) and glycogen synthase kinase 3 (GSK3), thus the ability of C-peptide to potentiate insulin receptor signaling might be used as a possible approach to improve insulin action in C-peptide deficient states.

Inhibitors of protein tyrosine phosphatase-1B (PTP-1B) act on protein tyrosine phosphatase B which dephosphorylate the insulin receptor β -subunit, terminating insulin-induced receptor tyrosine kinase activity. These phosphatases also dephosphorylate and deactivate insulin receptor substrate 1 (IRS1) and IRS2. Inhibitors of PTP-1B have shown to increase metabolic rate and resistance to diet-induced obesity in mice. Resistance to the hormones insulin and leptin are hallmarks in common for type 2 diabetes mellitus and obesity. Both conditions are associated with increased activity and expression of PTP-1B. Therefore, inhibition of PTP-1B activity or downregulation of its expression should ameliorate insulin and leptin resistance, and may hold therapeutic utility in type 2 diabetes mellitus and obesity control. Inhibition of PTP-1B might also improve endothelial function by improving insulin-induced endothelial nitric oxide synthase (eNOS) production. All these factors have accelerated the search for PTP-1B inhibitors in the recent years.

Protein kinase C (PKC) inhibitors act upon PKC which exerts negative feedback inhibition on the insulin receptor and postphosphorylation steps. The PKC- β inhibitor ruboxistaurin is in clinical trial as a potential treatment for diabetic retinal and glomerular microvascular disease.

Inositol derivatives such as D-chiro-inositol (INS-1) and the 3-methoxy analog of D-chiro-inositol (pinitol) improve muscle glucose uptake and reduce hyperglycemia in diabetic animal models and patients with type 2 diabetes mellitus.

NEWER PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS

Non-thiazolidinedione peroxisome proliferator-activated receptor (PPAR γ) agonists like halofenate and metaglidasen partially modulate PPAR γ , and do not activate exactly the same set of genes as a full PPAR γ agonist. Thus it may be possible to retain the desired therapeutic effects and reduce undesirable side effects.

Genetic overexpression or selective stimulation of PPAR δ improves insulin sensitivity, increases fatty acid oxidation, raises thermogenesis and prevents weight gain. Thus, a selective PPAR δ agonist or an agent with desired levels of selectivity for PPAR α , γ and δ could offer therapeutic advantages.

The glitazars were developed due to the dual PPAR α and γ agonist action. This leads to a combined effect on lipid (alpha) and glucose (gamma) control. Tesaglitazar and muraglitazar

were stopped on account of their adverse effects. However, aleglitazar seems to have a better side effects profile, and resulted in dose-dependent improvements in fasting and postprandial glucose, reduced insulin resistance and improved lipid variables. The effects of aleglitazar on cardiovascular disease and mortality is being studied in phase 3 trials (ALECARDIO).

Balaglitazone is a partial selective agonist of PPAR γ . By virtue of it being a partial agonist, hypothetically, the adverse effect profile may be more favorable. Phase 3 clinical trials are ongoing. Rivoglitazone is a complete agonist of PPAR γ . It appeared to be more potent in 2 mg and 3 mg doses when compared to pioglitazone with regards to glycemic control. However, there was more peripheral edema and weight gain associated with its usage. Lower doses of rivoglitazone are now being researched upon. Some other PPAR agonists in phase 2 trials include mitoglitazone and netoglitazone. Other PPAR agonists undergoing phase 2 studies are metaglidasen and indeglitazar.

NEW HEPATIC TARGETS FOR GLYCEMIC CONTROL IN DIABETES

Glucagon receptor antagonist: It counteracts active stimulation of glycogenolysis by glucagon but did not affect basal gluconeogenesis. There is a partial downregulation of the glucagon receptor and a lowering of plasma triglycerides. Detailed studies are lacking.

Use of glucagon receptor antagonists with GLP-1 agonists could partially offset the rise in plasma glucagon. Dual-acting peptide for diabetes (DAPD) is one such hybrid peptide that has GLP-1 receptor agonist and glucagon receptor antagonist property. DAPD is being studied for its glucose-lowering efficacy.

Glucose 6-phosphatase inhibitors: Glucose 6-phosphatase catalyzes the final reaction in hepatic glucose production from gluconeogenesis and glycogenolysis. It is induced by both insulin deficiency and hyperglycemia. Peroxovanadium compounds counteract the hyperglycemic response to glucagon and also have insulin mimetic properties.

- Limitations to their use may be an acute suppression of hyperglycemia posing a risk for hypoglycemia, enzyme inhibition leading to accumulation of glucose 6-phosphate and glucagon which may induce lipogenic enzymes resulting in hepatic steatosis.
- Another advantage of glucose 6-phosphatase inhibitors is that even though intermediate products in gluconeogenesis are elevated, glucose 6-phosphate is not elevated, thus circumventing the problem of secondary regulation of lipogenic genes.

Fructose 1, 6-bisphosphatase inhibitors: Fructose 1, 6-bisphosphatase catalyzes the penultimate reaction in gluconeogenesis and is regulated by the physiological inhibitors AMP and fructose 2, 6-bisphosphate. These drugs cause only a partial reduction of hepatic glucose output because of increased compensatory glycogenolysis, which helps to guard against hypoglycemia. Excessive use of these drugs might cause accumulation of lactate and triglyceride however, appropriate titration of such agents in early clinical trials has given encouraging results.

Glycogen phosphorylase inhibitors: Inhibition of hepatic glucose production by the phase 1 insulin secretion postprandially is mainly due to inhibition of glycogenolysis by inactivation of glycogen phosphorylase. Limited information is available regarding these and this may be potential area for more work in diabetology.

Glucokinase activators: Glucokinase has an important role on glucose metabolism in the liver by glycogen synthesis and glycolysis. It has been seen that mutations that increase the enzyme's affinity for glucose had a blood glucose lowering effect. The results of in vivo study on piragliatin, a glucokinase activator showed a dose-dependent reduction of plasma glucose both in the fasting state and after the oral glucose challenge and dose-dependent improvement of the estimated β -cell function. Concerns about this group of drugs causing hypoglycemia and the possibility that chronic administration may lead to excessive hepatic accumulation of not only glycogen but also triglycerides should be considered. The possibility of its effect on fertility and endocrine axis via its action on glucokinase on neuronal and neuroendocrine cells also warrant attention.

Adenosine monophosphate kinase activators: Drugs like metformin, adiponectin and thiazolidinediones also activate AMP kinase which contributes to their glucose-lowering effects. Various analogs of AMP such as AICAR (5-aminoimidazole-4-carboxamide-1- β -D-ribofuranoside) (AICAR) activate AMP kinase, and improve glycemic control in insulin-resistant diabetic animals. Other activators are being developed. Miscellaneous

Adiponectin is produced exclusively in large amounts by adipocytes. It improves insulin sensitivity with increased insulin receptor tyrosine phosphorylation and activation of AMP kinase. It also has anti-inflammatory activity and improves vascular reactivity. Adiponectin concentrations become reduced as adipose mass increases, and therapeutic approaches to raise adiponectin levels are being taken up. Part of the insulin-sensitizing effect of thiazolidinediones is thought to be due to adiponectin production.

α -lipoic acid, an antioxidant used to treat diabetic neuropathy, increases insulin sensitivity and improves glycemic control, probably brought about in part by its action as a cofactor for dehydrogenases involved in glycolysis and the Krebs cycle. Additionally, α -lipoic acid increases insulin receptor tyrosine kinase activity and IRS-1 tyrosine phosphorylation, with increased signaling via PI3K and increased glucose transporter type-4 (GLUT-4) translocation into the plasma membrane.

Glucocorticoid antagonists specific to glucocorticoid receptors in the liver have been shown to improve insulin sensitivity. However, due to its widespread action, specific targeting of glucocorticoid receptors in diabetes remains a challenge. Specific targeting of the liver has been achieved when glucocorticoid receptor inhibitors are conjugated to bile salts. This retains the inhibitor mostly within the enterohepatic circulation, reducing hyperglycemia and improving hepatic insulin sensitivity in animal models.

11 β -hydroxysteroid dehydrogenase type 1 (HSD-1) inhibitors try to reduce cortisol levels in the blood through another mechanism. This enzyme is inhibited so as to reduce cortisol formation from less active cortisone in the liver and adipose tissue. Reductions were seen in HbA1c, fasting blood glucose, homeostasis model of insulin resistance (HOMA-IR), and lipids which offer potential cardiovascular benefit.

Tagatose is a low-calorie hexokinase (monosaccharide) that occurs naturally in dairy products. It is generated by isomerization of galactose and is administered orally. It reduces the postprandial peaks in plasma glucose levels. The adverse effects include nausea, flatulence and abdominal bloating.

ADVANCES IN INSULIN THERAPY

Oral Insulin

Insulin's oral bioavailability is limited because insulin is too large and hydrophilic to readily cross the intestinal mucosa, and polypeptides undergo extensive enzymatic and chemical degradation, in particular by chymotrypsin. In the case of insulin, this enzymatic barrier is more important than that posed by the mucosa. Another major barrier for oral insulin administration, besides gastrointestinal proteolysis, is that no selective transport mechanism exists. The epithelial cells of the intestine do not normally transport macromolecules such as insulin and therefore may require extremely high doses to achieve some measurable insulin absorption. Other barriers that exist include the unpredictable transit time and the delayed absorption of encapsulated insulin. These factors may explain why only 0.5% of an oral insulin dose may reach the systemic circulation. Because of these obstacles, it would be extremely difficult to consider oral insulin therapy as a physiological option for premeal dosing. However, researchers have tried several steps to promote the bioavailability of oral insulin, including attaching caproic acid molecules and coating with chitosan, which stabilize degradation and improve permeability; facilitating absorption (e.g. with salicylates); concurrent administration with protease inhibitors; and entrapping insulin within microparticles. Other approaches have demonstrated that the chemical modification of insulin with fatty acids could improve insulin absorption from the intestine. In addition, engineered polymer microspheres were demonstrated to increase gastrointestinal absorption of insulin.

Inhaled Insulin

Most polypeptides used for therapy require injection for delivery, as oral administration results in loss of biopotency, owing to breakdown in the stomach. Several nonoral routes of administration have been explored, including transdermal, buccal, nasal and inhaled delivery. Specifically, the lung provides an attractive alternative for systemic administration of therapeutic polypeptides given its accessibility and large alveolar-capillary network for drug absorption. The concept of nasally administered insulin first appeared in 1935. A number of clinical trials have demonstrated proof of principle for pulmonary delivery of insulin for individuals with diabetes.

Inhaled insulin represents a paradigm shift for insulin delivery, as it differs not only in route of administration, but also dosing units, patient eligibility (precautions and exclusions related to lung disease and smoking) and required periodic testing for safety. An inhaled form of rapid-acting insulin (Exubera) was available for a short time (August 2006 to October 2007) before it was discontinued by the manufacturer as the new technology failed to gain acceptance by patients or clinicians. Currently, one formulation of inhaled insulin (Afrezza) completed the phase III clinical trials that use a different technology for insulin delivery (Technosphere).

Delivery system for insulin to be delivered through the lungs, inhalation devices that provide dose accuracy and consistency are critical. Due to its inefficient absorption, higher doses of inhaled insulin compared to subcutaneous must be administered to achieve a therapeutic

response. The formerly available inhaled insulin delivery system (Exubera) involved use of a bulky device to dispense human insulin as a dry-powdered formulation with little dosing flexibility. A different inhaled insulin formulation (2.5 μm in diameter), which appears to have a more convenient delivery system and greater dosing flexibility, is in development. This new technosphere formulation contains recombinant human insulin dissolved with powder (fumaryl diketopiperazine). Once inhaled, technosphere insulin is rapidly absorbed upon contact with the lung surface (half-life about one hour). The particles are delivered with a thumb-sized inhaler with increased dose-flexibility. Following inhalation, the particles under dissolution are absorbed fairly quickly from the pulmonary vasculature within 15 minutes, with onset of action in 20 minutes, lasting for up to 3 hours. Both the insulin and the powder are nearly completely cleared from the lungs of healthy individuals within 12 hours of inhalation; only 0.3% of the insulin and 0.4% of the powder concentration remain after 12 hours. In contrast, about 8–9% of the inhaled dose remained in the lungs 12 hours later with the old exubera formulation. Exubera 3, a new formulation is a liquid pulmonary device instead of dry powder pulmonary device. It is similar to an asthma inhaler—a hand-held mini-nebulizer.

- In one case report, inhaled insulin was used successfully to manage subcutaneous insulin resistance syndrome, an exceedingly rare condition thought to be due to rapid degradation of insulin in the subcutaneous tissue.
- In literature published on inhaled insulin, the glycemic control as assessed by mean decrease in HbA1c from baseline to end point was comparable between the inhaled insulin group (–0.32%) and the conventional treatment group. Inhaled versus subcutaneous insulin—a systematic review of six randomized trials (three in type 1 and three in type 2 diabetes) comparing inhaled insulin with rapidly-acting insulin injections concluded that glycemic control was equivalent, but patient satisfaction and quality of life was greater with inhaled insulin
- The frequency and nature of adverse events reported with inhaled insulins appear, in general, to be comparable with subcutaneous insulin, with the exception of cough (although this decreases in incidence and prevalence with continued use). Subjects treated with inhaled insulin may develop an increase in serum insulin antibody levels, but these levels thus far have not been related to any significant clinical change. Smoking, however, appears to greatly enhance insulin absorption. Pulmonary function tests, including forced expiratory volume in 1 second, forced vital capacity, total lung capacity, and diffusing capacity of the lung for carbon monoxide (DLCO) have been conducted in all inhaled insulin studies. Some studies reported a statistically significant decrease in the more variable DLCO relative to subcutaneous insulin. Further studies are ongoing to characterize the insulin antibody and DLCO changes, including whether a difference of this magnitude has any clinical significance, as well as any mechanistic or methodologic basis.

In June 2014, the U.S. FDA has approved Afrezza (insulin human) inhalation powder, a rapid-acting inhaled insulin to improve glycemic control in adults with diabetes mellitus. Afrezza is a rapid-acting inhaled insulin that is administered at the beginning of each meal. The drug's safety and effectiveness were evaluated in a total of 3,017 participants—1,026 participants with type 1 diabetes and 1,991 patients with type 2 diabetes. The efficacy of mealtime Afrezza in adult patients with type 1 diabetes patients was compared to mealtime insulin

aspart (fast-acting insulin), both in combination with basal insulin (long-acting insulin) in a 24-week study. At week 24, treatment with basal insulin and mealtime Afrezza provided a mean reduction in HbA1c (hemoglobin A1c or glycosylated hemoglobin, a measure of blood sugar control) that met the prespecified noninferiority margin of 0.4%. Afrezza provided less HbA1c reduction than insulin aspart, and the difference was statistically significant. Afrezza was studied in adults with type 2 diabetes in combination with oral antidiabetic drugs; the efficacy of mealtime Afrezza in type 2 diabetes patients was compared to placebo inhalation in a 24-week study. At week 24, treatment with Afrezza plus oral antidiabetic drugs provided a mean reduction in HbA1c that was statistically significantly greater compared to the HbA1c reduction observed in the placebo group.

- Afrezza is not a substitute for long-acting insulin. Afrezza must be used in combination with long-acting insulin in patients with type 1 diabetes, and it is not recommended for the treatment of diabetic ketoacidosis, or in patients who smoke. Afrezza has a boxed warning advising that acute bronchospasm has been observed in patients with asthma and chronic obstructive pulmonary disease (COPD). Afrezza should not be used in patients with chronic lung disease, such as asthma or COPD because of this risk. The most common adverse reactions associated with Afrezza in clinical trials were hypoglycemia, cough and throat pain or irritation. The FDA approved Afrezza with a Risk Evaluation and Mitigation Strategy, which consists of a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza.

Buccal Insulin

Liquid aerosol insulin is sprayed into the buccal cavity without entering the airways.

Bionic Pancreas to Replace Insulin Pumps

A New Dawn for Young People with Diabetes

Currently, people with type 1 diabetes walk an endless tightrope. Because their pancreas does not make the hormone insulin, their blood glucose levels can vary dangerously high and low. Several times a day they must use finger stick tests to monitor their blood glucose levels and manually take insulin by injection or from a pump. Recently, in two random-order, crossover studies with similar but distinct designs, Russel et al. of Massachusetts General Hospital compared glycemic control with a wearable, bihormonal, automated, “bionic” pancreas [cell phone-sized device (Fig. 28.1)] with glycemic control with an insulin pump (control period) for 5 days in 20 adults and 32 adolescents with type 1 diabetes mellitus. The device uses a smart phone, a continuous blood sugar (glucose) monitor and pumps to automatically deliver the correct quantity of hormones (Insulin and its counteracting hormone, glucagon) directly into the bloodstream. The researchers found about 37% fewer interventions for low blood glucose (hypoglycemia) and a more than twofold reduction in the time in hypoglycemia in adults using the bionic pancreas than with the manual pump. For adolescents using the bionic pancreas, results showed more than a twofold reduction in the need for interventions for hypoglycemia. As well, both groups had significant improvements in glucose levels with the bionic pancreas, particularly during the night. A bionic pancreas, like the one used in these studies would



Fig. 28.1: Cellphone-sized device to deliver insulin and its counteracting hormone, glucagon, via two automatic pumps.

Source: www.artificialpancreas.org/images and www.bbc.com/news/health-28810813

function more like an automated thermostat, automatically monitoring blood glucose and delivering insulin or glucagon when needed to keep glucose within the normal range. As well, these bionic pancreas devices could be monitored remotely by the patient's medical provider or parent. Thus, people with type 1 diabetes who use a bionic pancreas instead of manually monitoring glucose using finger-stick tests and delivering insulin using a pump are more likely to have blood glucose levels consistently within the normal range, with fewer dangerous hypos or high blood glucose. A cure is always the end goal. As that goal remains elusive, a truly automated technology, which can consistently and relentlessly keep people healthy and safe from harm of hypoglycemia, would lift an enormous emotional and practical burden from the shoulders of people with type 1 diabetes. The study was funded by the National Institutes of Health (N Engl J Med. 2014;371:313-25).

IMMUNOTHERAPY FOR TYPE 1 DIABETES

Immunomodulators

Humanized anti-CD3 Monoclonal Antibodies

Otelixizumab and teplizumab bind to CD3/TCR complex and block full T cell activation, proliferation and cytokine release. Downregulation of T-effector cells, may lead to a reduced autoimmune attack on the β -cells.

Otelixizumab has been administered for eight consecutive days in clinical trials and subjects have been followed up to observe remission of new onset type 1 diabetes mellitus. Teplizumab has been used in new onset type 1 diabetes mellitus, with the administration of 14 consecutive daily injections. An annual follow-up of these subjects in connection with glycemic remission and maintenance of C-peptide levels appears to be promising. However, a longer follow-up is required to assess whether remission of diabetes may be prolonged.

Rituximab

The actual mechanism of the effect of rituximab in type 1 diabetes is not known. It may reduce the production of proinflammatory cytokines that blunts the immune response locally within the pancreas or the pancreatic lymph nodes. In a preliminary trial involving 87 patients with new onset type 1 diabetes, the mean area under the curve for C-peptide levels during a mixed-meal tolerance test was significantly higher in the rituximab group compared to the placebo group.

Thymoglobulin

Preclinical studies have shown that non-obese diabetic (NOD) mice with recent onset diabetes, when treated with antilymphocyte serum undergo disease remission. Clinical studies in patients with newly diagnosed type 1 diabetes, equine antithymocyte globulin (ATG) appeared to prolong the honeymoon phase of the disease. A phase II placebo-controlled trial is already in progress.

Recombinant Human Glutamic Acid Decarboxylase (rhGAD65)

This is a vaccine that induces immunotolerance and may slow or prevent autoimmune β -cell destruction. In some subjects with LADA, there has been an associated improvement in glycemic control and rise in stimulated C-peptide levels. A lengthy follow-up of such subjects treated will be needed to establish the efficacy of this form of treatment.

Miscellaneous

The other immunomodulators which have been studied are (1) DAB-IL2, a diphtheria toxin conjugated to part of the interleukin-2 molecule designed to target activated T cells, (2) Bacillus Calmette-Guerin (BCG), (3) DiaPep277, an immunomodulatory peptide derived from 60 kDa heat shock protein and (4) Abatacept (also called CTLA4-Ig), a soluble fusion protein comprising cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) and the Fc portion of IgG1. These drugs have been studied in small scale studies which need additional data are needed before they can be used in routine clinical practice.

STEM CELL THERAPY

Type 1 diabetes mellitus more accurately, type 1A diabetes is thought to arise from selective immunologically mediated destruction of the insulin-producing β -cells in the pancreatic islets of Langerhans with consequent insulin deficiency. Type 1 diabetes characterized by the permanent destruction of insulin-secreting β -cells is responsive to cell-based treatments that replace lost β -cell populations, such as in the form of pancreas or islet transplantation. The current gold standard of pancreatic transplantation, usually in the context of renal transplantation has been applied successfully in patients with type 1 diabetes for over two decades. Both approaches to β -cell replacement result in dramatic improvements in prevailing glycemia, yet both are limited by the need for immune system alteration to prevent both

allorejection and recurrent autoimmunity, as well as the limited availability of tissue (cadaveric organ donation). With the already heightened demand placed on organ donation, stem cell therapy has become a tantalizing idea to provide glucose-responsive insulin-producing cells to type 1 diabetic patients as an alternative to transplantation.

Stem cells are undifferentiated cells capable of self-renewal and giving rise to virtually any tissue or organ. A stem cell is defined by two properties. First, it is a cell that can divide indefinitely, producing a population of identical offspring. Second, stem cells can undergo an asymmetric division to produce two dissimilar daughter cells: one is identical to the parent and continues to contribute to the original stem cell line and the other follows variable pathways. Eventually a stem cell becomes a “progenitor” or “precursor” cell, committed to produce one or a few terminally differentiated cells such as pancreatic β -cells, neurons or muscle cells. Such cells may be obtained from the fetus, the umbilical cord, the bone marrow and may also be deployed by peripheral blood and even from different somatic tissues. Both adult and embryonic stem cells have received an enormous amount of attention as possible sources of insulin-producing cells. Although adult stem cells lack the pluripotent nature of their embryonic counterparts, they appear to avoid the ethical debate that has centered on the latter. One must also consider the potential of stem cells to form teratomas, a complication which would prove devastating in an immunologically compromised transplant recipient.

The optimal therapeutic approach for type 1 diabetes should ideally preserve the remaining β -cells, restore β -cell function, and protect the replaced insulin-producing cells from autoimmunity. In regards to all three of these, much has been accomplished in animal models of type 1 diabetes. Stem cells possess immunological and regenerative properties that could be harnessed to improve the treatment of type 1 diabetes; indeed, stem cells may reestablish peripheral tolerance toward β -cells through reshaping of the immune response and inhibition of autoreactive T-cell function. Multiple groups have developed varied approaches to create a population of cells with the most appropriate characteristics. There has been progressive improvement in this field, first with insulin-expressing cells being created, then with insulin-producing cells being developed, and finally with the generation of glucose-responsive insulin-secreting cells. Furthermore, stem cell-derived insulin-producing cells are capable of engrafting and reversing hyperglycemia in mice models. Yet in human beings, success has been elusive.

