National Guideline on Diabetes Mellitus

First Edition

Non Communicable Disease Control Programme
Directorate General of Health Services
Ministry of Health & Family Welfare

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National Guideline on Diabetes Mellitus

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5.5

Father Of The Nation Bangabandhu Sheikh Mujibur Rahman


5.5

1st IDF Global Ambassador for Diabetes

Honourable Prime Minister of Bangladesh Sheikh Hasina has been nominated as 1st IDF Global Ambassador for Diabetes in recognition of her role to ensure affordable access to health care for people with diabetes and other non-communicable diseases during the opening ceremony of the International Diabetes Federation (IDF) world diabetes congress held in Lisbon, Portugal on 5 December 2022. The role will lasts for next two years.


5.5

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Honorable Prime Minister
Government of the People's Republic of Bangladesh &
1st IDF Global Ambassadorfor Diabetes

Message

Diabetes is a global issue. Like many other countries, Bangladesh is also suffering from an epidemic of diabetes. It makes a significant contribution to morbidity and mortality in Bangladesh. International Diabetes Federation (IDF) reported the total number of diabetic people is nearly 13.1 million in Bangladesh which is the 8th position in the world. By 2045, it is projected to move to the 7th position, with 22.3 million people with diabetes. In addition, the total number of diabetes-related death was nearly seventy-six thousand in 2021.

Diabetes is a chronic illness that requires continuing medical care and patient self-management education for optimal management outcomes and reducing the risk of complications. The impact of diabetes on families, communities, and nations is not sustainable and it is little wonder that the 2006 UN Resolution on Diabetes called on world governments to 'develop national policies for the prevention, treatment, and care of diabetes in line with the sustainable development of their healthcare systems'.

Remarkable progress has been made in the health sector of Bangladesh in the last 14 years despite having various limitations. The government has made healthcare services more affordable and reached almost every doorstep making Bangladesh self-resilient in screening and treating non-communicable diseases (NCD) including diabetes. The government has introduced around 290 NCD Corners at Upazila Health Complex throughout the country. Besides screening, registration, diagnosis, and treatment facilities, they provide free medications (including two oral antidiabetics, three antihypertensives, one lipid-lowering medication, and aspirin) to all eligible registered patients. The government is also providing free insulin to all type 1 diabetic people and insulin-dependent type 2 diabetic people. In addition, the availability of basic healthcare services with free diabetes and hypertension screening have also been possible at the primary care level due to the establishment of community clinics. The NCDC program of the DGHS recognizes that this chronic illness should require management and control, based on a national guideline. This guideline will ensure standardized medical care and patient self-management education to prevent acute complications and reduce the risk of long-term complications from the disease.

I appreciate NCDC and all the experts who have worked hard to make this guideline a reality and express my sincere gratitude and appreciation for their contribution. Thanks to the Centre for Global Health Research of the Diabetic Association of Bangladesh and JICA for their technical assistance. After all, a guideline is only valuable and useful when it is implemented in the field of day-to-day clinical practice. Therefore, I would like to recommend to all clinicians to use this diabetes care guideline for the optimal management of diabetes in their settings.

Joi Bangla, Joi Bangabandhu
May Bangladesh Live Forever

Sheikh Hasina, MP


5.5

Honorable Health Minister
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

Message

Diabetes Mellitus is running on an epidemic scale almost all over the world, Bangladesh is no exception. Day by day, the number of patients are increasing and they are more prone to be affected by different types of comorbid conditions. Physicians are playing an important role to ensure better care. But they face problems to individualize the treatment. I am happy to learn that NCDC has developed the first national diabetes guideline with technical assistance from JICA and the Diabetic Association of Bangladesh. I express my heartfelt thanks to all the members of the expert committee for putting their effort to develop the guideline. This guideline will help and guide a physician in making a decision towards treatment in addition to enriching their knowledge of the current treatment approach.

From the Government side, we want to maintain a collaboration with all the stakeholders to take such type of initiative in the future which is in line with the non-communicable disease control program of the Government.