The following are the various stem cells with potential role in type 1 diabetes therapy:

1. Cord blood stem cells (CB-SCs)
2. Mesenchymal stem cells (MSCs)
3. Hematopoietic stem cells (HSCs)
4. Embryonic stem cells (ESCs)
5. Induced pluripotent stem cells (iPS)

Cord blood stem cells have been shown to facilitate the generation of regulatory T cells, thereby reverting hyperglycemia in NOD mice. Bone marrow-derived MSCs have been shown to inhibit T cell-mediated immune response against newly formed B cells. Bone marrow stem cell therapy may provide the best treatment. In vivo murine studies have consistently shown that even without differentiating into B cells, bone marrow stem cell transplantation

causes a reduction in plasma glucose levels and an increase in systemic insulin through a variety of mechanisms. HSCs are, to date, among the most often used stem cells in the clinic for the therapy of autoimmune diseases. Autologous nonmyeloablative HSCs transplantation, with concomitant high-dose immunosuppression, has been reported in new-onset type 1 diabetes. These cells have been demonstrated to increase endogenous insulin production, while partially mitigating the autoimmune destruction of newly formed B cells. In a phase I/II study initiated in Brazil since 2003, during a mean follow-up of 30 months, 20 out of 23 patients became insulin free, their B cell function increased significantly, their anti-GAD antibody levels decreased, and their A1C levels were maintained at 7%. In another trial, a novel HSC-based strategy has been tested in individuals with new-onset type 1 diabetes. The aim of this study was to determine the effects of autologous nonmyeloablative HSC transplantation in 65 individuals with new-onset type 1 diabetes who were enrolled in two Chinese centers and one Polish center, pooled, and followed up for 48 months. A total of 59% of individuals with type 1 diabetes achieved insulin independence within the first 6 months after receiving conditioning immunosuppression therapy (with ATG and cyclophosphamide) and a single infusion of autologous HSCs, and 32% remained insulin independent at the last time point of their follow-up, i.e. 48 months after treatment. All treated subjects showed a decrease in HbA1c levels and an increase in C-peptide levels compared with pretreatment. Despite a complete immune system recovery (i.e. leukocyte count) after treatment, 52% of treated individuals experienced adverse effects. The studies suggests the following: That remission of type 1 diabetes is possible by combining HSC transplantation and immunosuppression; that autologous nonmyeloablative HSC transplantation represents an effective treatment for selected individuals with type 1 diabetes; and that safer HSC-based therapeutic options are required. Although HSCs rarely revert hyperglycemia in NOD mice, they exhibit profound immunomodulatory properties in humans. Newly diagnosed type 1 diabetes patients have been successfully reverted to normoglycemia with autologous nonmyeloablative HSC transplantation. Finally, ESCs also offer exciting prospects because they are able to generate glucose-responsive insulin-producing cells. However, potential oncogenicity of stem cells is a concern.

The discovery of human pluripotent stem cells (hPSC) opened the possibility of generating replacement cells and tissues in the laboratory that could be used for disease treatment and drug screening. Recent research has moved the stem cell field closer to that goal through development of strategies to generate cells that would otherwise be difficult to obtain, like neurons or cardiomyocytes. One of the rapidly growing diseases that may be treatable by stem-cell-derived tissues is diabetes, affecting more than 300 million people worldwide, according to the International Diabetes Federation. Diabetic patients, particularly those suffering from type 1 diabetes, could potentially be cured through transplantation of new B cells. Patients transplanted with cadaveric human islets can be made insulin independent for 5 years or longer via this strategy, but this approach is limited because of the scarcity and quality of donor islets. The generation of insulin-producing pancreatic B cells from stem cells *in vitro* would provide an unprecedented cell source for drug discovery and cell transplantation therapy in diabetes (Fig. 28.2). The generation of an unlimited supply of human B cells from stem cells

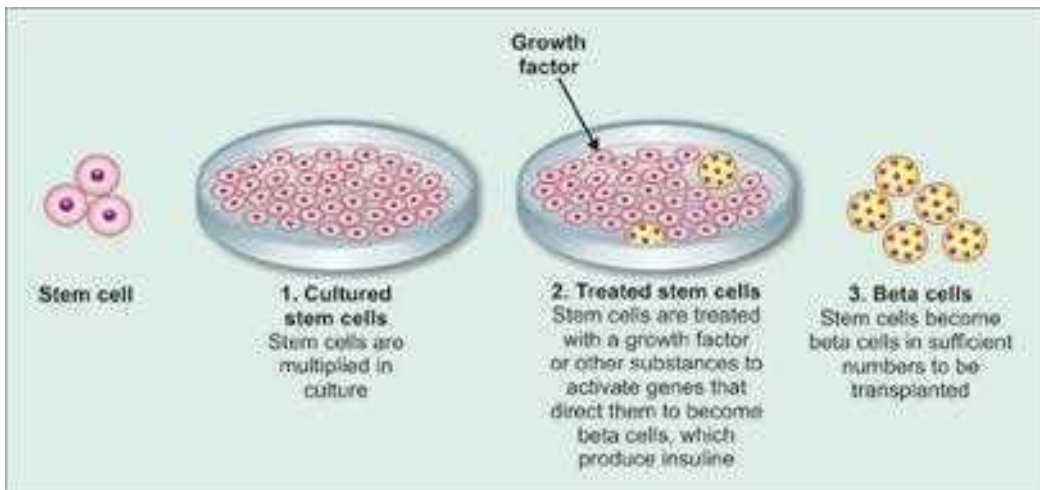


Fig. 28.2: Development of β -cells from stem cells.

could extend this therapy to millions of new patients, especially with type 1 diabetes and could be an important test case for translating stem cell biology into the clinic. This is because only a single cell type, the B cell, likely needs to be generated, and the mode of delivery is understood: transplantation to a vascularized location within the body with immunoprotection. However, insulin-producing cells previously generated from hPSC lack many functional characteristics of bonafide B cells. Recently, a scalable differentiation protocol has been that can generate hundreds of millions of glucose-responsive B cells from hPSC in vitro. These stem-cell-derived B cells express markers found in mature B cells, flux Ca^{2+} in response to glucose, package insulin into secretory granules, and secrete quantities of insulin comparable to adult B cells in response to multiple sequential glucose challenges in vitro. Furthermore, these cells secrete human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner, and transplantation of these cells ameliorated hyperglycemia in diabetic mice.

The use of stem cells holds great promise for the cure of type 1 diabetes due to their propitious immunological characteristics and their regenerative capabilities. With continued research, bone marrow stem cells, iPS and other stem cell-based treatments have the potential to move medicine toward a permanent cure for type 1 diabetes. Type 1 diabetes mellitus is a multifactorial disease with genetic predisposition and autoimmunity playing a major role. Current approaches aiming to cure type 1 diabetes have made a negligible number of patients insulin independent and are limited by potential complications that may develop with their use. It is more likely that combination therapies may enhance efficacy while lowering risk and may one day become the standard of care for newly diagnosed type 1 diabetes. It is, however, important to keep in mind that insulin therapy, while not easy or complication free, has led to a dramatic improvement of the mortality and morbidity associated with type 1 diabetes over the past 20–30 years. The history of diabetes is filled with many groundbreaking discoveries. If the past performance does predict future returns, the prevention of type 1 diabetes has a bright future.

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SELF-ASSESSMENT

1. Exenatide long-acting release is administered:

- | | |
|----------------------|------------------|
| (a) Once a week | (b) Once a month |
| (c) Once in 3 months | (d) Once a day |

2. Sodium-glucose linked transporter inhibitors have been found to:

- | | |
|-----------------------|-----------------------|
| (a) Cause weight gain | (b) Cause weight loss |
| (c) Be weight neutral | (d) Reduce glycosuria |

3. Tagatose is:

- | | |
|--------------------|--------------------|
| (a) Protein | (b) Monosaccharide |
| (c) Polysaccharide | (d) Fatty acid |

4. Which of the following is true about glucose 6-phosphatase inhibitors?

- (a) There is no risk of hypoglycemia
- (b) There is degradation of glucose 6-phosphate
- (c) There is accumulation of glucagon
- (d) They reduce hepatic steatosis

5. Resveratrol is:

- (a) Found in black grapes
- (b) Deactivates sirtuins
- (c) Delivered orally in rodents
- (d) Not tested in humans

6. Teplizumab is:

- (a) anti-CD3 polyclonal Ab
- (b) anti-CD4 monoclonal Ab
- (c) anti-CD3 monoclonal Ab
- (d) anti-CD4 polyclonal Ab

7. Which of the following is false about oral insulin?

- (a) It is too large and hydrophilic to be transported by GI mucosa
- (b) It is degraded the proteolytic enzymes
- (c) 10% of oral insulin can be absorbed
- (d) There is no selective transport mechanism available

8. The particle size of inhaled insulin is:

- (a) Less than 1 mm
- (b) Less than 2 mm
- (c) Less than 3 mm
- (d) Less than 45 mm

9. The most common side effects of powder form of inhaled insulin is:

- (a) Cough
- (b) Bronchospasm
- (c) Insulin antibodies
- (d) Skin rashes

10. Which of the following is not available?

- (a) Stem cell therapy
- (b) Pancreas transplantation
- (c) Islet transplantation
- (d) Beta cell transplantation

CHAPTER

29

In-hospital Management of Diabetes

Rahul Baxi, Nihal Thomas

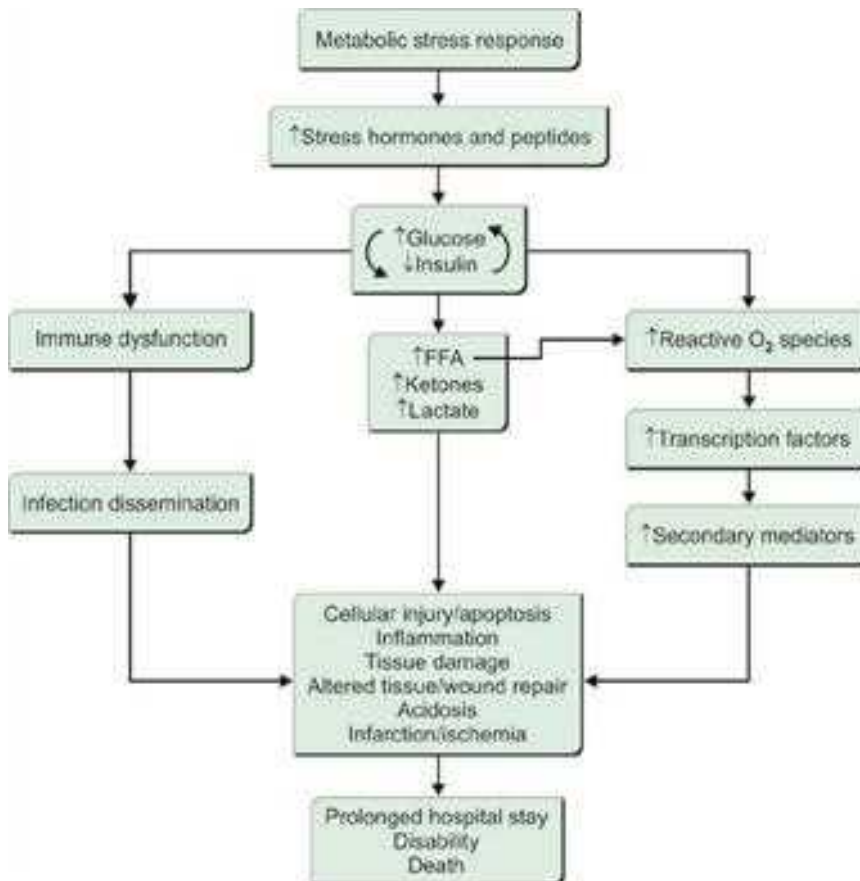
*“Enter the hospital and into the ward,
Whatever happens you need to try hard,
Maintaining sugar control you might as well ask,
Why on earth is it such a difficult task?”*

INTRODUCTION

Diabetes in India has attained epidemic proportions. Figures indicate that there are more than 62 million patients with diabetes in India and it is projected to increase to 100 million in 2030. Diabetes increases the risk for disorders that predispose individuals to hospitalization, including coronary artery, cerebrovascular and peripheral vascular disease, nephropathy, infection, and lower-extremity amputations. Recent studies have focused attention to the possibility that hyperglycemia in the hospital is not necessarily a benign condition and that aggressive treatment of diabetes and hyperglycemia reduces mortality and morbidity. A significant proportion of hospital inpatients with hyperglycemia have undiagnosed diabetes and stress hyperglycemia. Hospitalization presents an opportunity to diagnose diabetes and to identify those at risk.

EFFECTS OF HYPERGLYCEMIA IN HOSPITALIZED PATIENTS AND BENEFITS OF GLYCEMIC CONTROL

There is compelling evidence that poorly controlled glucose levels are associated with a higher in-hospital morbidity and mortality, prolonged length of stay, unfavorable postdischarge outcomes and significant excess healthcare costs. Metabolic stress causes hyperglycemia and relative insulin deficiency which leads to immune dysfunction and release of reactive oxygen species. The combined insults of infection, oxidative stress and other mediators lead to tissue and organ injury (Flowchart 29.1).

Flowchart 29.1: Links between hyperglycemia and poor hospital outcomes.

(FFA: Free fatty acids).

WHICH PATIENT SHOULD WE ADMIT?

Hospitalization of a patient for reasons related to diabetes may be indicated in the following situations:

- *Acute metabolic complications of diabetes:* Diabetic ketoacidosis, hyperglycemic hyperosmolar state, hypoglycemia with neuroglycopenia.
- Newly diagnosed diabetes in children and adolescents.
- Chronic poor metabolic control that necessitates close monitoring of the patient to determine the etiology and modify the treatment.
- Severe chronic complications of diabetes that require intensive treatment or other severe conditions unrelated to diabetes that significantly affect its control or are complicated by diabetes.
- Uncontrolled or newly diagnosed insulin requiring diabetes during pregnancy.
- Institution of insulin pump therapy or other intensive insulin regimens.

- Acute or chronic microvascular or macrovascular complications of diabetes may require hospital admission.

AIMS AND TARGETS

All patients with diabetes admitted to the hospital should have their diabetes clearly identified in the medical record and have an order for blood glucose monitoring, with results available to all members of the healthcare team.

Goals for Blood Glucose Levels*

- *Critically ill patients:* Insulin therapy should be initiated for treatment of persistent hyperglycemia starting at a threshold of no greater than 180 mg/dL (10 mmol/L). Once insulin therapy is started, a glucose range of 140–180 mg/dL (7.8–10 mmol/L) is recommended for the majority of critically ill patients. (A)
- *Noncritically ill patients:* There is no clear evidence for specific blood glucose goals. If treated with insulin, the premeal blood glucose target should generally be less than 140 mg/dL (7.8 mmol/L) with random blood glucose less than 180 mg/dL (10.0 mmol/L), provided these targets can be safely achieved. More stringent targets may be appropriate in stable patients with previous tight glycemic control. Less stringent targets may be appropriate in those with severe comorbidities. (E)
- Scheduled subcutaneous insulin with basal, nutritional and correctional components is the preferred method for achieving and maintaining glucose control in noncritically ill patients. (C) Using correction dose or “supplemental” insulin to correct premeal hyperglycemia in addition to scheduled prandial and basal insulin is recommended. (E)
- Glucose monitoring should be initiated in any patient not known to have diabetes, who receives therapy associated with high-risk for hyperglycemia, including high-dose glucocorticoid therapy, initiation of enteral or parenteral nutrition, or other medications such as octreotide or immunosuppressive medications. (B) If hyperglycemia is documented and persistent, treatment is necessary. Such patients should be treated to the same glycemic goals as patients with known diabetes. (E)
- A plan for treating hypoglycemia should be established for each patient. Episodes of hypoglycemia in the hospital should be tracked. (E)
- All patients with diabetes admitted to the hospital should have glycosylated hemoglobin (HbA1c) test done, if the result of testing in the previous 2–3 months is not available. (E)
- Patients with hyperglycemia in the hospital who do not have a diagnosis of diabetes should have appropriate plans for follow-up testing and care documented at discharge. (E)

THE DIABETES INPATIENT TEAM

- *The patient:* The patient forms the core of the team and is encouraged to participate in the formulation and conduct themselves their own care plan while admitted in the hospital.

*In parenthesis, are the levels of evidence (Refer Appendix 3).

- *Consultant physician/diabetologist/endocrinologist:* The primary role of the consultant is as a leader of the multidisciplinary team. They work closely to provide clinical support to diabetes specialist nurses and diabetes educators.
- *Diabetes educator:* They play a key role in patient and staff education and implementation of glycemic control strategies and are able to facilitate a smooth patient pathway from hospital to home.
- *Diabetes specialist nurses:* They deliver patient-centered care and influence care delivery at every stage.
- *Diabetes specialist dietitian:* They play a pivotal role in case of diabetic inpatients with complex nutritional needs, such as those who are unable to swallow, and those with renal failure, pregnant women and the elderly.

THE PARADOX: BARRIERS TO GLYCEMIC CONTROL IN HOSPITAL

In some situations, hospitalization may, in fact hamper the efforts to achieve optimum glycemic control.

- Majority of patients with diabetes are hospitalized for reasons other than diabetes, e.g. vascular complications. The care of diabetes per se becomes secondary to that for the primary diagnosis.
- Infection, fever, steroid therapy, surgical trauma and stress exacerbate hyperglycemia due to release of counter regulatory hormones.
- Decreased physical activity (in previously active patients) also exacerbates hyperglycemia.
- On the other hand, strict diet and supervised compliance with drugs may result in hypoglycemia in patients who were not compliant earlier.

COMMON ERRORS IN MANAGEMENT

- *High glycemic targets:* Blood glucose levels are commonly allowed to be more than 200 mg/dL without aggressive intervention. Diabetes management is often considered secondary to the primary presenting condition. More often than not, this leads to increased duration of hospital stay and increased morbidity and in some cases, mortality.
- *Orders on patient admission:* The outpatient treatment regimen for diabetes is often continued unchanged or withdrawn entirely upon admission. Although either of these choices may occasionally be indicated, patients more commonly will require some modification of their outpatient regimen to adapt to the effects of acute illness.
- *Lack of therapeutic adjustment:* The antihyperglycemic regimen is often left unchanged during the entire course of hospitalization, rather than being reassessed and modified based on the monitoring of blood glucose levels. For instance, patient may be treated with regular insulin alone during the entire hospital stay. Thus, an opportunity to observe a patient's response to a more conventional regimen that can be transferred to home is lost.
- *The "sliding scale":* A regular insulin "sliding scale" is used commonly to control blood glucose levels. In its simplest form, at a given blood glucose level, sliding scale delivers the same number of units of subcutaneous regular insulin to every patient. There are opinions that sliding scales are illogical, as they are designed to correct the therapeutic inadequacies

of the previous 4–6 hours period rather than anticipating future requirements. When used alone, without long or intermediate-acting insulin, sliding scales of short or rapid-acting insulin may lead to peaks and valleys of systemic insulin supply. By ordering sliding scale physicians may create the appearance of having designed a detailed and attentive care plan, while in reality they neglect to individualize care to meet the patient's needs.

Apart from certain situations as mentioned in Box 29.1, using sliding scale as the sole form of insulin coverage is usually inappropriate and strongly discouraged. Adding long intermediate-acting insulin will improve control substantially.

- *Underutilization of insulin infusions:* Intravenous insulin is an excellent method to attain glycemic control quickly. Intravenous route provides predictable insulin delivery and enables rapid control of glucose levels compared to subcutaneous route. Although adequate nurse training and supervision is required for their safe implementation, insulin infusions should be able to be administered in any well-staffed general medical or surgical ward. Box 29.2 mentions the indications for intravenous insulin infusion.

Glucose Monitoring

In patients on enteral or parenteral nutrition, glucose monitoring is optimally performed every 4–6 hours. Glucose testing should be performed every 1–2 hours in patients on intravenous insulin infusions. In patients eating usual meals, glucose levels should be monitored as fasting and 2 hours postprandial after 3 major meals or alternatively preprandially before the major

Box 29.1: Sliding scales may be useful in certain situations.

In physiologic adjustment of preprandial insulin based, in part, on the premeal capillary glucose level and the anticipated carbohydrate consumption in their outpatients
With basal insulin analogs, such as insulin glargine, sliding scales may be used initially
In evaluating a patient's initial response to insulin
In patients receiving parenteral nutrition, in whom each 6-hour period is similar to the last.

Box 29.2: Indications for intravenous insulin infusion among.

Nonpregnant adults with established diabetes or hyperglycemia*
Diabetic ketoacidosis and nonketotic hyperosmolar state (A)
General preoperative, intraoperative and postoperative care (C)
Postoperative period following heart surgery (B)
Organ transplantation (E)
Myocardial infarction (MI) or cardiogenic shock (A)
Stroke (E)
Exacerbated hyperglycemia during high-dose steroid therapy (E)
Nothing by mouth (NPO) status in type 1 diabetes (E)
Critically ill surgical patient requiring mechanical ventilation (A)
Dose-finding strategy, anticipatory to initiation or reinitiating of subcutaneous insulin therapy in type 1 or type 2 diabetes. (C)

*In parenthesis, are the levels of evidence (Refer Appendix 3).

Table 29.1: Conditions causing erroneous bedside blood glucose results.

Sources of analytical error
Low hematocrit
High hematocrit
Shock and dehydration
Hypoxia
Hyperbilirubinemia, severe lipemia
<i>Specimen additives:</i> Sodium fluoride
<i>Drugs:</i> Acetaminophen overdose, ascorbic acid, dopamine, fluorescein, mannitol, salicylate
Sources of use error
Inadequate meter calibration
Using a test strip that does not match the meter code or that has passed the expiration date
Inadequate quality-control testing
Poor meter maintenance
Poor technique in performing fingerprick
Poor technique of applying drop of blood to the test strip
Failure to record results in patient's chart or to take action, if blood glucose is out of target range

meals. Bedside glucose monitoring can be performed with glucometers, but a few fallacies should be kept in mind (Table 29.1).

GLUCOSE CONTROL

General Recommendations

- Patients with type 1 diabetes will require some insulin at all times to prevent ketosis, even when not eating.
- For patients treated with insulin, the regimen should be revised every 1–2 days based on the results of glucose monitoring.
- Patients should not remain on a sliding scale as their sole therapy. Adding long or intermediate-acting insulin once or twice daily, even at a small dose, will stabilize control.
- In the postoperative intensive care setting and after myocardial infarction (MI), glucose levels should be maintained as close to the normal range as possible.
- More conservative targets should be considered in patients prone to hypoglycemic reactions (e.g. brittle diabetes, hypoglycemia unawareness), in very elderly, in those who have a short life expectancy due to comorbid conditions, or when adequate nursing or monitoring supports are not available.

Recommendations in Specific Situations

The Patient on Oral Agents and who is not Eating

In patients on sulfonylurea or other secretagogues, hold the drug and use short-acting insulin temporarily. Consider adding intermediate-acting insulin to promote smoother control, if

insulin is needed for more than 24 hours. Metformin may be withheld due to concerns about altered renal function in the acutely ill. The α -glucosidase inhibitors should be avoided because they are effective only when taken with food and thiazolidinediones may be continued unless the patient has abnormal hepatic or cardiac function. Dipeptidyl peptidase-4 (DPP-4) inhibitors are relatively safe, but may be withheld in patients who are not eating.

The Patient on Oral Agents and who is Eating

Inpatients well controlled on oral agents, continue the medications. A dosage reduction of 25–50% may be considered in those who were not following diet as outpatients due to the likelihood of better dietary adherence. Metformin should be discontinued 48 hours before a major surgery, if radiocontrast studies are planned, if renal or hepatic functions are altered, or if hemodynamic instability, heart failure, or dehydration are suspected or anticipated. Continue α -glucosidase inhibitors, thiazolidinediones and DPP-4 inhibitors unless drug-specific contraindications exist. In the patient on oral agents, if glycemia does not improve rapidly, insulin should be initiated.

The Insulin-Treated Patient who is not Eating

Consider intravenous insulin infusion in patients with type 1 diabetes. Alternatively, half to two thirds of the patient's usual dose of long or intermediate-acting insulin may be given along with a short-acting insulin sliding scale. Unless the patient is hyperglycemic (> 200 mg/dL), provide a 5% dextrose solution at 75–125 mL/hour for safety and access purpose.

Some patients with type 2 diabetes on insulin may have improved control with diet restriction and require only short-acting insulin. These patients are frequently obese and poorly compliant with diet as outpatients. Alternatively, give one half of the patient's usual dose of intermediate-acting insulin, with a short-acting insulin sliding scale. If insulin has been given, provide a 5% dextrose solution intravenously at 75–125 mL/hour for safety and access, unless the patient is hyperglycemic (> 200 mg/dL).

The Insulin-Treated Patient who is Eating

Insulin should be continued, although dosage reduction (10–50%) should be considered in well-controlled patients because of the likelihood of more rigid dietary adherence, especially in those with type 2 diabetes or who were not following the dietary advice as outpatients.

Patients on Glucagon-like Peptide-1 Analogues

Exenatide and liraglutide are known to delay gastric emptying and may be withheld in a patient who is not eating or who has nausea or vomiting, due to the propensity of these drugs to cause gastric side effects.

Some Peculiar Clinical Situations

- *Enteral nutrition:* A continuous insulin infusion may provide optimal glycemic control for patients receiving enteral nutrition. This also helps in estimating the total dose of insulin required by the patient. For intermittent enteral feedings, neutral protamine Hagedorn

(NPH) insulin with small doses of regular insulin before each feed is adequate. Capillary glucose testing before each enteral feed would help to decide on the insulin dose. For continuous feeding once or twice daily long-acting insulin can be used. Ideally, start with a small basal dose and use correction-dose insulin as needed, while the basal dose is being increased.

- *Parenteral nutrition:* In a patient receiving total parenteral nutrition (TPN), continuous insulin infusion would provide adequate glycemic control. An alternative regimen is to add regular insulin to the TPN infusion, based on the grams of carbohydrate in the infusion. A reasonable initial regimen is 1 unit of insulin for every 15 grams of carbohydrate in the TPN infusion. The carbohydrate/insulin ratio is then adjusted based on the patient's blood glucose.
- *Steroid therapy:* The typical characteristics of hyperglycemia induced by corticosteroids include minimal effect on fasting glucose levels and an exaggeration in postprandial glucose elevations. The degree of elevation correlates with previous glucose tolerance. Patients with preexisting diabetes can have profound increases in blood glucose. For patients receiving high-dose intravenous glucocorticoids, an intravenous insulin infusion may be appropriate and it helps in calculating the approximate insulin requirement. When steroid dose is tapered, insulin dose should be proactively adjusted to avoid hypoglycemia.
- *Insulin pump:* Patients on continuous subcutaneous insulin infusion (CSII) therapy in the outpatient setting can continue using it in the hospital, provided they are mentally and physically fit to do so. The availability of hospital personnel with expertise and experience in CSII therapy is essential.
- *Transition from intravenous to subcutaneous insulin:* Most hospitalized patients who require intravenous insulin therapy to control hyperglycemia during acute illness will need smooth transition to a subcutaneous insulin regimen to maintain ongoing glycemic control. Ideally, this transition should occur only when the insulin requirement has been stable for at least 4 hours and the patient is able to eat or receive continuous enteral feedings. Intravenous insulin infusion should be discontinued 1–2 hours after administration of short-acting insulin, whereas intermediate or long-acting insulin must be injected 2–3 hours before discontinuing the insulin infusion.

DIABETES MANAGEMENT IN THE CRITICALLY ILL PATIENTS

Van den Berghe and colleagues (2006) suggested that intensive insulin therapy significantly reduced the risk of subsequent death and disease in the critically ill medical patients who were treated for three or more days. This view was challenged in 2009 by the Normoglycemia in intensive care evaluation and survival using glucose algorithm regulation (NICE-SUGAR) study investigators. They found that intensive glucose control increased mortality among adults in the intensive care unit (ICU). A blood glucose target of 180 mg/dL or less resulted in lower mortality than did a target of 81–108 mg/dL. This landmark trial forms the basis of current goals (as mentioned under “aims and targets”) in the critical care setting in medical patients.

Hypoglycemia in hospital setting: Fear of hypoglycemia is one of the biggest barriers to good glycemic management. Hypoglycemia is common in insulin-treated patients and may occur

Table 29.2: Risk factors for hypoglycemia in hospital.

<i>Common risk factors</i>	<i>Less common risk factors</i>
Mismatch of insulin timing, amount, or type for carbohydrate intake.	Endocrine deficiencies (cortisol, growth hormone or both)
Oral secretagogues without appropriate carbohydrate intake	Ingestion of large amounts of alcohol or salicylates
History of severe hypoglycemia	Sudden reduction of corticosteroid dose
Reduction of oral intake	Emesis
Prolonged period of fasting	Reduction of rate of intravenous dextrose
Critical illness (hepatic, cardiac and renal failure, sepsis and severe trauma)	Unexpected interruption of enteral feedings or parental nutrition
	Drug dispensing error

Table 29.3: Areas to be reviewed and addressed prior to hospital discharge.

Level of understanding related to the diagnosis of diabetes
Self-monitoring of blood glucoses (SMBG) and explanation of home blood glucose goals
Definition, recognition, treatment and prevention of hyperglycemia and hypoglycemia
Identification of healthcare provider who will provide diabetes care after discharge
Information on consistent eating patterns
When and how to take blood glucose-lowering medications including insulin administration (if going home on insulin)
Sick-day management
Proper use and disposal of needles and syringes.

in patients on insulin secretagogues. It may range from a very mild lowering of glucose (60–70 mg/dL), with minimal or no symptoms, to severe hypoglycemia, with very low levels of glucose (< 40 mg/dL) and neurological impairment. The risk factors associated with hypoglycemia are enumerated in Table 29.2.

Medical nutrition therapy (MNT) in the hospital: The goals of MNT are to optimize glycemic control, to provide adequate calories to meet metabolic demands, and to create a discharge plan for follow-up care. Current nutrition recommendations advise individualization based on treatment goals, physiologic parameters, and medication usage. Because of the complexity of nutrition issues in the hospital and associated comorbidities including dyslipidemia, hypertension, obesity, renal failure and hepatic failure, a registered dietitian skilled in MNT should serve as an inpatient team member.

Discharge planning: Transition from the hospital setting is a high-risk time for patients with diabetes mellitus. An outpatient follow-up visit with the primary care provider within 1 month of discharge is advised for all patients having hyperglycemia in the hospital. Clear communication with outpatient providers either directly or via hospital discharge summaries facilitates safe transitions to outpatient care. Table 29.3 enumerates the areas to be reviewed and addressed prior to hospital discharge.

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SELF-ASSESSMENT

- 1. Indications for hospitalization of a patient for reasons related to diabetes may be all the following *except*:**
 - (a) Newly diagnosed diabetes in children and adolescents
 - (b) Acute metabolic complications
 - (c) Vitreous hemorrhage
 - (d) Insulin pump initiation
 - (e) Newly diagnosed insulin-requiring diabetes during pregnancy
- 2. The target blood glucose in critically ill patients is:**
 - (a) Less than 160 mg/dL
 - (b) Less than 100 mg/dL
 - (c) Less than 140 mg/dL
 - (d) Less than 150 mg/dL
 - (e) Less than 180 mg/dL
- 3. Glucose monitoring should be initiated in any patient not known to have diabetes, but has the following:**
 - (a) High-dose glucocorticoid therapy
 - (b) Initiation of enteral or parenteral nutrition
 - (c) Immunosuppressive medications
 - (d) Octreotide
 - (e) All the above
- 4. The following situations hamper the efforts to achieve optimum glycemic control in hospitalized patients:**
 - (a) Infection
 - (b) Fever
 - (c) Acute liver injury
 - (d) Steroid therapy
 - (e) Surgical trauma
- 5. Sliding scales may be useful in certain situations:**
 - (a) In physiologic adjustment of preprandial insulin
 - (b) In septic shock
 - (c) With basal insulin analogs, such as insulin glargine
 - (d) In evaluating a patient's initial response to insulin
 - (e) In patients receiving parenteral nutrition, in whom each 6-hour period is similar to the last

6. The evidence for insulin infusion usage is strongest in the following situation:

- (a) Organ transplantation
- (b) Stroke
- (c) Critically ill surgical patient requiring mechanical ventilation
- (d) High-dose steroid therapy
- (e) Nothing by mouth (NPO) status in type 1 diabetes

7. All the following conditions can cause erroneous glucometer glucose readings except:

- (a) High hematocrit
- (b) Low hematocrit
- (c) Hypoxia
- (d) Shock
- (e) Quinolones

8. Patients receiving total parenteral nutrition (TPN) can be given:

- (a) Continuous insulin infusion
- (b) Regular insulin added to the TPN infusion
- (c) Neutral protamine Hagedorn (NPH) added to the TPN infusion
- (d) A and B
- (e) A and C

9. A patient with type 2 diabetes who is on 30 units of premixed insulin in the morning and 15 units in the evening is admitted with subacute intestinal obstruction and he is not eating orally. How will you manage his glycemia?

- (a) One half of the patient's usual dose of intermediate-acting insulin
- (b) Short-acting insulin sliding scale
- (c) 5% dextrose solution intravenously at 75–125 mL/hour if blood glucose is less than 200 mg/dL
- (d) Intravenous insulin infusion
- (e) All the above

10. The following are less common risk factors for hypoglycemia in hospital:

- (a) Hypocortisolism
- (b) Drug induced
- (c) Reduction of oral intake
- (d) Critical illness
- (e) Hepatic failure

CHAPTER

30

Integrating Systems

PART A: TEAM APPROACH TO MANAGEMENT OF DIABETES

*Flory Christina, Nihal Thomas, Abraham Joseph,
Mercy Jesudoss, Senthil Vasan K, Ross Kristal*

*"Diabetes is not just a doctor's dream,
It's all about having nurses on the team,
Let's join together and run your clinic,
With dietician and physio as part of generic."*

Diabetes is a disease that costs dearly, in terms of morbidity and mortality. The concept of the integrated clinic and teamwork is a basic necessity required to handle diabetes mellitus. People living with diabetes face many daily challenges managing their condition. The range of issues is different for every individual but includes diet and exercise, treatment taking, psychological stress and illness and disability. The support of many different professionals is required, alongside informal carers, in meeting this complexity of need.

INTRODUCTION

In routine clinical practice, diabetes is one of the most common chronic disorders handled by doctors of various specialties. Its management needs appropriate guidelines for glycemic control and for handling complications to reduce mortality and morbidity. Several aspects like diet, counseling, rehabilitation for complications and psychological management need specialized care. Thus management of diabetes mellitus involves teamwork. Moreover, the psychological aspect of self-glucose monitoring and its impact on glycemic control cannot be understated.

DISEASE PREVENTION

Disease prevention at various levels of healthcare seems to be the primary target approach in collective diabetes prevention. This will target both risk factors that predispose to diabetes,

and complete diabetes care from diagnosis to effective care of complications and rehabilitation. The various levels of prevention are:

- *Primordial*: Preventing the emergence of risk factors that lead to disease, e.g. obesity, stress, identifying persons at risk by eliciting family history, etc. and taking preventive measures like marriage counseling.
- *Primary*: Prevention of emergence of the disease, e.g. by maintaining ideal weight, detecting gestational diabetes, etc.
- *Secondary*: Early diagnosis and good management, e.g. by screening everyone over 30 years of age, annual checkup, etc.
- *Tertiary*: Prevention of complications and rehabilitation, e.g. strict control of blood sugars, ensuring treatment compliance of drug, diet and exercise, screening for complications (checking vibration and touch sensation, eye changes, renal changes, etc.)
- Notably diet, exercise and glucose monitoring play an important role at all these four levels.

PREVENTION AND ITS IMPORTANCE

It has been proved time and again the truth of the adage—Prevention is better than cure. It is easier to do, cheaper, take little time and is much appreciated by patients.

There are simple and effective strategies at each level of prevention. The single most important requirement is to develop a positive attitude towards the practice of prevention.

Simple strategies can be adopted for effective care in a busy clinic. These can originate both at the hospital with the help of healthcare providers and at the community by oneself. There are simple strategies to do prevention in a busy clinic, which is what all of us deal with. The following recommendations can be put to use.

In the Hospital

- A nurse educator to cover all preventive activities
- Educational posters in the waiting area in the local language
- A notice board dedicated to preventive messages
- Screening questionnaires in local language
- Patient education material in local language
- Identification of at-risk patient by charts with color stickers in the medical records
- Maintain a separate register of patients with diabetes, hypertension, etc. (this helps in an effective data base and community based approaches in education and treatment of subjects)
- A patient retained health record which has the blood results and other relevant investigations, the list of drugs, advice on diet, exercise, etc.
- Group health education while patients are waiting to see the doctor
- Screening videos in the waiting rooms on diabetes in the local language
- Annual screening of subjects over 35 years of age for diabetes and hypertension
- Educating clinical staff about preventive strategies in the management of diabetes
- All patients should be encouraged to spread the health messages in the communities that they live-in

- Encouraging subjects to discuss common health problems besides diabetes and other risk factors that predispose to diabetes, e.g. hypertension, obesity, lack of physical activity

In the Community

- Traditional methods of communication to deliver health messages, e.g. songs, folk drama, etc.
- Simple messages in vernacular language, with more pictorial description of symptoms, complications and diet.
- Group training, e.g. women's self-help groups, youth groups, etc. to deliver health messages
- Schools health programs
- Screening of diabetes with glucometers in outreach programs is simple but very effective. The health worker can be taught how to screen and refer on a routine basis.
- Outreach camps may be organized by any department, e.g. ophthalmology for cataract. These can also be used to screen for diabetes. The important thing is to identify patients as quickly as possible (even before they present with symptoms) within the community and refer for further care.
- A referral system should be in place and known to all members of the health team so that patients identified are followed up
- Collaboration with the government and other nongovernmental organizations (NGOs) in the area to spread health education
- The multidisciplinary approach has been emphasized in the management of diabetes. The health professionals included in this team are: Diabetes educator, physician, orthopedic shoemaker, dietician and ophthalmologist. Table 30.1 shows the interventions for prevention, early diagnosis and treatment of diabetes and complications.

INTEGRATED DIABETES CLINICS

The concept of integrated diabetes clinic has revolutionized the management of diabetes. These clinics play a major role in unifying different aspects of healthcare under one roof and offer the most comprehensive and cost-effective care to minimize mortality and chiefly morbidity associated with diabetes. This integrated multidisciplinary approach also offers consistent and equitable services and provides patient-centered support that will increase uptake of a wide range of interventions available to improve the outcome for patients with diabetes.

This clinic is operational in all levels of healthcare and is comprised minimally of a physician, diabetes nurse educator and dietician. The opportunities of extended services by a podiatrist and physiotherapist may also play an effective role toward healthcare.

The concept of integrated healthcare targets not only subjects with type 1 and type 2 diabetes, but also includes the following groups of individuals:

- Family members of patients with diabetes
- Gestational diabetes mellitus
- Impaired fasting and impaired glucose tolerance
- High-risk groups for diabetes
- Subjects with metabolic syndrome.

Table 30.1: Key cost-effective interventions for prevention, early diagnosis and treatment of diabetes and complications

<i>Intervention implementation priority</i>	<i>Interventions</i>	<i>Stage of disease</i>
Level 1	Glycemic control in those with poor control (HbA1c > 9%) Blood pressure control Foot care Aspirin use	Treatment of diabetes and complications
Level 2	Lifestyle management for preventing diabetes	Primary prevention
	Annual eye checkup Tobacco cessation Angiotensin-converting enzyme inhibitor use Patient health education	Treatment of diabetes and complications
Level 3	Metformin intervention for preventing diabetes	Primary prevention
	Screening for undiagnosed diabetes	Early diagnosis
	Intensive glycemic control (in those with HbA1c > 8%) Annual screening for microalbuminuria Cholesterol control (in those with total cholesterol > 200 mg%)	Treatment of diabetes and complications

FUNCTIONARIES OF AN INTEGRATED DIABETES CLINIC AND THEIR ROLE (FIG. 30.1)

Physician

The physician aims at providing a comprehensive care for diabetes and its associated complications. The physician will be involved in history taking, complete general physical examination, as well as fundus of the eye, feet and other stigmata of associated metabolic syndrome. The physician would then devise a management plan based on the glycemic status and schedule regular follow-ups. This class of individuals may also include a surgeon who will decide management of foot ulcers, peripheral vascular diseases, cellulites of the foot and various other diabetes morbidities that involve surgical management. An orthopedician may be involved in order to manage foot deformities and mobility problems in diabetes. Early recognition, appropriate and timely referral to other specialists also helps to reduce morbidity and mortality related to diabetes.

Diabetes Educator

A diabetes educator is a trained personnel who has completed a formal training in the management of diabetes or have completed a stipulated period of work at a diabetes center. They may be either nursing staff, individuals with a basic science background or a dietician; we have even experimented with the model of a school teacher being an effective diabetes

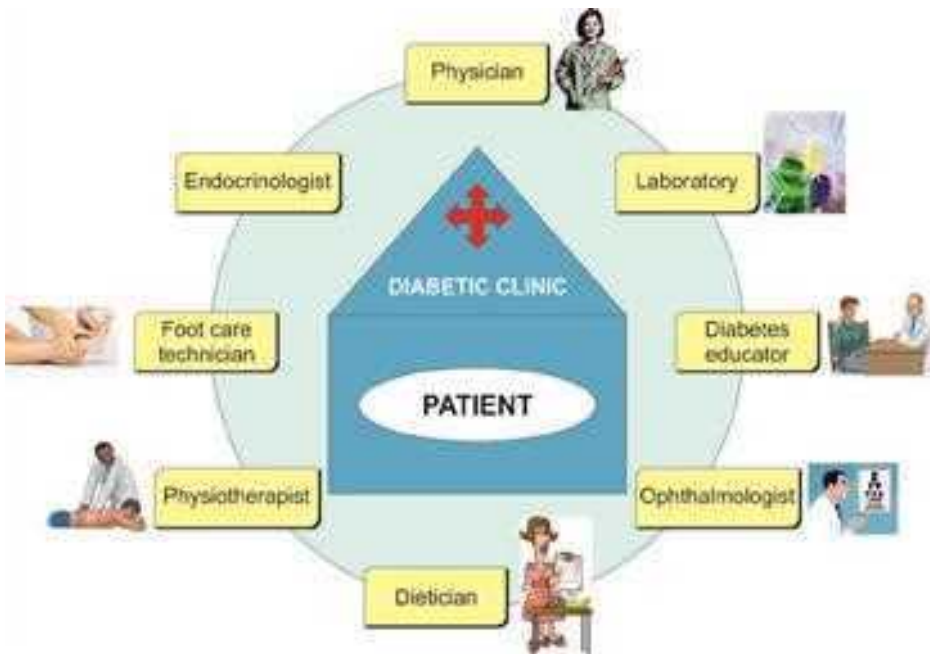


Fig. 30.1: Functionaries of an integrated diabetes clinic.

educator. The educator is a person who serves as a bridging link between the other health care providers and the patient. Their interaction with the patient is mainly to put them at ease with the disease and help them manage diabetes with confidence. The diabetes educator also plays the lead role in the diabetes clinic, superseding the role of the doctor and controlling the environment.

They form the most important category of healthcare providers in diabetes. The concept of educating a patient may involve a personal interview with a patient with or without their family member or a group discussion. They mainly aim at providing awareness to patients with diabetes in making them understand the disease and help them cope with their morbidities and prevent further complications.

The education involves understanding of the basic anatomy of pancreas and pathophysiology of diabetes. Symptom recognition of diabetes, hypoglycemia and self management during times of crisis, complications of diabetes, glycemic targets, monitoring, diet and exercise program, self-titration of insulin, administration of insulin, compliance with antidiabetic medications, foot care and regular follow-ups.

The education may include a wide spectrum of diabetes related discussions on a one-to-one basis with the patient. Through this method they ensure a strong rapport with the patient and also understand their patient's perception of the disease, the problems they face, the myths and beliefs they may embody that hinders adherence to the treatment and follow-ups. After a session of discussion and understanding the nature of the patient, the educator provides a set of simple and complete management guidelines based upon the patient's ethnic and cultural

practices on how to manage diabetes in an easier way in day-to-day life. Nurse educators are also involved in following up patients during their periodic visits to the clinic to reassess the patient, ensure better compliance and reinforcement.

The capacity of a diabetes nurse educator is limitless, to the point where they may lead to adjustment of insulin dosing independent of the physician's instructions.

Dietician

One of the primary management goals is aimed at providing a diabetes diet which is suitable for the individual including their cooking practices, eating habits, food fads and taboos that every individual has. This challenge is taken up by a trained dietician who prescribes the patient a diabetes diet of suitable calories based upon their body mass index and physical activity. The food that is provided is aimed to contain the necessary nutrients in adequate proportions in order to balance the low carbohydrate, low fat, low-cholesterol diet that is usually recommended. The diet is usually divided into 3 meals, 3 snack pattern in order to prevent hypoglycemia and distribute calories equally during the course of the day.