I sincerely hope this guideline will be helpful to physicians and will serve a useful purpose in daily practice.

Zahid Maleque, MP


5.5

President
Diabetic Association of Bangladesh&
Chair, IDF South East Asia

Message

It gives me immense pleasure to know that NCDC, DGHS is publishing the country's first national diabetes guideline. I express my heartfelt thanks to all the members of the task force team and expert committee for putting their effort to develop the guideline.

The world is suffering from an epidemic of diabetes and this epidemic is rising faster in developing countries like Bangladesh; hence the number of increasing patients need to get access to quality care for getting optimal control. It is well known that to ensure quality care competence building of physicians is of utmost need.

I believe this guideline will help the physician to choose the right regimen for treating people with diabetes. I also believe this initiative will expand the specialist physician base and will empower the physicians to enhance the treatment of diabetes ensuring quality care.

I look forward to the success of this guideline.

National Prof. AK Azad Khan


5.5

Secretary
Health Service Division
Ministry of Health & Family Welfare
Government of the People's Republic of Bangladesh

Message

I am immensely delighted to know that NCDC, DGHS is publishing the country's first national diabetes guideline. I would like to take this moment to express my heartfelt gratitude to all members who worked relentlessly to develop this guideline. Thanks to JICA and BADAS for their technical assistance.

The number of Diabetic Patients is increasing worldwide and also in Bangladesh at an alarming rate. As a result, an increased number of patients need to get access to quality care for achieving optimal control, and capacity building of the physicians is a time-demanding need.

I believe these initiatives will expand the specialist physicians base and will empower the physicians and will help to progress further towards fulfilling the vision of creating a Smart Bangladesh.

I look forward to the success of this guideline.

Dr. Md. Anwar Hossain Howlader


5.5

Director General
Directorate General of Health Services
Government of the People's Republic of Bangladesh

Message

Across the world diabetes is a common burden. We are facing the same challenges in Bangladesh. About 13.1 million people in Bangladesh have diabetes. This figure would be just doubled by the year 2045. We are struggling to provide quality care to people with diabetes due to the limited number of diabetes specialists. I believe this national diabetes guideline from NCDC will guide a physician to select appropriate therapy to manage diabetes as well as boost the treatment knowledge of physicians and ensure a better treatment in individualized care.

We are happy to see such type of initiative of NCDC and appreciate their effort to publish this guideline.

We look forward to the success of this and believe it would be a widely used guideline among physicians.

Prof. Dr. ABM Khurshid Alam


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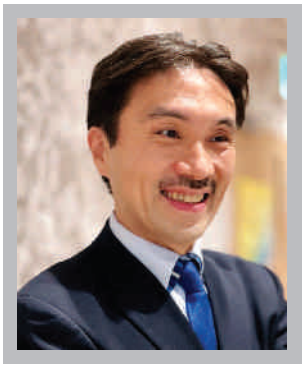

Chief Representative
JICA Bangladesh Office

Message

It is my great pleasure that the National Diabetes Guidelineis launched by the Government of Bangladesh (GOB).JICA recognizes that Non-Communicable Diseases (NCDs), including diabetes, are a growing public health concern in Bangladesh, affecting a significant portion of the population and leading to high morbidity and mortality. Nevertheless, thanks to initiatives by the GOB to improve people's access to NCDs services, remarkable progress has been made over the past few years in instituting measures against NCDs, particularly diabetes and hypertension.

JICA has been providing support in the health sector through financial and technical cooperation with the GOB. Currently, the prevention of NCDs is one of our prioritiesas seen inJICA's implementation of the "Project for Strengthening Health Care Systems for Organizing Communities (known as SHASTO)"until 2022. The project worked closely with the Non Communicable Disease Control Program(NCDC) and theDirectorate General of Health Services (DGHS) to develop and implement the NCDC Program activities, including promoting the NCDs management model to prevent hypertension and diabetes. We are happy to celebrate the lauchning of this guideline as a output of SHASTO project. JICA is delighted to continue the collaboration with NCDC and DGHS for launching anew project on strengthening healthcare systems for preventing NCDs this year.