Physiotherapist

A physiotherapist devises an exercise program that best suits the patient in order to maintain the body mass index (BMI) within acceptable levels. This may either be in the form of individual sessions or group discussions with individual and group sessions involving the patients actively in the exercise program.

Foot Care Technician

The role of a foot care technician is to improve the mobility and enhance the independence of individuals with diabetes by prevention and management of pathological foot problems secondary to diabetic neuropathy and associated morbidity. This is achieved by providing advice on foot health, assessment and diagnosis of foot pathology, identification of treatment and other requirements, referral to other disciplines as appropriate, formulation of care plans, and provision of direct care as deemed appropriate and agreed to by the individual. Common problems tackled by the foot care technician include the neuropathic foot, ulcers of the foot, foot care for callosities, fissures and debridement. A competent foot care technician can make independent decisions regarding off-loading and prescription for the type of footwear.

The foot care technician may be assisted by footwear technicians (orthopedic shoemakers) who make appropriate footwear based on the needs of the individual. Footwear made of micro cellular rubber, silicon insoles and rocker bottom shoes are a few examples of footwear designed by trained footwear technicians.

Ophthalmologist

The physician is trained in examining every optic fundus with an ophthalmoscope in the clinic, identify patients at high-risk and refer them to an ophthalmologist.

The above concept of an integrated diabetes clinic will improve the quality of life survival of patients with diabetes, help them cope effectively with their ailments, reduce comorbidities and establish a comprehensive and complete healthcare in a holistic approach under one roof.

Laboratory Quality Control

A good and reliable lab again plays a vital role in the management of diabetes and is very much a part of an integrated diabetes care.

The biochemistry department at Christian medical college Vellore runs an excellent quality control system that covers 2,500 hospitals in the country where in their laboratory systems are monitored periodically at a nominal cost. Such an audit of the quality of individual laboratory tests is vital for the success of the proper management of diabetes.

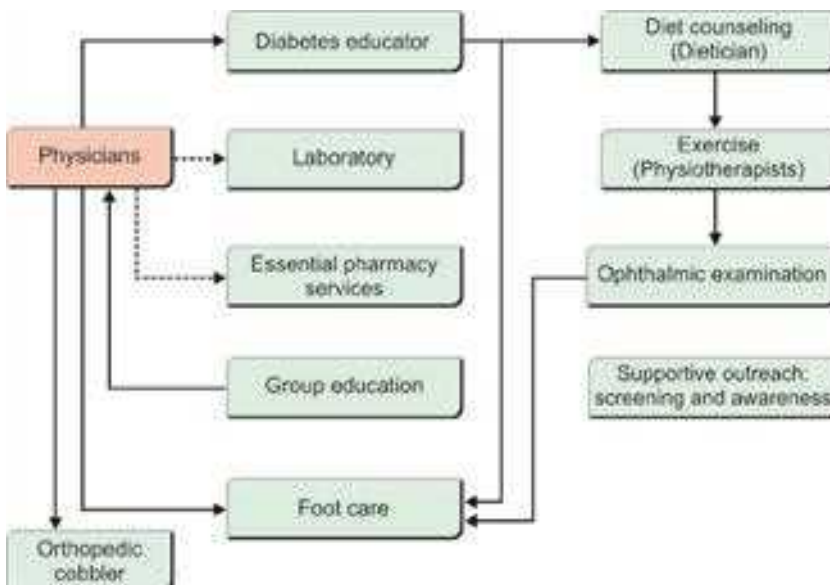
Essential Pharmacy Services

Pharmacies are advised to stock relevant medications and stocks including other ward supplies and devices which are relevant.

In our experience, the impact on holistic care at these peripherally trained hospitals with regards to device handling and foot care has been gratifying. From foot care practice of 14 percent, the practices have evolved to 68%. For essential drug services of 50%, the progress has improved to 90%. For inpatient use of glucometer of 15% (formerly associated with the inappropriate usage of urine sugar monitoring), the use has progressed to 90% in these hospitals.

Flowchart 30.1 shows the model of the diabetes clinic.

Flowchart 30.1: A model diabetes clinic.



Outreach Activities

These activities play an important role in improving public awareness about the pathogenesis of obesity and diabetes. These programs include camps and educational programs on the mass media. They also involve schools and educational institutions, so that children may imbibe the importance of a healthy lifestyle. Moreover, the community develops a bonding to the hospital employees which may perpetuate a long-standing relationship between the hospital and the community in general.

In our experience, the causes for clinics not to function are multiple, however, some of the major ones are: Poor quality laboratory facilities in 30%, discontinuation of trained paramedical staff in 25%, lack of administrative and/or peer support in 15%, lack of functionality of a team in 12% and lack of egalitarianism which is difficult to quantify.

We recommend that hospitals setup a clinic once a week and subsequently once organizational logistics have been sorted out and challenges overcome, to run the clinic twice a week. There is a role for these integrated clinics not only for the large hospitals but also for the smaller ones. A well run integrated diabetes clinic will provide ample support for the infrastructure in enhancing preoperative care and rapid control of sugars prior to surgery, improving the cardiovascular outcomes and enhancing preventive foot care and thereby reducing amputation and ulcer formation rates. It may seem surprising but they can act as significant income generators for systems that may show signs of flagging.

IMPROVING FOOT CARE FOR PEOPLE WITH DIABETES MELLITUS: AN INTEGRATED CARE APPROACH

Our department in collaboration with the vascular surgeon, physiotherapist, orthotic specialist, nurse educator and a diabetes specialist run an integrated diabetes foot clinic (Fig. 30.2) once a week catering the needs of more than 1000 patients every year. The following problems in these patients with diabetic foot problems are assessed and managed in this clinic.

- Ulcer with evidence of spreading infection/cellulitis, gangrene or digital necrosis: A same day referral
- Ulcer defined as any full thickness penetration of the dermis on the plantar aspect of foot not responding after one week's treatment
- Suspected Charcot's arthropathy
- Patients with high-risk feet who have inappropriate footwear and consequently may require footwear provision, pressure relieving insoles or specialist advice regarding footwear.

DIABETES SUPPORT GROUPS

India contains a heterogeneous population made up of different cultures, religions and socioeconomic strata. These factors can have profound effects on the psychosocial statuses of patients with diabetes. Because of the potential stigma, patients oftentimes do not feel comfortable managing their condition or talking about it in public, which can contribute to poor diabetes management. Therefore, having diabetes can be a confusing and lonely experience. Many of these people either have the same questions about living with diabetes or

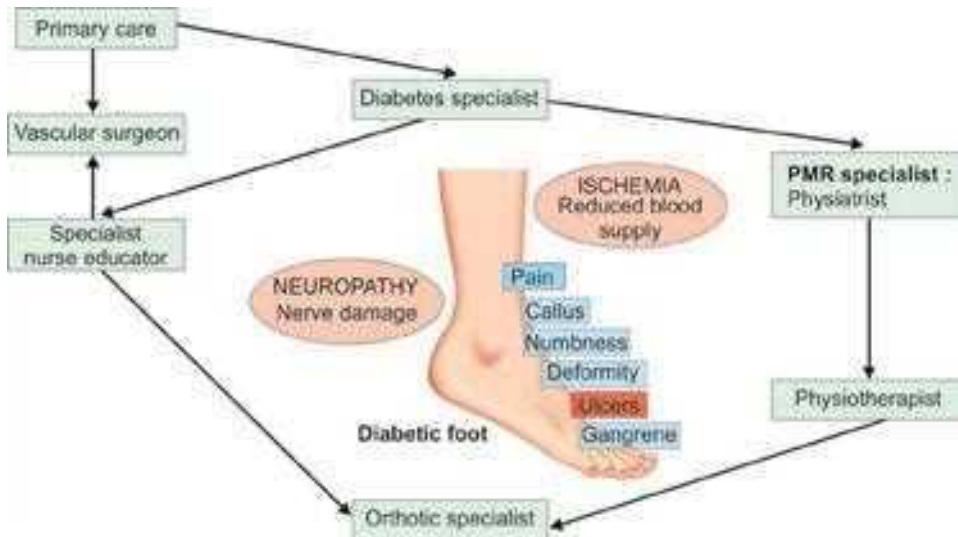


Fig. 30.2: Integrated diabetes foot clinic department. (PMR: Physical Medicine and Rehabilitation).

they have suggestions to answer these questions. Furthermore, bringing patients with diabetes together to discuss various topics provides them with the opportunity to meet other patients with diabetes and to express their experiences in the hope that they can provide educational, social and emotional support for each other in a cooperative atmosphere. Anyone, ordinary people with diabetes, family members and healthcare professionals, can organize a diabetes support group. This chapter provides one method for organizing a diabetes support group, but there are many recipes for success.

Steps for Starting a Diabetes Support Group

- *Research:* Before embarking on the task of organizing a diabetes support group (Table 30.2), one should perform research to distinguish if a local support group already exists. If a support group already exists, it would be more beneficial to strengthen and support the already established group.
- *Seek help from others:* One person should not take on the large task for starting a support group. Rather, the initial organizer should find other people interested in sharing the responsibilities of forming a support group. One can establish a core group of 2–3 volunteers. Support group leaderships can be from its members.
- *Hold an initial planning meeting for the core group of volunteers:* After the formation of a core group of volunteers, the group should meet and write a mission statement or purpose of establishment, decide how often the support group will meet, as well as agree on topics to be discussed during the first few meetings. In addition, the tasks of creating the group should be divided amongst the core volunteers.
- *Find a time and place:* The diabetes support group should meet in an easily accessible location. Some example locations include doctor's offices, hospitals and community

Table 30.2: Sample support groups			
Group	Name	Age	Leader
1	V.K.	11	
	R.S.	9	
	J.N.	10	
	M.P.	9	X
	S.V.	12	
	G.W.	12	
2	A.L.	15	
	R.K.	18	X
	S.A.	16	
	J.M.	19	
	D.S.	17	
	E.T.	17	
3	P.B.	25	
	D.F.	27	
	J.K.	24	
	L.O.	26	
	R.I.	27	X

centers. Organizers should check that the location can provide enough chairs and the space is large enough so that the chairs can be arranged in a circle. The meeting should take place at a time when most people can meet.

- *Recruit members for the support group:* Obtain a list of diabetic patients, either type 1 or type 2 depending on the focus of the group. Organize the list by age and other pertinent characteristics, including socioeconomic level and then, create groups of 5–9 patients based on the similar characteristics. Traveling distances should be taken into consideration because long-traveling distances can cause inconsistent attendance. The organizers should select a patient to be the “group leader” in each group. This patient should have a good history of properly managing their diabetes and act as a role model for the other group members.
- Once the final list is established, contact each patient to invite them to the support group. In the event that some patients do not partake in the support group, the members assigned to each group might have to be reorganized to balance the amount of patients per group.

Meeting Scheme

- Before the group session
 - Arrive to the meeting site early to place chairs in a circle, which will promote dialog
 - Provide writing implements, paper and clipboards for support group attendees
 - If a guest speaker will be presenting, verify that they are able to present
 - Make copies of evaluation forms.

• How would you rank today's support group?

1 2 3 4 5 6 7 8 9 10

• Did you enjoy the introduction activity?

1 2 3 4 5 6 7 8 9 10

• Did you find the topic discussed today helpful?

1 2 3 4 5 6 7 8 9 10

• Are there any topics you wish to discuss during future sessions?

• Do you have any additional comments?

Fig. 30.3: Sample evaluation form.

Table 30.3: Sample schedule of the group session.

<i>Time</i>	<i>Task</i>
5–10 minutes	Introductions/explain purpose of event
10–15 minutes	Icebreaker game
10–20 minutes	Guest speaker or organizer presents topic
30–60 minutes	Group discussion of topic
10 minutes	Recap main points discussed
5–10 minutes	Thank group members for attending and fill out evaluation forms
10–25 minutes	Partake in refreshments and informally discuss the topic

- During the group session (Table 30.3)
 - Kindly and enthusiastically greet all patients as they arrive
 - The atmosphere of the session can be dependent on first impressions, and it is important for patients to feel comfortable and at ease during the session. Therefore, the organizers should place extra effort into greeting patients as they arrive
 - Introduction and explanation of the purpose of session
 - Present the purpose of the support group
 - Pledge that everyone will have the opportunity to share their ideas and experiences
 - Request everyone to show respect for everyone else's ideas
 - Assure members that whatever they say in the support group will remain confidential
 - Promote the asking of questions.
 - Diabetes Support Group Evaluation Form (Fig. 30.3)

Table 30.4: Methods to introduce and discuss topics

<i>Method</i>	<i>Introduction</i>	<i>Discussion</i>
1	Presentation by an expert on the topic	Organizers should ask open-ended questions to the members to generate dialog. The expert can give insight as needed.
2	Presentation of a case scenario related to the topic	Organizers should ask questions to relate the group members' personal experiences to the case study. When discussing solutions to the case study, see if the solutions can be applied to the member's lives
3	Presentation of a one to two sentence description of the topic	Organizers should ask open-ended questions to the members to generate dialog

- Icebreaker game
 - An icebreaker game reduces the tension amongst the group members and promotes conversation.
 - One example of an icebreaker is to have the members pair up and then learn each other's name, age, how long they have had diabetes and a fun fact about themselves. After 5–10 minutes, the partners' can present the other person's information to the rest of the group.
- Presentation and discussion of the topic by the organizer or a guest speaker (Table 30.4)
 - The group should discuss one topic per session.
 - Members should partake in the discussion and the organizers should only facilitate the discussion.
 - Group leaders should frequently give their insight without taking over the discussion.
 - Good points should be written down on a board for all group members to see.
 - Positive reinforcement should be given frequently.
- Recap the topic and good points discussed
 - During long discussions, patients sometimes can not see the wood for the trees. Therefore, it would be helpful to take a step back and review the general topic of the session and the good points discussed (Fig. 30.4). In addition, writing the good suggestions on a board can improve patients' retention of information.
- Closing remarks
 - Thank the group members for attending
 - Pass out and collect evaluation forms
 - Remind members when the next session will take place.

After Session

- Review the evaluation forms
- Make arrangements for future sessions
- Plan sessions to accommodate the identified needs and overcome the identified obstacles. With the number of people diagnosed with diabetes growing every year, information about managing diabetes, raising awareness and providing support is vital. Diabetes support

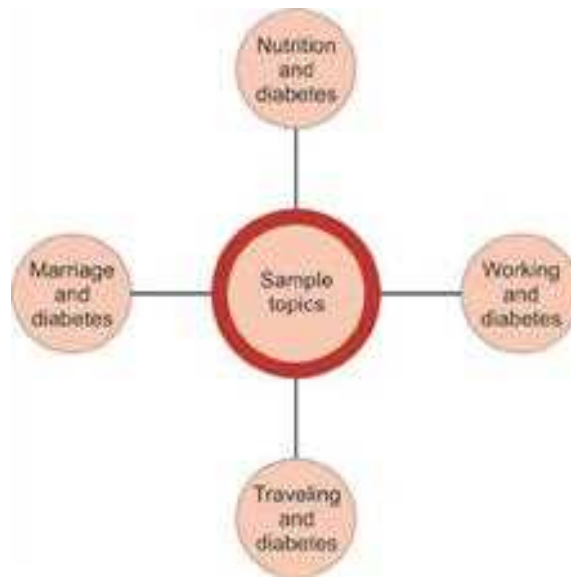


Fig. 30.4: Sample topics.

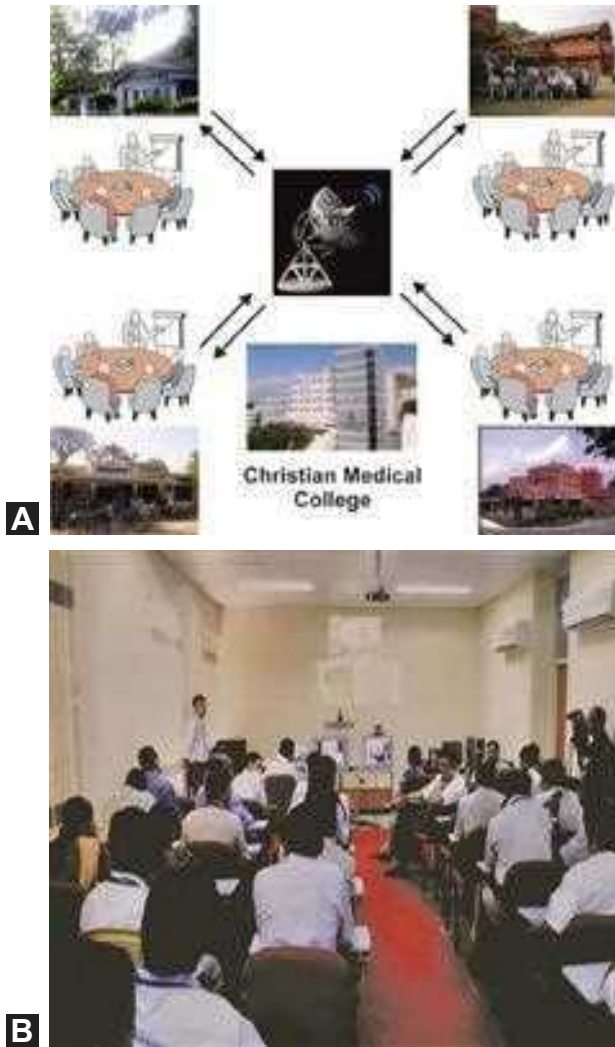
groups are an excellent way to meet other people with diabetes, share information, and hear about other people's experience of living with diabetes. They can provide a positive reinforcement through support and education in an exclusive environment of peer, family and care givers. Support groups play a vital role in involving family members in the process of assisting their patients through their adaptation to lifestyle modifications and treatment regimen. Support groups provide an opportunity to patients to interact with different group of individuals managing diabetes in different parts of the world, through video conferences. Patients who attend support groups find support important as it helps them to be more positive in managing diabetes. Patients who attend support groups have relatively less depression, fewer complications, more confidence and good compliance to the treatment.

PART B: TELEHEALTH—BRIDGING DISTANCES IN DIABETES

Vinod Shah, Hasna Rajesh, Nihal Thomas

INTRODUCTION

The Greek word “tele” simply means “distant” and telemedicine means being able to teach, train or therapeutic from a distance. There are 500,000 physicians in India and close to 250,000 are without postgraduate qualification. They are the ones who will manage the diabetics of this country—estimated to be whopping 16% of those above the age of 30 of India's population. How can we get them to accept standard diabetes protocols? The answer would be in providing a structured course in diabetes through distance education and having recourse through telemedicine technology. We can indeed make a huge impact!!



Figs. 30.5A and B: Telehealth classroom setup.

Telemedicine has brought the whole gamut of teaching, training, consultation and follows up within the realms of possibility. The term telemedicine is now being supplanted by Telehealth and covers use of electronic information and communications technologies to provide and support health care education when distance separates the participants.

TELEHEALTH CLASSROOM SETUP

A telehealth setup (Figs. 30.5A and B) involves specialized application software, data storage devices, database management, medical devices capable of being interfaced with the transmitting equipment, storage and transmission with appropriate network like internet protocol

(IP), integrated services digital network (ISDN) or satellite. The telehealth based on technologies used can be divided into two modes: Synchronous and asynchronous. Videoconference is one of the most common forms of synchronous technology.

Videoconferencing System—Dedicated and Desktop Dedicated System

The components required for a dedicated videoconference system:

- Videoconference unit (VC) consists of a console (also called base) and a remote controlled Pan-tilt-zoom (PTZ) video camera with good resolution. The console contains all electrical interfaces, the AV ports and the software or hardware-based codec for digital compression of audio and video streams.

The other components required for a videoconferencing system include:

- *Video input*: PTZ camera attached to the console of the VC unit or document camera
- *Video output*: Television or projector
- *Audio input*: Microphones, any other source of preamplifier audio outlet
- *Audio output*: Inbuilt speakers associated with the display device like television or PA speakers
- *Computer*: Connected to the VC unit for transmitting any multimedia presentations and videos

Good room acoustics followed with false ceiling, rough walls, carpeted floors to avoid echo and noise interference. Power backups (UPS) are essential.

Communication Media

- *IP/Internet*: A dedicated broadband with static IP address of minimum 384 kbps (per site) with equal upload and download data speed.
- *Integrated Services for Digital Network (ISDN)*: The traditional transport for digital videoconferencing because it provides dedicated channels end-to-end. Now ISDN usage has mostly given way to networks that use the Internet protocol (IP) due to its expensive call rates. The bandwidth is the multiples of 64 kbps allocated in basic rate interface (BRI) and primary rate interface (PRI). 1 BRI = 128 kbps and 1 PRI = 1920 kbps. For good transmission a minimum of 3 BRI connectivity speed is required.
- *Satellite (VSAT)*: It is supported by the Indian Space Research Organisation (ISRO) and a specific bandwidth is assigned to each hospital. The ISRO project uses this connectivity to reach the remote hospitals to link up with the tertiary hospital and thus improve access to specialty care.
- *Multiprotocol label switching (MPLS)*: This is the private virtual private network (VPN) connection over the shared network. The cost of MPLS depends on the bandwidth requirements and the number of sites.

Software

For online patient consultation or case discussion, good software is required to transfer patient records and diagnostic images. Digital imaging and communications in medicine (DICOM) is a standard for handling, storing, printing and transmitting information in imaging without loss in resolution. It enables image acquisition, display and transmission

to other units that are capable of receiving image and patient data in DICOM format. These images can be stored in picture archiving and communication system (PACS) server. It is recommended to use DICOM for image transfer and telemedicine link to discuss the case between doctors.

DESKTOP CONFERENCE: WEB-BASED LEARNING METHOD

Desktop setups are the cheapest method of videoconferencing and designed entirely in software, a cost-effective method for a remote interactive classroom. There is no need to have a separate hardware systems installed at every remote location to access the online meeting.

This setup includes:

- A computer with USB ports
- Small web camera mounted on top
- A microphone
- Internet connection with a speed of minimum 384 kbps (existing internet connection that allows multimedia communication can be used)
- Software to perform the job of the codec. The desktop software is a simple web browser plug-in that is centrally managed and deployed without any installation issues and no license fee. The participant may simply click on a link and in moments the computer turns into a powerful visual communication device enabling face-to-face interactive online meeting. This software can be reinstalled on as many computers as needed. The administrator can opt for named account licenses or floating licenses to control participants.

The presenter is allowed to show documents such as a slide presentation or websites to the candidates online through desktop sharing. Along with microphone, communication can also be facilitated via chat box where instant messaging is possible. This design is more appropriate for the student at a distance but not conducive to main classroom.

Multipoint Control Unit

Multipoint control unit (MCU) is a bridge that interconnects the multiple calls simultaneously. MCU is a stand-alone hardware device and with the combination of software, the desktop participants can be integrated to dedicated VC units. Hence, the candidate joining through the desktop can be linked to main classroom's dedicated VC via MCU. It is based on H.323 standards (IP) but ISDN calls can also be connected with the help of a gatekeeper. It can handle multiple calls simultaneously depending on the license factor. It gives continuous presence in which multiple participants can be seen on-screen at once.

Live Streaming to Desktop/Laptop

Remote students can watch the live high quality video at any desktop/laptop via web browser and standard media player. It uses one communication stream for a number of users. This is ideal for the presentation that does not require two-way communication. Students with streamed lectures have the benefit of watching the lectures with interaction from various locations and thus have richer learning experience than watching a prerecorded video lesson.

Archiving the Lectures

Recorded archives can be made available to the students at the scheduled time either as a streamed real time streaming protocol (RTSP) feeds or downloadable media files. This is asynchronous learning mode where participants access course materials on their own schedule and so is more flexible.

Telepresence

A telepresence system is a high-end room-based videoconferencing system between two or more points that feels like a live meeting. Telepresence conference rooms use state-of-the-art room designs with matching furniture and backdrops creating the illusion that the remote participants are in the same meeting room. Notable features are multiple screens, high-quality directional audio system, multiple video cameras and processors. It requires very high-capacity bandwidth transmissions and is quite expensive system.

REQUIREMENTS FOR QUALITY TRANSMISSION

Image

The quality of moving images depends on the amount of bandwidth. Low bandwidth leads to imperfect transmission of moving images, as the object moves the images blurs and the fast action is not transmitted well. There will be delay in the sound too. So availability of the adequate bandwidth should be ensured with the internet service provider (ISP).

Audio

Although the videoconferencing relies on both the audio and video quality, videoconference can still be maintained even if the quality of video drops out. However, this cannot be possible the other way around. While capturing audio there are several factors to be taken into account. Often a lot of ambient sound is present like technical equipments' hum, fans, air conditioners that may not be conspicuous during regular course of session, but noticeable only when captured and transmitted to other end. Another important aspect is the positioning of the microphones. If it is set too close to the public address speakers, the feedback may occur and if near to the computer there can be ambient noise. At the same time, if microphone is too far from the presenter the audio level may be too low. All of this can be easily overcome with appropriate staff training.

Lighting

The venue must have appropriate light; it can be natural or artificial. Sufficient amount of light has to be available to cover all of the participants in the videoconference.

Positioning of the Camera

The design of positioning of the camera should be mainly aimed at two groups:

1. Larger groups in a bigger venue such as a classroom with students and a lecturer.

2. Smaller groups often in standard rooms for small meetings, teleconsultations, teleconference, etc.

The larger groups require two cameras, one facing the speaker and the other facing the audience at far end. The far-end camera can be handy connected to videoconferencing equipment positioned near to the speaker. While in smaller groups, the whole group can face one camera.

ADMINISTRATIVE CHALLENGES AND ISSUES

- Internet protocol/Integrated services digital network is not available in all places. Satellite connection is the solution for remote places, but it is expensive
- The participant joining through desktop uses the existing internet connection, so the video quality has to adjust to the current available bandwidth. The low bandwidth deteriorates the quality of conference
- The overall quality of the videoconference is dependent on the connections and technologies at all of the participating sites. Bandwidth availability is the major constraint.
- Unable to give emergency care when required
- Doctors overburdened with regular patient consultation find time a constraint for online consultations
- Instructor should adapt teaching styles taking into consideration the needs and expectations of multiple remote audiences.

Impact of Telemedicine on Diabetes and Health

- Closely resembles traditional classroom-based education, permits learners to be active participants in the process
- More candidates can be trained faster without increasing training resources
- Guest lecturers can be easily integrated into the course
- Training doctors at the remote end on correct use of new medical equipment and techniques and also in treatment and dosage of medicines
- Online patient consultation where records are sent through software and live interaction through videoconferencing takes place with remote end doctor and patient; thus global positioning system (GPS) can manage certain specialty cases at their center.
- Clinical case discussions with many hospitals through multipoint conferencing
- Diabetes training programs is transmitted online to peripheral hospitals to train general practitioners
- Reaching rural health care in diabetes: Rural diabetes projects have been started for the provision of modernized and affordable diabetic care to people in rural areas. Establishment of ambulatory diabetes care units with telemedicine facility are integral part of these projects.

CONCLUSION

In view of India's fast growing population, diabetes is reaching epidemic proportions. Videoconferencing can thus play a key role in bridging the yawning gap between the rural hospital

and the well-equipped tertiary care center. Virtual classrooms can help bring diabetes education close to the millions in a country like India and physicians based in rural areas will be able to take the best of diabetes care to the grassroot level.

SUGGESTED READING

1. Esterson YB, Carey M, Piette JD, et al. A systematic review of innovative diabetes care models in low-and middle-income countries (LMICs). *J Health Care Poor Underserved*. 2014;25(1):72-93.
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3. Singh A, Milton PE, Nanaiah A, et al. Awareness and attitude toward diabetes in the rural population of Arunachal Pradesh, Northeast India. *Indian J Endocrinol Metab*. 2012;16.
4. Thomas N, Asha HS, Spurgeon R, et al. Type 2 diabetes in rural India—new paradigms in its epidemiology and evolution. *J Indian Med Assoc*. 2009;107(11):785-6, 788, 790.

SELF-ASSESSMENT

1. **Functionaries of an integrated diabetic clinic include all *except*:**
 - (a) Laboratory
 - (b) Diabetes educator
 - (c) Nutritionist
 - (d) Microbiologist
2. **A foot care technician is expected to do all *except*:**
 - (a) Improve the mobility of the patient
 - (b) Provide advice on foot health
 - (c) Teaching foot exercise
 - (d) Identify callosities, fissures etc
3. **All of the following are considered level 1 intervention implementation, in priority**
 - (a) Glycemic control
 - (b) Aspirin use
 - (c) Foot care
 - (d) Tobacco consumption
4. **The major reasons for outreach clinic malfunction include all of the following *except*:**
 - (a) Poor lab facilities
 - (b) Discontinuation of trained medical staff
 - (c) Lack of peer support
 - (d) Lack of drugs
5. **Impact of telemedicine on diabetes and health include all *except*:**
 - (a) Ease of guest lectures integrated into a course
 - (b) Clinical case discussions with multi point conferencing
 - (c) Online patient consultations
 - (d) One sided teaching without much patient interaction



The Health Sciences Publisher

Final Evaluation

MULTIPLE CHOICE QUESTIONS

Single Best Response Type: 1 to 75

- 1. A patient with diabetes has a callosity on the right foot which is located on the 1st metatarsal head and recurs after removal. Examination of the foot shows mild clawing and she has a monofilament sensation perception of 10 g. After removal again, which of the following methods would you use to prevent a recurrence?**

 - Total contact cast.
 - Patellar tendon bearing brace
 - Microcellular rubber foot wear without a broad toe box and a back strap
 - Footwear with a metatarsal bar
- 2. A 70-year-old man has below knee amputation following progressive wet gangrene. He is obese and has osteoarthroses. The stump ulcer is about 4 cm in size. He wishes to have prosthesis on a long term basis following healing of the ulcer. Which of the following forms of therapy would you use for now?**

 - Patellar tendon bearing brace.
 - Silver sulphadiazine dressing.
 - Walker
 - MCR foot wear with metatarsal bar
- 3. A 30-year-old man presented with polyuria and polydipsia, abdominal pain and weight loss of 10% of his body weight, and is normotensive. He has been married for 3 years and is infertile. His urine ketones were negative. His blood sugars were 420 mg/dl. C-peptides were 3.0 ng/dl. GAD Antibodies are negative. Urine microscopy shows numerous WBCs and the culture grows *E coli*. A CT Scan done to rule out pyelonephritis shows a normal pancreas, liver and bilateral renal cysts with normal sized kidneys.**

Your most likely diagnosis is:

(a) MODY 1	(b) MODY 3
(c) MODY 5	(d) MODY 7

4. A 40-year-old gentleman with diabetes presents pain in the medial aspect of his foot and which is persistent. Examination shows edema and tenderness of the medial aspect of the foot. His monofilament testing reveals non-perception of a 10 g monofilament and Biothesiometry of 35 mV. A plain X-ray reveals features of Charcot's type 2 arthropathy, by the Mdjernovic classification. He is otherwise physically fit with a BMI of 22 kg/m², and can walk 6 km a day, but for the pain in his foot, and feels well otherwise and his sugars on Glimiperide and metformin are equivalent to a HbA1c of 6.7%. The most suitable form of therapy would be:
- A moulded insole with a rigid rocker, with a shore value of less than 16 and more than 8 for the insole.
 - A clog with the cutout of the outer-sole on the medial aspect below the first metatarsal head and an insole with a shore value of less than 16 and more than 8.
 - Ankle-foot orthosis with a boot and an insole with a shore value of more than 8 and less than 16.
 - Standard microcellular foot -wear with a back-strap and a insole with a shore value of less than 16 and more than 8.
5. A 50-year-old man has diabetes for 10 years duration; he is on maximum dosage of oral hypoglycemic agents with which he has been compliant with. He is currently on Metformin, Pioglitazone, Voglibose, Linagliptin and Glimiperide. He did not want to take insulin till this point. On examination his BMI is 21kg/m² and he has no complications of diabetes. Self Monitored sugars on 5 days of the week, show an average of 250 mg/dl and HbA1c is 9.0%. He is willing for a single daily add-on drug to the current medications. Cost is not an issue, essentially it should be effective and the dosage can be escalated if required in multiple increments. Which one would you choose?
- Degludec
 - Glargine
 - Gliclazide-XL
 - Liraglutide
6. A 40-year-old gentleman has been on monotherapy for his diabetes for 6 months. He is experiencing recurrent urinary tract infections, which his doctor is ascribing to pharmacological therapy. Which one is the most likely cause?
- Sitagliptin
 - Glucokinase inhibitors
 - Dapagliflocin
 - Albiglutide
7. A 50-year-old lady is on metformin therapy for diabetes for 4 years. She is very cautious with pharmacotherapy and has heard that adding on other oral drugs can cause hypoglycemia, some of which may pose a risk for pancreatic tumors. (Though not proven), some cause abdominal distension, some cause edema and some cause urinary tract infections. Which oral drug approved by the FDA, then would you use as an add-on which does not have any of the adverse effects that have been mentioned?
- Sitagliptin
 - Liraglutide
 - Acarbose
 - Bromocriptine

8. A 28-year-old gentleman presented with hypertension, diabetes and cardiac failure. He had a weight loss of 20 kg and subsequently his bone marrow showed evidence of histoplasmosis. He was advised to take the following medication for 2 years after initial stabilization:
- (a) Itraconazole (b) Ketaconazole
(c) Voriconazole (d) Metronidazole
9. A 50-year-old gentleman with diabetes and on chronic corticosteroid therapy for SLE presents with cough with expectoration. There are gram-positive filamentous organisms in his sputum. After stabilization he is given a 6 week course of oral medications and is well after that. What has he been given?
- (a) Cotrimoxazole (b) Voriconazole
(c) Fluconazole (d) Ampicillin
10. A 40-year-old gentleman has difficulty trying to control diabetes requiring 200 units of insulin per day. Which of the following infections would he possibly have which could be responsible for this insulin requirement?
- (a) Hepatitis A (b) Hepatitis B
(c) Hepatitis C (d) Hepatitis E
11. The maturity onset of diabetes in the young (MODY) subtype of diabetes is defined as:
- (a) A form of type 1 diabetes in the young
(b) A syndromic form of diabetes with exocrine dysfunction
(c) A form of early-onset familial non-autoimmune diabetes
(d) A ketogenic variety of diabetes affecting middle-aged people
12. Following is true about MELAS, *except*:
- (a) Maternal inheritance only
(b) Stroke like episodes
(c) Deafness, diabetes, dystonia
(d) Associated with porphyria
13. Prediabetes is associated with all of the following *except*:
- (a) Increased risk of developing type 2 diabetes
(b) Impaired glucose tolerance
(c) Increased risk of heart disease and stroke
(d) Increased risk of developing type 1 diabetes
14. Excessive thirst and a high volume of very dilute urine may be symptoms of:
- (a) Urinary tract infection (b) Diabetes insipidus
(c) Viral gastroenteritis (d) Hypoglycemia
15. Among female subjects in particular, the first sign of diabetes may be:
- (a) Rapid weight gain (b) Constipation
(c) Genital candidiasis (d) Insomnia
16. Hyperinsulinemia may be caused by all of the following *except*:
- (a) An insulinoma (b) Nesidioblastosis
(c) Insulin resistance (d) LADA

- 17. Proliferative retinopathy is often treated using:**
- (a) Tonometry
 - (b) Fluorescein angiogram
 - (c) Antibiotics
 - (d) Laser surgery
- 18. Which of the following diabetes drugs acts by decreasing the hepatic glucose output?**
- (a) Sulfonylureas
 - (b) Meglitinides
 - (c) Biguanides
 - (d) Alpha-glucosidase inhibitors
- 19. The benefits of using an insulin pump include all of the following *except*:**
- (a) By continuously providing insulin they eliminate the need for injections of insulin
 - (b) They simplify management of blood sugar and often improve A1C
 - (c) They enable exercise without compensatory carbohydrate consumption
 - (d) They help in weight reduction
- 20. Which of the following regimens offers the best blood glucose control for persons with type 1 diabetes?**
- (a) A single anti-diabetes related medication
 - (b) Once daily insulin injections
 - (c) A combination of oral anti-diabetic medications
 - (d) Three or four injections per day of different types of insulin.
- 21. An overweight man with type 2 diabetes mellitus and peripheral neuropathy asks you about starting an exercise program to lose weight. Which *one* of the following is NOT a beneficial effect of incorporating increased physical activity and weight loss into the regimen of this patient?**
- (a) Reduction in blood glucose
 - (b) Reduction in blood pressure
 - (c) Improvement in lipid profile
 - (d) Smoking cessation becomes easier
- 22. Which *one* of the following mechanisms MOST likely contributes to accelerated vascular disease associated with insulin resistance?**
- (a) The direct effect of elevated insulin levels on the vessel wall
 - (b) A pro-inflammatory state.
 - (c) Accelerated fatty acid oxidation in vascular smooth muscle cells
 - (d) Reduced plasminogen activator inhibitor-1 (PAI-1) levels
- 23. Which *one* of the following vaccines is recommended for all patients with diabetes between the ages of 18–64 years?**
- (a) Meningococcal
 - (b) Pneumococcal once and yearly influenza
 - (c) Hepatitis B
 - (d) Pneumococcal every 5 years and influenza yearly
- 24. For the oral antidiabetic agent:Metformin, select one lettered primary mechanism of action largely associated with it.**
- (a) Reduces gluconeogenesis in the liver
 - (b) Stimulates post-prandial insulin secretion

- (c) Delays the absorption of carbohydrates in the gut
(d) Enhances insulin sensitivity in the peripheral tissues
- 25. A 55-year-old man with type 2 diabetes for 13 years complains of sudden loss of vision in left eye alone following lifting a 10 liter container of oil off the floor. Which of the following causes of visual loss are most likely?**
- (a) Macular edema (b) Vitreous Hemorrhage
(c) Cataract (d) Neovascular glaucoma
- 26. Which of the following agents does not have a direct or indirect impact on peripheral tissues in aiding glucose uptake into the cells?**
- (a) Glimiperide (b) Pioglitazone
(c) Rosiglitazone (d) Acarbose
- 27. A 35-year-old man presents with recurrent episodes of hypoglycemia while traveling on the highway between Bangalore and Chennai in a car. He has been on solitary oral hypoglycemic therapy for 14 years. The most likely reason for these hypoglycemic attacks is:**
- (a) Repaglinide (b) Nateglinide
(c) Glipizide (d) Chlorpropamide
- 28. Which of the following is not true with regards to glucose metabolism in patients with hyperthyroidism?**
- (a) Carbimazole may be occasionally responsible for hypoglycemic episodes.
(b) Glycogen depletion in the liver may lead to fasting hypoglycemia
(c) Antibodies to the insulin receptor do not cause hypoglycemia
(d) Postprandial hyperglycemia is not due to reduced GLP-1 levels in blood
- 29. Which of the following are false?**
- (a) Glargine should not be mixed with other insulins because of its acidic pH and may precipitate when mixed with pH-buffered insulin.
(b) Hexamers are the prevalent form of insulin when present in solution.
(c) NPH insulin has an effective duration of action of 7 hours.
(d) The normal basal insulin secretion in the body is about 0.5 to 1.0 u/hour at night.
- 30. All except one of the following is associated with hyperglycemia:**
- (a) Diazoxide (b) Glucocorticoids
(c) Growth hormone (d) Sodium valproate
- 31. A 50-year-old diabetic individual presents with chronic infection of the right foot. Which of the following investigations will be ideal in diagnosing underlying osteomyelitis?**
- (a) X-Ray foot (b) Probe test
(c) Bone scan (d) MRI scan
- 32. Which of the following statements is not true with regards to diabetic nephropathy?**
- (a) May be functionally silent for long periods
(b) Is associated with enlarged kidneys

- (c) Is associated with normal size kidneys
(d) Is associated with contracted kidneys
- 33. All except one of the following can be associated with fasting hypoglycemia:**
- (a) Hypopituitarism (b) Insulinoma
(c) Glucagonoma (d) Adrenal insufficiency
- 34. Fictitious hypoglycemia due to sulfonylurea containing medications is associated with all except one of the following:**
- (a) High plasma insulin (b) High insulin/glucose ratio
(c) Normal proinsulin (d) Decreased C-peptide
- 35. The most common course for hypoglycemia in hospitalized patients is:**
- (a) Renal failure (b) Liver disease
(c) Sepsis (d) Medication
- 36. A 25-year-old male patient on treatment for type 1 diabetes presents with a history of chronic diarrhea for the past 3 months, associated with weight loss. Which of the following is most likely in this patient?**
- (a) Pancreatic exocrine dysfunction
(b) Thyrotoxicosis
(c) Coeliac disease
(d) Immunoglobulin deficiency
- 37. A 45-year-old male patient on twice daily insulin presents with persistent high fasting blood sugar levels, in spite of increasing night doses of insulin. What will be the most appropriate action in this situation?**
- (a) Increase the night dose of insulin
(b) Shift calories from dinner to lunch
(c) Check early morning blood sugar
(d) Add Pioglitazone
- 38. A 25-year-old lady on treatment for type I diabetes presents with recent of worsening of her blood sugar levels. What could be the most likely cause in this age group?**
- (a) Non compliance with medication
(b) Associated thyrotoxicosis
(c) Non compliance with diet
(d) Pregnancy
- 39. Which of the following will be the most appropriate medication to use in a patient type 2 diabetes and decompensated liver disease?**
- (a) Glimiperide (b) Metformin
(c) Pioglitazone (d) Insulin
- 40. Which of the following can most frequently contribute to high blood sugar in patient with type 2 diabetes?**
- (a) Chlorpromazine (b) Haloperidol
(c) Sertalin (d) Olanzapine

41. **All except one of the following can contribute to frequent hypoglycemia in a diabetic individual:**
- (a) Insulin over dose
 - (b) Associated renal insufficiency
 - (c) Associated liver disease
 - (d) Hypothyroidism
42. **Which one of the following oral hypoglycemic agents is *advisable* in a patient with type 2 diabetes and renal impairment (Creatinine 2.4 mg/dl)?**
- (a) Glibenclamide
 - (b) Glimiperide
 - (c) Gliclazide
 - (d) Metformin
43. **Which of the following anti-epileptic agents *can contribute* to uncontrolled blood sugar?**
- (a) Phenytoin
 - (b) Carbamazepine
 - (c) Sodium Valproate
 - (d) Gabapentin
44. **A seventy year old man was admitted with random plasma glucose of 680 mg/dl. His electrolytes were as follows:**
Na 128 mEq/liter
K 4.8 mEq/liter
HCO₃ 23 mEq/liter
He probably has
- (a) Depletional hyponatremia
 - (b) Dilutional hyponatremia
 - (c) Pseudohyponatremia
 - (d) Euvolemic hyponatremia
45. **Which is *false* regarding neovascularization in diabetic retinopathy?**
- (a) New vessels may be present on the disc
 - (b) New vessels may be present anywhere on the retina
 - (c) New vessels are adherent to the anterior vitreous and not the posterior vitreous.
 - (d) New vessel formation may be flat or elevated and may be associated with fibrosis.
46. **A 40-year-old man with diabetes for 9 years has recurrent episodes of painless vomiting. He is now on Glargine and appears to be getting multiple episodes of hypoglycemia. An endoscopy reveals food in the stomach even after 6 hours. Which of the following are *false*:**
- (a) Exenatide is not an appropriate agent for treating his current status of diabetes.
 - (b) DPPV-4 inhibitors do not delay gastric emptying significantly.
 - (c) It may be appropriate to administer insulin after a meal in such a situation
 - (d) Liraglutide if available may be more suitable for this gentleman.
47. **The patient mentioned above is now on medications to relieve his current symptoms. Even after standard medications are used, he has only partial relief. Which of the following are *false*?**
- (a) Erythromycin in a dosage of 400 mg thrice a day is sometimes used.
 - (b) Good glycemic control helps in reducing the symptoms partially
 - (c) If he has chronic renal failure coinciding, erythropoietin therapy is sometimes used for anemia
 - (d) Using bulk laxatives in case he has constipation could worsen his gastric symptoms

- 48. A 31-year-old man with Type 1 diabetes for 16 years is on a split-mix regimen with soluble insulin 12 units and 14 units of NPH in the morning and 18 units of soluble at night with 18 units of NPH at night. His sugars are: Fasting: 80 mg/dl, post breakfast 160 mg/dl, post lunch 260 mg/dl and post dinner 160 mg/dl. Which of the following are least likely to be true?**
- (a) You may consider increasing the morning dose of NPH.
 - (b) You may consider trying soluble insulin with lunch as an add on.
 - (c) You may increase the morning dose of soluble insulin
 - (d) You may ask him to reduce the lunch time calories and increase the bedtime snack
- 49. A 28-year-old lady with a history of pregestational diabetes and homozygous hypercholesterolemia on treatment is about to deliver. Her fetal scan shows certain anomalies. Which of the following are *least* likely to be true?**
- (a) Transposition of great vessels could be due to uncontrolled diabetes mellitus.
 - (b) Low birth weight may predispose for diabetes later on in life.
 - (c) Atorvastatin could cause cleft lip and palate.
 - (d) Ezetimibe could cause duodenal atresia.
- 50. A 20-year-old type 1 diabetes subject is currently on insulin for the last 12 years. She is currently on Glargine 14 units at bed-time, Humalog 4 units with breakfast, lunch and dinner. She has sudden episodes of hunger and dizziness hours after a meal, 6-7 times a week. She has never had palpitations or tremors on any occasion recently. Glycosylated hemoglobin levels are currently 4.5%. On one occasion, the profile of sugars is:**
- Fasting: 210 mg/dl, post bnf: 160 mg/dl, post lunch: 90 mg/dl and post dinner: 60 mg/dl. Which of the following statements is least likely to be true?**
- (a) She is at risk for severe hypoglycemia
 - (b) Humalog is the first ever short acting insulin analog to be marketed
 - (c) A Somogyii phenomenon is likelihood in this patient
 - (d) Autonomic neuropathy is less likely to be present in her
- 51. A 40-year-old patient with type 2 diabetes for 6 years duration comes to your clinic. He is under going a regular check up. You wish to exam the optic fundus. Which of the following are *least* likely to be true?**
- (a) The conventional drops used are 5.0% tropicamide
 - (b) 0.5% tropicamide alone or with 2.5% phenylephrine
 - (c) In case of a history of myocardial ischemia, do not use phenylephrine
 - (d) Dilatation of a patient with narrow angle glaucoma should be performed only if a prophylactic iridectomy has been done.
- 52. You are sent on a mission to examine the quality of laboratory procedures in a secondary care hospital. The laboratory has creatinine measurements, glycosylated hemoglobin and glucose done regularly. Which of the following are *least* likely to be true?**

- (a) The Folin Wu methods and O-Tolidine methods are more likely to be seen in the laboratory rather than the glucose oxidase and peroxidase method for measuring glucose levels
- (b) The Jaffe method causes a significant negative error with bilirubin levels more than 10 mg/dl
- (c) An anticoagulant may be used in subjects who need a sample to be collected for HbA1c, this is generally EDTA
- (d) Elevations in creatinine levels are seen in case of diabetic ketoacidosis due to acetate interference

53. Which of the of the following are *least likely to be true*?

- (a) The insulin receptor is a glycoprotein tetramer consisting of 2 alpha and 2 beta subunits.
- (b) Fatty acids are transported across the outer mitochondrial membrane by carnitine acyl transferases
- (c) GLUT-4 is a glucose transporter in muscle.
- (d) GLP-2 stimulates insulin gene transcription and islet cell growth.

54. Insulin increases the movement of which of the following glucose transporters in cerebrospinal system?

- (a) GLUT 1
- (b) GLUT 2
- (c) GLUT 3
- (d) GLUT 4

55. Insulin causes

- (a) Increased gluconeogenesis
- (b) Increased glycogenolysis
- (c) Increased glycogen synthesis
- (d) Decreased protein synthesis

56. The compensatory response to hypoglycemia causes all the following *except*:

- (a) Hypotension
- (b) Tachycardia
- (c) Diaphoresis
- (d) Dilated pupil

57. All the following are side effects of pioglitazone *except*:

- (a) Osteopenia
- (b) Weight gain
- (c) Cardiac failure
- (d) Hepatic steatosis

58. All the following in patients with diabetes regarding heavy alcohol consumption are *false except*:

- (a) For those with type 2 diabetes, alcohol is best substituted for carbohydrate calories
- (b) Glucagon is not effective in treating hypoglycemia
- (c) Four alcohol equivalents per day is permitted for men
- (d) Two alcohol equivalent is permitted for women

59. All are the symptoms of hypoglycemia in children *except*:

- (a) Nightmares
- (b) Argumentative
- (c) Satiety
- (d) Aggression

- 60. Goals of therapy for managing diabetes in young children include all the following *except*:**
- (a) Maintenance of normal growth and development
 - (b) Avoidance of symptomatic hypoglycemia and hyperglycemia
 - (c) HbA1C level below 7
 - (d) Provision of realistic expectations
- 61. All the following statements about ketone bodies are least likely to be true *except*:**
- (a) In DKA, the ratio of beta hydroxy butyrate to that of acetoacetate is 10:1
 - (b) Glucagon stimulates acetyl CoA carboxylase
 - (c) Glucagon inhibits Carnitine Palmitoyl Transferase 1
 - (d) Normally ketone bodies inhibit insulin release
- 62. The central feature of diabetic dyslipidemia is**
- (a) Increase in VLDL
 - (b) Decrease in HDL
 - (c) Increase in LDL
 - (d) Decrease in insulin sensitive lipase
- 63. Indications for cardiac testing in diabetic patients include all the following *except*:**
- (a) Atypical cardiac symptoms
 - (b) Peripheral artery disease
 - (c) Carotid artery disease
 - (d) LDL cholesterol of more than 190 mg/dL
- 64. Sildenafil is contraindicated in all *except*:**
- (a) Severe hypertension
 - (b) Retinitis Pigmentosa
 - (c) Unstable angina
 - (d) Peripheral vascular disease
- 65. All the following are likely to be true about dermatological manifestations of diabetes *except*:**
- (a) Shin spots are not the common manifestation.
 - (b) Necrobiosis is seen in 2.0 percent of diabetic individuals
 - (c) Granuloma annulare has strong association
 - (d) Diabetic erythema are usually seen in upper limbs of children
- 66. Which *one* of the following statements is true regarding Leptin?**
- (a) Acts on the lateral hypothalamus
 - (b) Increases release of α -MSH
 - (c) Acts via MC4R to increase feeding
 - (d) Acts via MC3R to decrease energy expenditure
- 67. Symptoms of Vitamin-D toxicity include all of the following *except*:**
- (a) Hypercalcemia
 - (b) Polyuria
 - (c) Hypophosphatemia
 - (d) Headache
- 68. A 20-year-old lady was admitted to the ICU with high grade fever and drowsiness. What is your interpretation of the following ABG at admission to the ICU?**
pH = 7.10; PaCO₂ = 30 mm Hg; HCO₃ = 9 m Mol/l
- (a) Metabolic acidosis
 - (b) Metabolic acidosis and respiratory alkalosis

- (c) Respiratory acidosis
- (d) Metabolic acidosis and respiratory acidosis

69. All are true about phase-II clinical trial except:

- (a) This phase involves fairly small scale investigations to determine the effect and safety of new treatment
- (b) To compare reasonably effective new drug to standard drug/placebo under well defined protocol
- (c) Fairly it also involves small scale investigations to determine the effect and the safety of new treatment
- (d) To assess the probable benefits that may out way risk

70. Kaplan-Meier curves are used in the clinical trials for:

- (a) Sensitivity analysis
- (b) Specificity analysis
- (c) Cross-over design data analysis
- (d) Survival analysis

71. A 42-year-old lady, Type 2 Diabetic presented to emergency department with breath lessness and upper respiratory symptoms of 5 days duration. On examination she was tachypenic with the respiratory rate of 28/min and an ABG showed pH = 7.55; PaCO₂ = 25; HCO₂ = 21; PaO₂ = 40 mm Hg (on room air). What is the interpretation of ABG?

- (a) Metabolic acidosis
- (b) Respiratory acidosis
- (c) Metabolic alkalosis
- (d) Respiratory alkalosis

72. A 60 year female with history of Grave's thyrotoxicosis for which she underwent radioiodine ablation 3 years prior subsequently she developed hypothyroidism and was irregular medication. She was last visited 1 year before. She was currently admitted with altered sensorium. On examination she had generalized body swelling, breathing difficulty, low body temp, Heart rate of 56/min. Her ABG showed pH -7.2; PCO₂ - 65, PO₂ - 76 and SPO₂ -89%. She has no prior history of diabetes and hypertension.

Which of the following is unlikely to be the cause of her altered sensorium?

- (a) Myxedema coma
- (b) Hyponatremia
- (c) Hypoglycemia
- (d) Hyperosmolar state

73. A 22-year-old man presents to a local emergency room with severe muscle cramps and exercise intolerance. His symptoms have been worsening over a period of months. He has noticed that his urine is frequently dark. Examination reveals tenderness over all major muscle groups. A creatine phosphokinase (CK) is markedly elevated. He reports a normal childhood but since age 18 has noticed worsening exercise intolerance. He no longer plays basketball and recently noticed leg fatigue at two flights of stairs. After intense exercise, he occasionally has red-colored urine. Which of the following is the most likely diagnosis?

- (a) Glucose-6-phosphatase deficiency
- (b) Lactate dehydrogenase deficiency
- (c) McArdle disease (type V glycogen storage disease)
- (d) Pyruvate kinase deficiency

74. The curve that graphically represents the family of cutoff points for a positive vs. negative test is a receiver operating characteristic (ROC) curve. The area under this curve is a quantitative measure of the information content of a test. The ROC axes are

- (a) Negative predictive value vs. (1-positive predictive value)
- (b) Positive predictive value vs. (1-negative predictive value)
- (c) Sensitivity vs. (1-specificity)
- (d) Specificity vs. (1-sensitivity)

75. Which of the following are true about Chloroquine as an Antidiabetic agent?

- (a) Phase 3 clinical trials have been performed for treating diabetes
- (b) It has been approved by the FDA (USA) for the treatment of diabetes.
- (c) It acts by inhibiting the absorption of carbohydrates.
- (d) It may cause severe spontaneous hypoglycemia.

Case Analysis: 76 to 78

76. A 70-year-old gentleman with diabetes for 11 years presents with fever and chills for 4 days. Urine microscopy shows multiple white blood cells in the analysis. A urine culture is performed and reveals Extended Spectrum Beta Lactamase organisms present in significance. What would you do next?

- (a) Start Meropenem
- (b) Start Amoxicillin
- (c) Start Gentamicin
- (d) Start Nitrofurantoin

77. The fever persists after three days. An ultrasonogram is performed which shows edema of the right kidney and gas in the perinephric space. What is the most likely organism as a cause?

- (a) *E Coli*
- (b) *Klebsiella*
- (c) *Clostridium*
- (d) *Peptostreptococcus*

78. Following a urological procedure, the fever persists, and the patient has a unilateral nephrectomy. The infection spreads to the opposite side and the opposite side is nephrectomised as well. The patient is started on hemodialysis. After that, the fever subsides. Functionally he is well, and leads an independent life, he would like to spend much of his time at home, without frequent hospital visits. What would you give as an option for this patient for long term renal replacement therapy?

- (a) Hemodialysis
- (b) Cadaver based renal transplantation
- (c) Live related renal transplantation
- (d) Continuous ambulatory peritoneal dialysis

Case Analysis: 79 to 81

A 30-year-old gentleman, a long distance runner presents with chest pain on exertion. Historically, he is a nonsmoker and teetotaler. On examination he is 178 cm tall and has an arm-span of 190 cm. An ECG shows evidence of an anterior wall myocardial infarction.

79. What other clinical anomaly would you find in this patient?

- (a) Mitral regurgitation
- (b) Aortic aneurysm
- (c) Dislocated lens
- (d) Aortic regurgitation

80. Following his recovery, he has a fall while climbing down the staircase and fractures his tibia on trivial trauma. A DXA scan is done, the most likely finding in this patient is:

- (a) T score +1.0, Z score +1
- (b) T Score -2.5, Z score -3.5
- (c) T score +1.0, Z score +0.0
- (d) T score -3.0, Z score -.2.0

81. One therapeutic agent that has been tried in this condition is:

- (a) Hematin
- (b) Betaine
- (c) Ascorbic Acid
- (d) Xanthine

Case Analysis: 82 to 84

A 25-year-old gentleman presents with a sudden onset of loss of consciousness. He is found to have serum sodium of 106 mmol/l. He does not have any previous history of illness and is not on any medications. He has not had vomiting or been on diuretics. His urine spot sodium is 60 mmol/l.

82. Which of the following are not relevant in this situation to establish a conclusive diagnosis?

- (a) 8.00 am Cortisol
- (b) Urinary Delta ALA levels
- (c) TSH/T4
- (d) Serum electrophoresis.

83. He is an occasional social drinker, but claims he had a binge the previous night with a large ingestion of alcohol. He is started on 3% saline and thiamine as well. He recovers. The next day, he passes very dark colored urine. The urinary microscopy is negative. What other symptom would you expect him to have?

- (a) Renal stones
- (b) Peripheral neuropathy
- (c) Angina
- (d) Emphysema

84. This condition is commonly:

- (a) Autosomal dominant
- (b) Autosomal recessive
- (c) X-linked dominant
- (d) X-linked recessive

Case Analysis: 85 to 87

A 31-year-old, economically challenged farmer presents with abdominal pain and diarrhoea for 12 years.

He is on premixed insulin for diabetes for 5 years, the Hba1c is 9.5% and he His BMI is 18 kg/m². He has frequent hypoglycemic attacks early morning and also postmeal. The 72 stool fat measurement is 34 g. The CT Scan shows duct dilatation in the pancreas and large pancreatic calculi within the ducts.

85. The most likely problem that he has is:

- (a) Cystic fibrosis gene mutation
- (b) Serine kinase 4 mutation
- (c) SPINK-1 mutation
- (d) Alcoholic pancreatitis

86. For better control of blood sugars, you put him on three meals and three snacks, give him pancreatic enzyme supplements. Which of the following insulin regimens would you prefer?

- (a) Aspart insulin thrice a day with a pen and glargine at bedtime
- (b) Soluble insulin with a syringe thrice a day and NPH at bedtime
- (c) Degludec insulin once a day and Humalog thrice a day
- (d) Try out Glimiperide with metformin and top up with Acarbose if still uncontrolled

87. You are located in a tertiary care center and he comes to you annually for a follow-up. Your protocol would include:

- (a) DOTATE scan and Ca 19.9 once a year
- (b) CT abdomen and CEA once year
- (c) DOTATE scan and CEA once a year
- (d) Ultrasound abdomen and Ca19.9 once a year

Case Analysis: 88 to 90

A 26-year-old nurse is applying for a job. She is found to have a fasting plasma glucose of 130 mg/dl, her postprandial sugars are normal. She is otherwise well, with a normal blood pressure, a BMI of 21kg/m², no features of insulin resistance and has no dysmorphic features. She has no ketones in her urine. Her GAD antibodies are negative, C-peptides are 3.0ng/dl and she has a normal ultrasound of the abdomen. Her father had diabetes diagnosed at the age of 31 and her grand-father at the age of 44. Her only brother had a urinary tract infection and was diagnosed at the age of 29 years to have diabetes.

88. Going by the textbook, she is most likely to have:

- (a) MODY 1
- (b) MODY 2
- (c) MODY 3
- (d) MODY 4

89. Two years later she gets married, conceives within 6 months. She is started on insulin early in pregnancy. Her controls of sugars are reasonable during her pregnancy, for instance her sugars on a typical day: fasting 93 mg/d/, post-breakfast 1 hour- 110 mg/dl, post lunch- 134 mg/dl, post dinner 150 mg/dl. She monitors sugars 4 times a day, 5 days a week. She has a normal delivery at 38th week of gestation and her baby weight is 2.0 kg. The baby is normal otherwise. Is normoglycemic at birth? There are no other features of dysmorphism.

Which of the following statements are most likely? The child:

- (a) Does not have the same mutation and is unlikely to develop diabetes before the age of 45 years.
- (b) May have the same mutation, and has a chance of having hyperglycemia in childhood
- (c) May have the same mutation, but will not get diabetes before the age of 60 years.
- (d) Has growth hormone deficiency to account for the small baby size.

90. After three years, the lady decides on having another child. However, by now she has gained 12 kg of weight, and owing to domestic upheavals, finds it difficult to maintain good glycemic during pregnancy. The baby that is born, now weighs 4 kg, at the time of delivery, she is in a remote area and undergoes a home delivery. After 12 hours, the baby develops a seizure and the monitored blood glucose is 18 mg/dl. What are the other anomalies that you may expect in this child?

- (a) Caudal regression syndrome
- (b) Tetralogy of Fallot
- (c) Macrocephaly
- (d) Congenital hypothyroidism

Extended Matching Types: 91 to 95**Medications in Diabetes**

- | | |
|------------------|------------------|
| A. Metformin | B. Pioglitazone |
| C. Dapagliflozin | D. Acarbose |
| E. Sitagliptin | F. Liraglutide |
| G. Bromocriptine | H. Gliclazide XL |
| I. Glargine | J. Degludec |

- 91. The longest acting antidiabetic agent available on the list.**
- 92. A 40-year-old gentleman has been on monotherapy for his diabetes for 6 months. He is experiencing recurrent urinary tract infections, which his doctor is ascribing to pharmacological therapy. Which one is the most likely cause?**
- 93. The medication most likely to worsen osteoporosis**
- 94. A 45-year-old lady has been experiencing progressive numbness of the feet, which has been worsening rapidly over the last 3 months. She has instability while walking. She is not a user of alcohol. On examination she is pale and her MCV is 104. Which medication do you think is responsible for this problem?**
- 95. A 40-year-old gentleman is using a medication for treating diabetes for 3 years. More recently he has come across an internet article which mentions that the drug which he is taking will protect him from several malignancies. Which agent is he taking?**

Extended Matching Types: 96 to 100

Complications of Diabetes

- | | |
|----------------------------------|------------------------------|
| A. Hypertension | B. Ischemic heart disease |
| C. COPD | D. Urinary Tract Infections |
| E. Peripheral neuropathy | F. Proliferative retinopathy |
| G. Patient without complications | H. Amputation |
| I. Intermittent claudication | J. Charcot's foot |

96. A 70-year-old patient was on the ORIGIN trial till about 4 years ago. The outcomes being studied were related to which disease in association in diabetes:
97. The HOT study looked at outcomes in which disorder:
98. Published studies in the last two years in India, have shown that after cardiovascular disease the commonest cause for in-hospital death is diabetes is due to:
99. A 50-year-old patient with diabetes has osteoporosis. Alendronate may also be helpful for this complication of diabetes:
100. A 40-year-old patient has already been immunized at his home workplace for Hepatitis B. You would put him in a higher risk category for adult immunization if he had this complication:

Extended Matching Types: 101 to 105

Viral Infections and Diabetes

- | | |
|-------------------|-----------------------|
| A. Hepatitis A | B. Hepatitis B |
| C. Hepatitis C | D. HIV-1 |
| E. Varicella | F. Epstein-Barr-virus |
| G. Herpes Simplex | H. Adenovirus |
| I. Ebola virus | J. Coxsackie B virus |

101. This virus has an association with Type 1 Diabetes Mellitus
102. A 30-year-old gentleman has been ill on therapy for 6 years. A bone density of minus 3 t score in the lumbar spine. Which of the following illnesses is this a complication of therapy?
103. A 56-year-old woman has a t-score of plus 3 in the spine. Which of the following viruses can cause this problem?
104. Particles that have been genetically engineered and are similar in morphology to this particular virus for the purpose of gene therapy include:
105. Vaccine regularly available outside the regular protocols for child immunization and hospital staff includes a vaccine for:

Extended Matching Types: 106 to 110

Opportunistic Infections and Diabetes

- | | |
|------------------|----------------------------|
| A. Metronidazole | B. Amoxicillin+Clavulanate |
| C. Meropenem | D. Piperacillin-Tazobactam |

- | | |
|-------------------|-----------------|
| E. Cotrimoxazole | F. Fluconazole |
| G. Amphotericin B | H. Itraconazole |
| I. Ketoconazole | J. Voriconazole |

- 106. A 28-year-old gentleman presented with hypertension, diabetes and cardiac failure. He had weight loss of 20 kg and subsequently his bone marrow showed evidence of Histoplasmosis. He was advised to take the following medication for 2 years after initial stabilization:**
- 107. A 40-year-old patient with Type 1 diabetes presents with fever and abdominal pain. An ultrasound of the abdomen shows gas in the calyces of the right kidney. Which is the agent to be of most use in this patient?**
- 108. A 40-year-old patient with diabetes has diffuse fungal infection on the skin of his trunk, soles of the feet and intertriginous areas. He also has candidal balanitis. You would like to treat him with a course of:**
- 109. A 50-year-old gentleman with diabetes and on chronic corticosteroid therapy for SLE, presents with cough with expectoration. There are gram-positive filamentous organisms in his sputum. After stabilization he is given a 6 week course of oral medications and is well after that. What has he been given?**
- 110. A 60-year-old gentleman with diabetes and an underlying lymphoma is given chemotherapy. His white blood cell counts drop to a total count of 700. He develops cough with blood streaked sputum and the microbiologist characterizes a member of the deuteromycetes fungus in his sputum. After stabilization, he is sent on long-term oral therapy with:**

Multiple True or False: 111 to 120

A 40-year-old lady presents with sudden loss of vision in the right eye with a duration of diabetes for 10 years:

- 111. Which has been poorly controlled. The cause for the sudden visual decline may be:**
- (a) Vitreous Hemorrhage
 - (b) Open angle glaucoma
 - (c) Retinal detachment
 - (d) Macular edema
- 112. With Macular edema in diabetes:**
- (a) Bevacizumab may be used
 - (b) Panretinal Photocoagulation is useful
 - (c) Laser is not useful if there is dominant ischemia
 - (d) Less likely to happen in the presence of growth hormone deficiency
- 113. With regards to laser therapy in the eye in diabetes:**
- (a) Ruby LASER has been associated with creeping
 - (b) Visual decline can happen following LASER therapy

- (c) LASER causes damage to the retina
- (d) LASER therapy is now outmoded for retinopathy

114. Stem Cell therapy has been tried in diabetes in Type 1 diabetes:

- (a) It is not useful if there is a history of ketoacidosis
- (b) It is not useful if the duration of diabetes has been more than 4 months
- (c) The relapse rates can amount to more than 50% in 5 years
- (d) Is only recommended under the domain of research and is not standard of care

115. In therapy of problems in the kidney in diabetes:

- (a) Rennin inhibitors (Aliskiren) are useful in improving survival
- (b) Nephrotic proteinuria is a marker of more rapid progression
- (c) Gas forming organisms are most likely to be due to anaerobes in emphysematous pyelonephritis
- (d) In case of live related renal transplant with diabetes induced, CKD—when choosing between two family members to be Donors who are fit and do not have diabetes, choose the 48-year-old brother to donate over the 40-year-old brother to donate the kidney.

116. With regards to the risk for diabetes and hypertension in the fetus in connection with the intrauterine environment.

- (a) If the baby is > 4.0 kg and the mother is not diabetic or insulin resistant, then there is no added risk for adult onset diabetes in adulthood
- (b) Barker's hypothesis states that in a low birth weight baby, the risk for Diabetes is higher in adulthood, provided that there is an adverse environmental exposure with decreased exercise and diet.
- (c) Frenkel-Pedersen hypothesis indicates that in case of uncontrolled sugars. In pregnancy, the risk of a large baby with fetal hypoglycemia is lower.
- (d) There appears to be an epigenetic link associated with low birth weight which is a proponent of the changes which increase the risk for diabetes, hypertension, obesity and osteoporosis.

117. In a patient with long standing diabetes and chronic renal failure,

- (a) Immature cataracts should be operated, before visual loss occurs
- (b) Sitagliptin can be used even when the GFR is less than 50 ml/minute
- (c) Dapagliflozin is contraindicated if the GFR is less than 50 ml/min
- (d) Pregnancy is best avoided in case of a GFR less than 30 ml/min OR in case of heavy proteinuria

118. With regard to glucometer strips:

- (a) Storage of glucostrips should be in the refrigerator
- (b) Monitoring is not required in patients not on insulin
- (c) Glucostrips have an expiry date
- (d) Glucometer strips generally measure venous blood glucose

119. Regarding continuous glucose monitoring systems (CGMS):

- (a) They can measure sugars for 72 hours and record the sugars every 5 minutes
- (b) They are of particular use when trying to identify a Somogyi phenomenon

- (c) It is of particular use in patients with Type 1 Diabetes adjusting to use an insulin pump
- (d) CGMS measures venous blood glucose

120. Diabetic ketoacidosis is:

- (a) Associated with hyponatremia
- (b) Associated with hyperkalemia
- (c) Expected to be common in pancreatic diabetes
- (d) Not expected in maturity onset diabetes of the young type-2 (MODY-2)

ANSWER KEYS

- | | | | | | | |
|-------------------------------|----------|----------|----------|----------|----------|----------|
| 1. (d) | 2. (c) | 3. (c) | 4. (b) | 5. (a) | 6. (c) | 7. (d) |
| 8. (a) | 9. (a) | 10. (c) | 11. (c) | 12. (d) | 13. (d) | 14. (b) |
| 15. (c) | 16. (d) | 17. (d) | 18. (c) | 19. (d) | 20. (d) | 21. (d) |
| 22. (b) | 23. (b) | 24. (a) | 25. (b) | 26. (d) | 27. (d) | 28. (c) |
| 29. (c) | 30. (d) | 31. (d) | 32. (d) | 33. (c) | 34. (c) | 35. (d) |
| 36. (c) | 37. (c) | 38. (d) | 39. (d) | 40. (d) | 41. (d) | 42. (c) |
| 43. (a) | 44. (c) | 45. (c) | 46. (d) | 47. (a) | 48. (c) | 49. (d) |
| 50. (d) | 51. (a) | 52. (a) | 53. (d) | 54. (a) | 55. (c) | 56. (a) |
| 57. (d) | 58. (b) | 59. (c) | 60. (c) | 61. (a) | 62. (d) | 63. (d) |
| 64. (d) | 65. (a) | 66. (b) | 67. (c) | 68. (d) | 69. (b) | 70. (d) |
| 71. (d) | 72. (d) | 73. (c) | 74. (c) | 75. (a) | 76. (a) | 77. (a) |
| 78. (d) | 79. (c) | 80. (b) | 81. (b) | 82. (d) | 83. (b) | 84. (a) |
| 85. (c) | 86. (b) | 87. (d) | 88. (b) | 89. (b) | 90. (a) | 91. (j) |
| 92. (c) | 93. (b) | 94. (a) | 95. (a) | 96. (b) | 97. (a) | 98. (d) |
| 99. (j) | 100. (c) | 101. (j) | 102. (d) | 103. (c) | 104. (h) | 105. (e) |
| 106. (h) | 107. (c) | 108. (f) | 109. (e) | 110. (j) | | |
| 111. (a, c) True (b, d) False | | | | | | |
| 112. (a, c, d) True (b) False | | | | | | |
| 113. (a, b, c) True (d) False | | | | | | |
| 114. (a, b, c, d) True | | | | | | |
| 115. (b, d) True (a, c) False | | | | | | |
| 116. (a, b, d) True (c) False | | | | | | |
| 117. (b, c, d) True (a) False | | | | | | |
| 118. (a, c) True (b, d) False | | | | | | |
| 119. (a, b, c) True (d) False | | | | | | |
| 120. (a, b, d) True (c) False | | | | | | |

Answers to Self-Assessment

Chapter 1: Physiology

1. (d) Amino acids
2. (c) Usually shows marked improvement in glucose tolerance if body weight is reduced to normal
3. (a) Hyperglycemia
4. (c) Increased glycogenesis
5. (b) Inhibits both insulin and glucagon
6. (c) Increased extracellular and decreased intracellular glucose
7. (c) Metabolic acidosis
8. (a) Metabolic acidosis
9. (b) Osmotic diuresis
10. (b) 180 mg%

Chapter 2: Introduction and Overview of Glycemic Disorders

1. (a) Body mass index less than 23 kg/m² indicates malnutrition
2. (c) He does not have an increased cerebrovascular risk
3. (e) A systolic BP of 142 mm Hg is acceptable in a patient with diabetes mellitus
4. (d) T2DM
5. (a) MODY
6. (b) LADA
7. (a) High LDL
8. (b) Increased TG, Decreased HDL, Normal LDL
9. (a) MODY
10. (b) Blood sugar levels above which prevalence of retinopathy increases

Chapter 3: Practical Medical Nutritional Therapy

1. False
2. True
3. False
4. True
5. False
6. True
7. False
8. False
9. True
10. True

Chapter 4: Exercise

1. (b) Microvascular complications will interfere with her ability to exercise
2. (d) None of the above
3. (d) Physical activity like Valsalva like maneuvers should be included in her exercise regimen
4. (a) 50–70% of maximal
5. (d) Increased predilection for coronary risk factors
6. (d) Renal failure.
7. (b) To eat a carbohydrate snack
8. (e) All of the above
9. (a) Strengthening exercises
10. (d) Walking is contraindicated in patients with Type 2 DM with cardiovascular complications

Chapter 5: Counseling

1. (d) Assessment of patient's level of coping
2. (c) The Proactive patient
3. (d) The Casual patient
4. (b) In-depth casework
5. (d) All of the above
6. (d) Previous family history
7. (d) Low cost of treatment
8. (d) All of the above
9. (a) Burn-out of the caregiver
10. (d) All of the above

Chapter 6: Oral Antidiabetic Agents

1. (c) Glimepiride
2. (d) Obesity with a body mass index of more than 40 kg/m²
3. (d) Acarbose
4. (a) Chlorpropamide
5. (a) Metformin
6. (c) Glimepiride may be used in early renal impairment; (d) Chlorpropamide has a shorter half-life than glipizide; (e) There is no impact on the SUR-receptor
7. (f) None of the above
8. (a) Pioglitazone
9. (b) Gastrointestinal
10. (b) Metformin; (d) Pioglitazone
11. (d) Pioglitazone; (e) Sitagliptin
12. (a) Glibenclamide
13. (b) Metformin
14. (d) Pioglitazone
15. (d) Pioglitazone 45 mg
16. (e) Sitagliptin
17. (b) Metformin
18. (a) Glibenclamide
19. (d) Pioglitazone
20. (b) Metformin

Chapter 7: Parenteral Therapeutic Agents

1. (b) Best option is to add another oral hypoglycemic agent for better control of sugars
2. (a) 0.15 units/kg/dose
3. (a) MODY
4. (b) They are superior to human insulin in preventing complications of diabetes
5. (b) Detemir
6. (c) Detemir
7. (c) Pioglitazone
8. (c) Insulin
9. (b) Has type 2 diabetes, requires insulin
10. (d) Gallstone disease is a contraindication

Chapter 8: Insulin Therapy—Practical Aspects

1. (b) Starting her on once daily long acting insulin analogs; (c) Stop Rosiglitazone and start twice daily premixed insulin

2. (c) Lipohypertrophy which will resolve by just foregoing the site and injecting elsewhere in the abdomen
3. (d) Take him to the nearest hospital
4. (a) Insulin Glargine can be mixed with Insulin Lispro
5. (b) Change the site of injection
6. (c) Subcutaneously
7. (c) Plain + NPH; (d) Lispro + NPH
8. (b) Insulin when taken out of cold storage should be used after a minimum of 15-20 minutes
9. (c) Anterior abdominal wall
10. (c) 31

Chapter 9: Blood Glucose Monitoring

1. (d) May benefit from inhalational insulin
2. (b) Using disposable insulin pens
3. (c) After administration, insulin pen should be immediately withdrawn
4. (c) Impaired glucose tolerance
5. (a) Light
6. (b) Capillary blood glucose
7. (c) Hematocrit
8. (c) 1 hour postmeals
9. (b) 15-20%
10. (d) 72 hours

Chapter 10: Peripheral Neuropathy

1. (e) None of the above
2. (d) Tremors
3. (e) None of the above
4. (e) None of the above
5. (b) When the patient does not appreciate 10 g monofilament testing
6. (a) 128 Hz
7. (b) Vibration
8. (c) Swimming
9. (d) Methylcobalamin tablets are effective in ameliorating nerve regeneration
10. (b) Best option is to add another oral hypoglycemic agent for better control of his sugars

Chapter 11: Feet, Foot Care and Neuroarthropathy

PART-A: Foot Care and Neuroarthropathy

1. (d) a and c
2. (d) Amlodipine
3. (b) Charcot's arthropathy
4. (c) Treadmill exercises
5. (e) None of the above
6. (b) The risk of vascular disease associated with diabetes is secondary to obesity, lipid disorders, and increased blood pressure, but not diabetes per se
7. (a) The ABI is not a good screening tool for persons with diabetes
8. (g) All of the above
9. (d) It should be performed for the same indications in diabetic and nondiabetic patients
10. (e) All of the above

PART-B: Wound Care in Patient with Diabetes

1. (e) E stands for eschar
2. (e) Flavine
3. (e) Electromagnetic
4. (a) *Lucilia cuprina* can be used to debride the dead tissues
5. (d) Film can absorb exudate
6. (d) Film
7. (e) Silver dressings are for granulation
8. (d) HEIDI is used to describe the wound
9. (d) Hemostatic properties
10. (c) Hydrogen peroxide

Chapter 12: Therapeutic Footwear

1. (a) Low pressure over a short period of time
2. (a) Microcellular rubber sandals with medical arch support
3. (b) Fixed ankle brace
4. (c) Will shift body weight from the heels to the ball of the foot
5. (c) It increases
6. (c) Entire forefoot
7. (b) Microcellular rubber sandal with combined pad (Medial arch support with metatarsal bar)

8. (a) Microcellular rubber sandal
9. (b) Loose fitting footwear; (c) Detects plantar intrinsic foot muscle paralysis; (d) Measure foot pressure; (e) A substitute for fatty pad tissue; (a) Measure softness of microcellular rubber
10. (b) Low risk foot; (a) Loss of protective sensation with/without intrinsic muscle paralysis; (e) Neuropathy with no pressure lesion in mobile flat feet; (c) Very badly scarred feet (> two thirds of weight bearing surface); (d) Unstable ankle and subtalar joint

Chapter 13: Hypertension

1. (b) 140/90 mm Hg
2. (e) Can be used safely in pregnancy
3. (c) Thiazides are preferred in end-stage renal failure
4. (d) Cilnidipine belongs to centrally acting group of drugs
5. (e) Once diagnosed angioplasty or bypass surgery should be done in all patients
6. (a) Sodium
7. (b) Diuretics
8. (d) 1 mm Hg
9. (b) Lisinopril
10. (e) 2–3 mm Hg

Chapter 14: Nephropathy

1. (a) Microalbuminuria
2. (d) Tight control of blood pressure
3. (a) Occurs within 1 to 5 years of onset of diabetes
4. (d) Usage of multivitamins and micronutrients
5. (c) It is important to measure lipid profile in patients with diabetic nephropathy, mainly for assessing cardiovascular risk
6. (a) The target hemoglobin in these patients should be more than 12 gm%
7. (d) Vitamin D analogs are commonly used in patients with diabetic nephropathy
8. (d) Graft loss due to diabetic nephropathy is common in practice
9. (d) Nitric oxide pathway
10. (d) Rapid onset of proteinuria

Chapter 15: Macrovascular Complications in Diabetes

1. (d) All of the above
2. (c) To stop oral drugs and initiate insulin

3. (d) All of the above
4. (a) Insulin, aspirin, statins, ACEI
5. (b) Renal failure
6. (b) Due to the absence of lipid lowering drugs; (d) Hypoglycemic episodes precipitating acute ischemia
7. (a) Reduce the dose of all the drugs
8. (c) Antilipid drugs are contraindicated in renal failure
9. (b) The predominant action of fibrates is to reduce triglyceride production
10. (c) All diabetic subjects irrespective of their age should undergo intensive cardiac testing

Chapter 16: Ocular Disease and Retinopathy

1. (c) Laser treatment would prevent worsening of proliferative diabetic retinopathy
2. (b) Development of tumors of the retina
3. (d) The patient has nonproliferative diabetic retinopathy
4. (b) Patient has mild to moderate NPDR
5. (a) Argon
6. (a) Involvement of large blood vessels only
7. (c) Well controlled sugars
8. (a) Indicates worsening of diabetic retinopathy; (d) Requires urgent referral to ophthalmologist
9. (b) Will help in the early detection of retinopathy
10. (d) All of the above

Chapter 17: Autonomic Neuropathy

1. (c) MIBG SPECT scan
2. (b) Fludrocortisone
3. (b) Valsalva ratio < 1.2
4. (c) Organic causes like candidiasis, stenosis, cancer, etc.
5. (d) Celiac disease
6. (d) Gastric emptying scintigraphy
7. (a) Domperidone 10 mg thrice a day
8. (c) Urgency
9. (d) 150 mL
10. (a) Bethanechol

Chapter 18: Infections in Diabetes

1. (b) Prophylactic antibiotic therapy required for next 6 months
2. (e) All of the above
3. (a) Urinary tract infection
4. (c) Emphysematous pyelonephritis
5. (b) Fluconazole IV
6. (b) The dose of rifampicin may need to be increased in patients on OHAs; (c) The clinical features and symptoms of TB in diabetics are different from that of normal population; (d) The Sputum conversion rate of a diabetic on ATT is less than of a normal individual
7. (b) In pregnancy
8. (b) *Pseudomonas*
9. (c) Fluid resuscitation
10. (b) Cloxacillin and gentamicin

Chapter 19: Hyperglycemic Emergencies

1. (a) 317 mm/kg
2. (a) Isotonic saline
3. (d) No need for potassium
4. (c) No need for bicarbonate correction
5. (d) Imaging by CT scan
6. (b) Administration of 25 mL of 50% dextrose
7. (d) Use of short acting insulin
8. (d) 76 years old type 2 diabetic with dementia
9. (d) He would be predominantly excreting β -hydroxyl butyrate
10. (a) Cerebral edema

Chapter 20: Hypoglycemia

1. (b) Somogyi Phenomenon
2. (c) Endogenous hyperinsulinemia
3. (c) Diabetic nephropathy
4. (d) Increase her after dinner short acting insulin dose
5. (b) To reduce her short acting insulin in morning as she has fasting hypoglycemia

Chapter 21: Pregnancy and Diabetes

1. (c) 24–28 weeks
2. (a) Severe preproliferative retinopathy

3. (b) Glibenclamide; (d) Metformin
4. (e) 4–6 weeks
5. (c) Sudden death in 2nd trimester
6. (c) Transposition of great vessels
7. (e) Age < 25 years
8. (b) Congenital anomalies
9. (e) Brain
10. (b) It is known to cause lactic acidosis in pregnancy

Chapter 22: Diabetes in Childhood and Adolescence

1. (e) Coeliac disease
2. (b) FPG
3. (b) Patients who are refusing to feed should not be given insulin
4. (c) Thyrotoxicosis
5. (a) 95th centile
6. (b) Bile acid resins
7. (c) Albumin/creatinine ratio
8. (a) < 8%
9. (c) Glimepiride
10. (c) Treated with metformin

Chapter 23: Diabetes in the Elderly

1. (d) Sitagliptin
2. (b) Urinary tract and genital infection
3. (c) Steroid therapy
4. (d) 7.5%
5. (c) Increase in muscle mass
6. (d) All of the above
7. (b) Metformin
8. (d) All of the above
9. (c) Alcohol intake is protective against hypoglycemia
10. (a) Liraglutide

Chapter 24: Secondary Diabetes and Other Specific Types

1. (c) The occurrence of microvascular complications in FCPD patients is very rare
2. (a) She has probably type 1 diabetes

3. (c) Both A and B are true
4. (b) Insulin dose should be tapered down when the steroid dose is being reduced
5. (b) The most probable type of diabetes is MODY
6. (d) Absence of ketosis, recurrent abdominal pain and low BMI
7. (d) All of the above
8. (a) Carbamazepine will be a better drug for his seizures
9. (d) All of the above
10. (c) Thyroid function tests and antithyroid drugs

Chapter 25: Perioperative Care

1. (b) Regional anesthesia
2. (d) All of the above
3. (a) Autonomic neuropathy
4. (b) Metoclopramide
5. (a) Stiff joint syndrome
6. (d) Promote lipolysis and proteolysis
7. (d) 4 unit actrapid in 100 ml 5% glucose over 1 hour
8. (c) All of the above
9. (b) Diabetic patients are prone for increased cardiovascular instability during anesthesia
10. (d) All of the above.

Chapter 26: Obesity with Diabetes

1. (c) Head Circumference
2. (d) Mobile
3. (a) High metabolism
4. (e) Hypersomnia
5. (d) Liposuction
6. (d) SDH-B deficiency
7. (d) Obstructive sleep apnea
8. (d) DXA Scan
9. (d) Glipizide
10. (d) Good Scholastic performance

Chapter 27: Laboratory and Analytical Methods

1. (b) Brain
2. (d) 12–15%
3. (a) Carbamylated Hb

4. (d) All of the above
5. (b) Stable control materials
6. (e) Glucose 6 phosphatase deficiency
7. (c) Na-F
8. (c) Muscle
9. (c) Bilirubin
10. (d) Decreased gluconeogenesis

Chapter 28: Recent Advances

1. (a) Once a week
2. (b) Cause weight loss
3. (b) Monosaccharide
4. (c) There is accumulation of glucagon
5. (c) Delivered orally in rodents
6. (c) anti-CD3 monoclonal Ab
7. (c) 10% of oral insulin can be absorbed
8. (c) Less than 3 mm
9. (a) Cough
10. (d) Beta cell transplantation

Chapter 29: Inhospital Management of Diabetes

1. (c) Vitreous hemorrhage
2. (e) Less than 180 mg/dL
3. (e) All the above
4. (c) Acute liver injury
5. (b) In septic shock
6. (c) Critically ill surgical patient requiring mechanical ventilation
7. (e) Quinolones
8. (d) a and b
9. (d) Intravenous insulin infusion
10. (a) Hypocortisolism

Chapter 30: Integrating Systems

1. (d) Microbiologist
2. (c) Teaching foot exercise
3. (d) Tobacco consumption
4. (d) Lack of drugs
5. (d) One sided teaching without much patient interaction

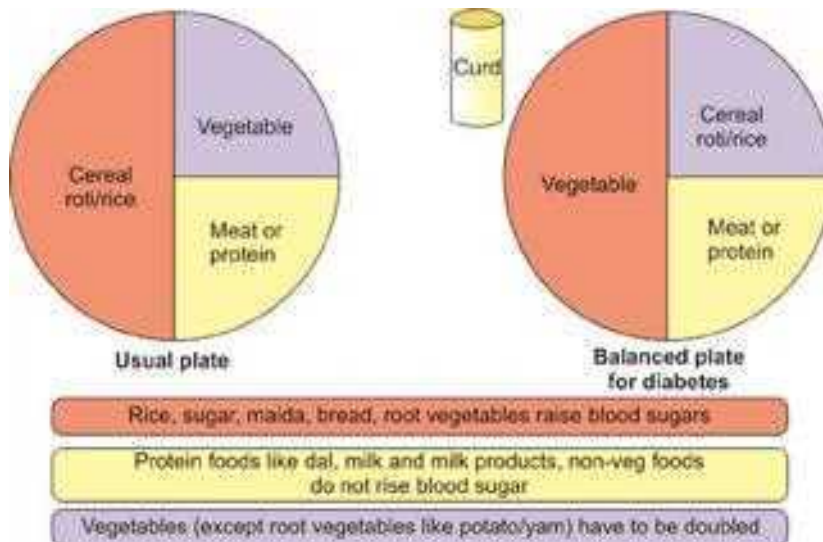
Appendices

- 1. Dietary Recommendations**
- 2. A Quick Guide for Choosing Footwear, MCR Add-ons and Braces**
- 3. Evidence in Medicine**
- 4. Diabetes Case Record**
- 5. Patient Handouts and Educational Material**

1

Dietary Recommendations

CHANGE PROPORTIONS OF FOOD → CONTROL DIABETES



The word *exchange* refers to the fact that each item on a particular list in the portion/amount listed may be interchanged with any other food item on the same list. Each list is a group of measured or weighed foods of approximately the same nutritional value like calories, carbohydrate, protein, and fat.

Cereal Exchange

Quantity: 30 gm of any cereal mentioned in the table below:

Calories: 100 kcal

21 gm of carbohydrate

1-3 gm of protein

Uncooked cereals have negligible fat.

Recommended intake for adults with type 2 diabetes—2 exchanges of cereal per meal and upto 6 exchanges per day.

If the patient is consuming more, the quantity should be gradually reduced to the recommended intake.

30 gm (raw weight) of each of the food items provide 100 kcal	
Rice/Rice flakes/Rice flour/Rice rawa vermicelli/ Sago/Noodles Wheat/Wheat flour Broken wheat (Dalia)/Wheat rawa ragi flour/Jowar/ Sooji/Bajra (Pearl millet)/Corn Oats/Wheat flakes/Corn flakes	Idli—1 medium size Dosa—1 (9 inch diameter) Chapati/Phulka/Paratha* —Dough ball of the size of lemon (as shown in the picture)—1 Bread—2 medium slices Thepla/Kakra—1 Bakri—¼ th Dhokla/Khandvi —3-4 pieces Pongal—1 cup (15 gm rice + 15 gms dal)

*Dough ball that is used to make chapati/phulka/paratha of the size of lemon gives 1 exchange and of sapota size gives 2 exchanges.

Cereals and products that have to be restricted:

- Refined wheat flour (maida), noodles, suji (rawa), vermicelli, white bread, naan, bhatura, kulcha, all bakery items made with refined wheat flour, pizza
- Rice, rice flour, rice rawa, puffed rice.
- Cereals and products that can be recommended:
- Oats—soaked oats can be added to dosa batter, made into upma/uppittu or had with low fat milk
- Broken wheat (Dalia/large grain brown rawa) is a better option than white suji/rawa
- Lot of vegetables can be added to vermicelli upma or Dalia or poha (rice flakes)
- Stuffed parat as can be made oil free. Stuffing can be with low fat paneer, vegetables, dhals or peas. Avoid stuffing with potato
- Kichidi/Pongal to be made with equal quantities of cereal and pulse
- Bengal gram chutney or vegetable chutneys like tomato, mint, coriander or any other vegetable to be preferred over groundnut chutney or coconut chutney which usually accompanies breakfast items in the south.



1 cereal exchange: 30 gm rice = 21 gm CH₂O = 100 kcal



1 cereal exchange: 30 gm wheat flour = 21 gm CH₂O = 100 kcal

Pulse Exchange

Quantity: 30 gm (uncooked) of any pulse/dal/legume

Calories: 100 kcal

17 gm of Carbohydrate

7 gm of Protein

Negligible fat when uncooked

Recommended intake—minimum of 2.5 exchanges per day, minimum 1 exchange per meal.

30 gm (raw weight) of each of the food items provide 100 kcal, 7 gm of protein	
Bengal gram dal/Red gram dal/Black gram dal/Green gram dal/Bengal gram flour Rajmah/Cholae or chick pea/Cow pea	Besan ka cheela (Bengal gram flour dosa)—1 Adai Dosa—1 Moong dal dosa/Pesarattu—1 Sprouts—1 cup Sambar (thick)—1 cup Cooked dal (thick)—1 cup

Nonvegetarian Exchange

Recommended Quantity: 1 exchange

Food Item	Quantity (gm)	Kilocalories	Protein (gm)	Carbohydrate (gm)	Fat (gm)
Mutton	50	100	8	—	7
Fish/Chicken	100	100	20	—	2
Egg	1	85	6.5	—	6.5

- Fried preparations to be avoided
- To be included as curry, baked or grilled
- Non-veg can be mixed with vegetables to make a curry
- To be avoided in the night.



Vegetable Exchange

Recommended intake: 5 exchanges per day or 500 gm per day.
(Excluding root vegetables)

Food Item	Quantity (gm)	Kilocalories	Protein (gm)	Carbohydrate (gm)	Fat (gm)
Leafy vegetable	100	25	1	6	—
All vegetable grown above the ground	100	50	1	10	—
Root vegetable*	100	100	1	24	—

*Raw carrot/turnip/onion/raddish can be included as the fiber content is high
Yam/potato/colocasia/sweet potato/tapioca/beetroot are to be avoided.

Fruit Exchange

Recommended Quantity: Minimum of 1 exchange per day.

Carbohydrate—10 gm

Calories—50 kcal

Recommended fruits	Quantity (edible portion)	Fruits to be restricted	Quantity (edible portion)
Apple	1 small/½ medium	Banana	½ big or 40 gm
Guava	1 medium	Chickoo	1 small
Orange	1 medium	Mango	½ medium or 75 gm
Papaya	1/3 medium or 3 slices	Sitaphal	½ big size or 50 gm
Pineapple	2-3 slices	Grapes	10-12 pieces
Pear	1 medium		
Sweet lime	1 medium		
Water melon	2-3 slices		
Pomegranate	1/3rd medium		
Coconut water	150 ml		
Jamun	100 gm		

- Fruit juices are to be avoided.
- Fruit to be avoided with meal as it increases the carbohydrate load of the meal.
- Fruit can be had 2 hours after a meal/midmorning snack or in the evening.

Nuts and Oil Seeds

Food Item	Quantity (gm)	Kilocalories	Protein (gm)	Carbohydrate (gm)	Fat (gm)
Coconut (dry)	15	100	1.02	2.5	10
Coconut (fresh)	25	100	1.12	3.0	10.4
Groundnut	15	100	3.79	8.0	6

- Fist ful of mixed nuts can be included by patients with normal BMI and controlled diabetes
- Use of nuts and oilseeds in food preparations to be avoided as the intake of invisible fat increases in the diet.

Milk Exchange

Each milk exchange contains protein 1–3 g, carbohydrates 4 g, fat 4, kcals 65.

Cow's milk	100 mL (½ cup)
Buffalo's milk	50 mL (¼ cup)
Curds	100 mL (½ cup)
Skimmed milk	200 mL (1 cup)
Skimmed milk powder	18 g (5 Tbsp)
Whole milk powder	13 g (3 Tbsp)

Fat Exchange

Each fat exchange contains fat 10 g, protein and carbohydrate nil, kcal 90.

Oil (any variety)	10 g (3 Tbsp)
Ghee	10 g (2 Tbsp)
Butter	12 g (2½ Tbsp)
Vanaspathi	10 g (2 Tbsp)
Margarine	10 g

Foods to Avoid

Sugar	Jams	*Horlicks
Glucose	Jellies	*Bournvita
Honey	Preserved fruits	Chocolate drinks
Syrup	Dried fruits	Chocolates
Jaggery	Aerated drinks	Proprietary drinks
Sweets	Cake	Alcohol
Halwas	Pastries	Fried foods
Burfies	Candy	

*Could be taken in measured amounts if you are ill and have difficulty in taking solid food. Consult your dietitian.

Free Foods

Clear soups	Tomato juice—1 small glass
Gelatin (unsweetened)	Soda water
Lemon	Raw vegetables salads
Soup cubes	Flavoring extracts
Pepper water	Seasonings like onion, mint,
Plain coffee or tea	pepper, garlic, curry leaf,
Skimmed butter milk	coriander, vinegar, mustard
Unsweetened lime juice	and spices
Artificial sweeteners may be used as advised by the physician.	

2

A Quick Guide for Choosing Footwear, MCR Add-ons and Braces

<i>Risk categories</i>	<i>Foot problems</i>	<i>Foot appliances</i>
		Footwear
Low risk	—	MCR footwear
Moderate risk	Loss of protective sensation and/or intrinsic muscle paralysis	MCR sandals
	<i>MCR sandal with MCR add-ons</i>	
	Low arch	Tarsal cradle or medial heel wedge
	High arch	Tarsal platform or lateral heel wedge
	Low arch with pressure lesion at metatarsal heads	Tarsal cradle and metatarsal pad with cut out
	High arch with pressure lesion at metatarsal heads	Metatarsal pad with cut out
	Low arch with pressure lesion at heel	Elephant pad
	High arch with pressure lesion at heel	Heel meniscus
	Low arch with excessive forefoot scarring	Tarsal cradle with anterior rocker
	High arch with excessive forefoot scarring	Tarsal platform with anterior rocker
High risk	<i>Shoes and braces</i>	
	Rigid foot with > 50 scarring in the weight bearing surface	Moulded insole with rigid rocker outsole
	Unstable ankle due to neuroarthropathic joints	Fixed ankle brace/Air Cast walker
	As above + Less than 1/3rd of weight bearing surface	Patellar tendon bearing brace/Patellar Tendon bearing foot orthosis



3

Evidence in Medicine

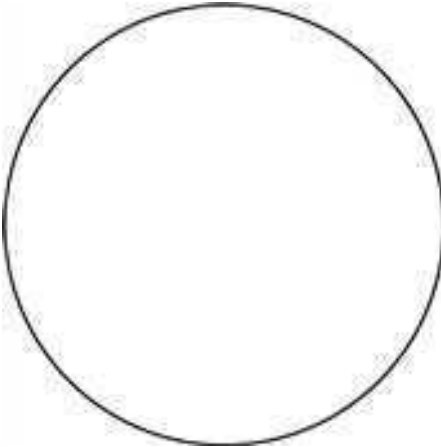
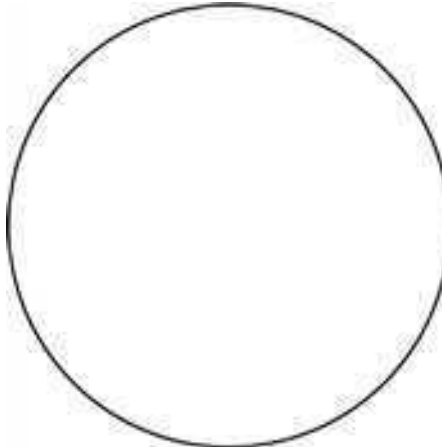
<i>Level of evidence</i>	<i>Description</i>
A	<p>Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none">• Evidence from a well-conducted multicenter trial.• Evidence from a meta-analysis that incorporated quality ratings in the analysis.• Compelling nonexperimental evidence, i.e. “all or none” rule developed by the “Center for Evidence Based Medicine at Oxford”. <p>Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:</p> <ul style="list-style-type: none">• Evidence from a well-conducted trial at one or more institutions.• Evidence from a meta-analysis is that incorporated quality ratings in the analysis.
B	<p>Supportive evidence from well-conducted cohort studies, including:</p> <ul style="list-style-type: none">• Evidence from a well-conducted prospective cohort study or registry.• Evidence from a well-conducted meta-analysis of cohort studies.
C	<p>Supportive evidence from a well-conducted case-control study.</p>
D	<p>Supportive evidence from poorly controlled or uncontrolled studies, including:</p> <ul style="list-style-type: none">• Evidence from randomized clinical trials with one or more major or three minor methodological flaws that could invalidate the results.• Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls).• Evidence from case series or case reports.• Conflicting evidence with the weight of evidence supporting the recommendation.
E	<p>Expert consensus or clinical experience.</p>

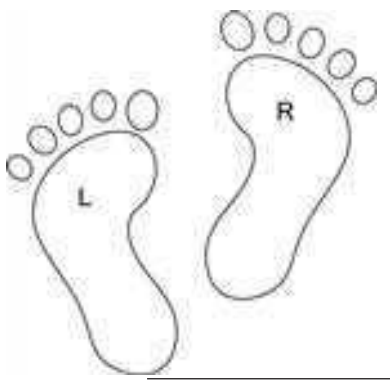

4

Diabetes Case Record

 Christian Medical College, Vellore - 632004 Department of Endocrinology, Diabetes & Metabolism Outpatient Diabetes Case Record 		
Name:	Sex: M/F	Hosp. No:
Occupation:	Year of Birth:	Date:
Address:	Type of Diabetes:	
PIN:	Year of Diagnosis:	
Phone No:	Personal History: No. of children	
E-mail:	Last Child Birth	
ASSOCIATED DISEASES:	Date detected:	Menstrual cycles (Frequency):
		Smoking: yes /no
		Alcohol: yes/no
		DIABETIC COMPLICATIONS:
		Retinopathy: yes/no
		type
		laser treatment: yes/no
		Microalbuminuria: yes/no
		Nephropathy: yes/no
		Peripheral neuropathy: yes/no
		type
		Autonomic neuropathy: yes/no
		type
PREVIOUS SURGERIES: yes/no	Current medication:	
Previous hospitalization: yes/no		
DKA: yes/no		
Current problems:		
	Drug allergy: yes/no	

Pedigree Chart	History of family illness:			
	Immunization:			
	Hepatitis B	0 mth	1 mth	6 mth
	Influenza			
Pneumococcal				
Others				
History:				
Examination				

Date:			Nails			
Pulse Rate/minute			Teeth			
BP (mm Hg)			AC/PC (9 mg/dl)			
Height (cm)			HbA1c (%)			
Weight (Kg)			Total Cholesterol (mg/dl)	Triglycerides (mg/dl)		
BMI (Kg/m ²)						
Waist Circumference			Creatinine (mg %)			
Angina/Claudication/TIA			Microalbumin (mg/g of creat) 24 Hr. Protein (g/24 hours) Urine sport protein/creatinine ratio			
Ankle-Brachial Index						
Bruit (Carotoid)						
Impotence			Calculated eGFR (ml/min)			
Distal Pulses/Reflexes			ECG/Treadmill			
Monofilament	R		Others			
	L					
Vibration/Pinprick						
Biothesiometer						
Durometer						
Hair loss, Dry skin						
Fungal infection						
Deformities						
Fundus Examination:		Right:			Left:	
						

<p>Foot Examination:</p>  <p>Dorsum:</p> <p>Findings: Discoloration Fungal Infection Deformities Ulceration</p>	<p>Plantar:</p>  <p>Findings: Callous Ulceration Flat foot Fissures Clawing</p>
<p>Doctor's Treatment & Advise:</p>	
<p>Date:</p>	
<p>Date:</p>	
<p>Date:</p>	

5

Patient Handouts and Educational Material

A gentleman from Orissa attended our outpatient, late one Monday afternoon. He was 55 years old and had been a patient of diabetes mellitus for 6 years. He followed a diet “free of sugar” and took a tablet of Daonil before breakfast.

For the last 6 months he complained of burning of the soles of his feet, particularly excruciating at night. He noticed some puffiness around his eyes on rising from bed in the morning. He had last checked his blood sugar 9 months ago. On investigation, he was found to have a fasting blood sugar of 210 mg% (normal < 140 mg %) and a post-breakfast level of 240 mg% (normal < 200 mg%). On examining his eyes with an ophthalmoscope, there were changes indicating early involvement of the retina, without causing impairment in eyesight. He was losing about 1.5 g of protein in his urine per day (normal < 300 mg).

This gentleman, like many others presents with uncontrolled blood sugars and an advanced phase of diabetes mellitus with damaged nerves, eyes and kidneys. These complications were largely preventable, though at present they are irreversible in part (like the kidney involvement in this case).

WHAT IS DIABETES MELLITUS?

It is a disorder that involves the hormone producing part of the pancreas, leading to a partial or complete deficiency of insulin. There are essentially two varieties:

Type I and type II: Type I is much less common in India (< 5% of the total number of diabetic patients) and is associated with a near total lack of insulin at the time of presentation. It is characterized by a dramatic onset usually below the age of 30 years. Type II is the dominant form and usually comes on after the age of 30 years, though exceptions aren't infrequent. It is associated with urbanization, modern lifestyle and obesity. About 4% of rural adult Indians have type II diabetes mellitus in contrast to 8-15% of urbanites. Type II diabetics have an incomplete insulin deficiency to start with and an additional element of 'insulin resistance', where the body's own insulin does not perform its function properly.

WHAT ARE THE SYMPTOMS OF DIABETES MELLITUS?

Thirst

Excessive hunger

Excessive passage of urine

Weight loss

Non-healing wounds Increased propensity for infection (e.g. urinary)
Weakness Burning feet

Asymptomatic/Incidental: This group is ever increasing; in fact, above the age of 35 years one should be routinely screened for raised blood sugar at least once in 2 years.

WHAT DOES THE MANAGEMENT OF DIABETES MELLITUS INVOLVE?

One needs to undergo a significant lifestyle modification to maintain good diabetic control. This involves a crucial triad of:

- Diet
- Exercise
- Drugs.

An absence or irregularity in one of these three leads to treatment failure. To protect the heart, kidney and eyes from damage, in addition to good blood sugar control, one needs to maintain these other parameters under control:

	Therapeutic modality
Cholesterol	Diet ± Drugs (Simvastatin, lovastatin, atorvastatin)
Blood pressure (< 140/85 mm Hg)	Drugs (‘ACE-inhibitors’: Enalapril, lisinopril, ramipril)
Smoking	Stop smoking!!!

Once again, adherence to treatment reduces the complications of diabetes mellitus. Some physicians no longer refer to diabetes mellitus as a disease, but call a combination of diabetes (blood sugar elevation), high blood pressure, cholesterol, truncal obesity (‘the paunch!’) and minimal urine protein leak—the *Metabolic Syndrome*.

Annual screening for complications should be done:

- *Eyes:* Ophthalmologist
- *Kidney:* Check serum creatinine, urine microalbumin (laboratory tests)
- *Nerve:* Check vibration sensation and ankle reflexes (physician’s examination).

HOW OFTEN SHOULD ONE CHECK BLOOD SUGARS?

Following detection, as diet control is established and the dosage of tablets increased, the physician monitors sugars frequently, till tight control is achieved. Thereafter, *if sugar control and other components of the metabolic syndrome are satisfactory, monitoring once in three months is adequate.*

Monitoring Blood Sugar Control

A special test called *glycosylated hemoglobin (HbA1c)* indicates the average control over three months, this is useful since on the given day of checking blood sugars, the sugars themselves may be normal and may not give the true picture of happenings over the last three months.

Patients on several medications and especially those on insulin can check their own blood sugars at home using an instrument called a glucometer. This measurement can be obtained at any time of the day. In case of symptoms of a low blood sugar, an approximate confirmation can be obtained. Alternatively, *strips with a color coding system* can be utilized, this being much cheaper. Urine sugars that are commonly used for monitoring diabetes are unfortunately very often inaccurate and frequently misleading.

WHAT ARE THE TABLETS UTILIZED IN TREATING DIABETES MELLITUS?

Tablets (Oral hypoglycemic agents)			
Group	Example	Advantages	Side effects
Biguanides	Metformin	May induce weight loss No hypoglycemia	Nausea, diarrhea (in <10%)
Sulphonylureas	Glibenclamide Glipizide Gliclazide Glimepiride	Weight neutral Less hypoglycemia	Hypoglycemia Mild weight gain
Meglitinide	Repaglinide Nateglinide	Minimal hypoglycemia Can use in renal failure	
Alpha glycosidase inhibitors	Acarbose Voglibose	No hypoglycemia	Diarrhoea/bloating
Thiazolidi-nediones	Pioglitazone	No hypoglycemia Can use in renal failure	Leg swelling Mild weight gain Precaution: Avoid in liver disease
DPP4 Inhibitors	Sitagliptin Vildagliptin Linagliptin Saxagliptin	Weight neutral No hypoglycaemia	Nausea Decreased appetite
Dopamine Agonists	Bromocriptine	Nausea Weak anti-hyperglycemic drug	Cardiovascular Benefit
Anti-Malarial Drug	Hydroxy-Chloroquine	Lipid friendly	Warrants ocular screening
SGLT-2 Inhibitors	Canaglifozin Dapaglifozin	Weight neutral Blood pressure reduction	Polyuria Urogenital Infections

WHAT ARE THE SYMPTOMS OF A LOW BLOOD SUGAR (“HYPOGLYCEMIC ATTACK”)?

When on medications like insulin or sulphonylureas, blood sugars may drop below normal, especially when diet and exercise are incompletely balanced against the medication dosage. The patient may have:

- *Weakness*
- *Perspiration*
- *Palpitations*
- *Light-headedness*
- *Hunger*
- *Drowsiness*
- *Coma/convulsions (rarely).*

A mild attack of hypoglycemia, once in two weeks is common in well-controlled diabetes mellitus, but more frequent attacks may go unrecognized. A diabetic on medications or insulin should always carry some sweet foodstuffs on his/her person to counter a hypoglycemic attack.

WHEN SHOULD INSULIN BE USED?

- Inability to control sugar with the maximum dose of tablets
- Advanced complications of diabetes (eye, kidney, nerves, heart)
- Before a surgical procedure in the presence of an infection
- Pregnancy.

HOW SHOULD INSULIN BE ADMINISTERED?

Hygienic precautions should be employed. A disposable syringe and needle is best utilized. An instrument resembling a ballpoint pen with a much finer needle is now available, Novopen/Humapen reducing the discomfort and minimizing pain. Injection can be injected over the front of the abdomen, arm or thigh. But the abdomen is best utilized since there is a wider area to use, absorption is more predictable and absorption is rarely altered by physical activity. Most patients on insulin require a twice-daily dosage. Only a few can be managed with a single dose.

WHAT EXTRA ATTENTION DOES THE FEET REQUIRE IN DIABETES MELLITUS?

The feet are prone for injury and infection in a diabetic patient for a number of reasons:

- *Decreased sensation* due to nerve damage
- *Decreased circulation* due to blocked blood vessels
- Poorer immunity
- *Loss of the normal arch of the foot* due to loss of 'joint sensation' causing subconscious damage
- *Decreased moisture* due to impairment of nerves supplying the sweat glands
- To prevent infection and severe damage to the feet it is important to:
 - Wear soft *footwear* with a proper fit and sole (e.g. microcrepe rubber footwear)
 - Keep the feet *clean and dry* at all times
 - Examine the feet daily in between the toes to look for fungal infestation
 - *Cut nails carefully and horizontally* without injuring the adjacent nail bed.

CONCLUSION

Diabetes mellitus is a disorder that has reached epidemic proportions in the community. Good control of blood sugar in association with weight, blood pressure and cholesterol ensures a healthier and longer life.

THE IMPORTANCE OF FOOT CARE IN DIABETES MELLITUS

Diabetes mellitus is a major public health problem and this goes without saying, the people's awareness is increasing in leaps and bounds.

When one talks in terms of poor blood sugar control, a high blood sugar by itself is surprisingly responsible for symptoms only in a small segment of the population. You are probably aware of this by now—too much urine, excessive thirst and excessive hunger.

However, it is often understated, that more pressing problems emerge in a silent fashion rather than in a sudden catastrophic manner. The complications of diabetes that occur in a gradual manner are in the form of three “pathies” —retinopathy (the eyes), nephropathy (the kidneys), vasculopathy (the blood vessels—thereby the heart, the brain and blood vessels to the legs) and neuropathy which involves the nerves.

Let me tell you how the feet are involved in diabetes. As I mentioned above, there may be involvement of the nerves in diabetes and this in fact the most common complication. The onset is silent initially and subtle and may be picked with the doctor checking for vibration sensation with a tuning fork or a special instrument called a biothesiometer which is available in large institutions like CMC, Vellore and/or with a special monofilament fiber.

Symptoms may occur only later on; these may be in the form of a sensation of ‘pins and needles’ in the limbs, or a burning sensation or numbness with a loss of normal sensory perception in the feet.

The nerves which supply the sweat-producing glands in the skin also get involved and this leads to dryness of the skin and loss of the normal lubrication.

Picture things in the right perspective now—if sensation is lost and the skin is dry, if you were to walk around barefoot, you are more likely to have injury to the soles of your feet without knowing about it.

Diabetes also affects your ability to handle germs and infection, as a result of impairing the body's immune system. Thus, if you develop a non-healing wound under the sole of your foot and if a minimal amount of dirt contaminates it, you are more likely to develop a serious infection which may take a long time to heal, even the response to antibiotics may be slower than normal. The infection may spread up the leg and may get into the bloodstream, endangering not only the limb, but also life.

Additionally, in some diabetic patients, circulation may pose a problem to the limbs, further impairing the ability for an ulcer to heal. If circulation is extremely poor, one of the problems encountered is that of progressive death of the limbs leading to what is known in common terms as gangrene.

I am not telling you all this just to scare you! It is the right of the individual to know as to what potential problems he or she may encounter when he/she has a certain disease. It is also important to know as how to prevent complications, before they occur, since prevention is better than cure.

One of the cardinal recommendations is to avoid walking barefoot at all times when a person has diabetes, even when inside the house. This will reduce the risk of ulceration multifold. If there is even early impairment in nerve function in the feet, it may be necessary to recommend footwear made out of a special material called microcellular rubber (MCR). One has to be very cautious while purchasing microcellular rubber footwear, there are a lot of imitation products in the market. The problem with these imitation products is that they are extremely soft and even though they appear to feel very comfortable while walking, since they are so soft, the foot actually makes more contact with the hard ground, increasing the liability for trauma to the sole.

Maintaining moisture over the surface of the limbs is also important. Soaking the feet twice a day for 15 minutes in cool or lukewarm water is a good practice. Drying the feet after this is important. It is important not to use hot water which may result in blister formation especially if sensory perception is lost.

Self-examination of the feet is also important on a routine basis, checking in between the toes and looking for fungal infestation is a simple process, the infestation if present is easily treatable with application of an antifungal cream for a period of 6 weeks.

Cutting the toenails and keeping them clean is important. While cutting the edges of the toenails, it is important not to cut them too close to the skin as it may lead to injury and also the tendency to develop in-growing toenails later on.

If, per chance, corns or callosities develop on the undersurface of the feet, it is better to have them attended to by a skilled dermatologist or a diabetic foot specialist or a surgeon. Self-treatment is not advisable since it may lead to injury, ulceration and infection.

In conclusion, proper foot care is an important part of good diabetes management, as important as diet, exercise and medications.

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