This national diabetes guideline aims to provide evidence-based guidance for the prevention, diagnosis, and management of diabetes in Bangladesh, which is tailored to local needs, practices, and resource availability. It covers various aspects of diabetes care including risk assessment, screening, glycemic control, lifestyle intervention, the use of medications and insulin therapy, and the management of diabetes-related complications, such as neuropathy, retinopathy, and nephropathy.

The guideline, which was developed through the efforts of experts on diabetes care in Bangladesh,fully reflects the accumulated expertise in such care. We believe this will help healthcare professionals responsible for those with diabetes ensure essential, high-quality healthcare services that improve the health outcomes and quality of life of patients while reducing the burden the disease places on those patients and on the healthcare system.

We remain committed to working with the Government of Bangladesh and our other partners to reduce the impact of NCDs on the country

T. Ichiguchi

Ichiguchi Tomohide


5.5

Line Director
Non-communicable Disease Control Program
Directorate General of Health Services

Preface

I express my heartiest thanks to all the members of the task force and the expert committee of the National Diabetes Guideline for their brilliant contribution to publishing this guideline. Thanks to BADAS and JICA for their technical support.

Diabetes is a chronic lifelong disease. If undetected or uncontrolled, it can lead to life-threatening acute emergencies and long-term chronic complications leading to blindness, end-stage kidney disease, neurological complications, and cardiovascular disease. Research has proved that all these complications are largely preventable by early detection and good control of diabetes. I believe this guideline will guide our physicians to choose the appropriate treatment regimen for the management of their patients properly.

We look forward to your gracious support to these and make it a grand success.

Prof. Dr. Md. Robed Amin
Editor-in-Chief


5.5

Abbreviations

ACEI	Angiotensin-Converting Enzyme Inhibitors
AER	Albumin Excretion Rate
AGI	Alpha-Glucosidase Inhibitors
ALA	Alpha Lipoic Acid
ALT	Alanine Amino Transferase
ARB	Angiotensin II Receptor blockers
ASCVD	Athero Sclerotic Cardio Vascular Disease
BG	Blood Glucose
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CCr	Creatinine Clearance
CGM	Continuous Glucose Monitoring
CKD	Chronic Kidney Disease
CVD	Cardio Vascular Disease
DHA	Docosa Hexaenoic Acid
DIC	Disseminated Intravascular Coagulation
EPA	Eicosa Pentaenoic Acid
DKA	DM- Diabetes Mellitus
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GAD	Glutamic Acid Decarboxylase
GFR	Glomerular Filtration Rate
GI	Gastro Intestinal
HbA1c	Glycated Hemoglobin
hCG	Human Chorionic Gonadotropin
HDL	High-Density Lipoproteins
HHS	Hyperosmolar Hyperglycemic State
HIV	Human Immunodeficiency Virus

HLA	Human Leukocyte Antigen
IDF-DAR	International Diabetes Federation- Diabetes and Ramadan
IHD	Ischemic Heart Disease
ISPAD	International Society for Pediatric and Adolescent Diabetes
LAD	Left anterior Descending Artery
LDL	Low-Density Lipoproteins
LGA	Large for Gestational Age
MDI	Multiple Dose Injection
MEN-2	Multiple Endocrine Neoplasia Syndrome Type 2
MI	Myocardial Infarction
MNT	Medical Nutrition Therapy
MTC	Medullary Thyroid Cancer
NAFLD	Non Alcoholic Fatty Liver Disease
NCD	Non Communicable Disease
NPH	Neutral Protamine Hagedorn
NPO	Nothing by Mouth
PCI	Percutaneous Coronary Intervention
PCOS	Poly Cystic Ovary Syndrome
PDE5	Phospho Diesterase 5
PPAR	Peroxisome Proliferator-Activated Receptors
RTI	Respiratory Tract Infection
SC	Sub Cutaneous
SMBG	Self-Monitoring of Blood Glucose
SU	Sulfonyl Ureas
TDD	Total Daily Dose
TPN	Total Parenteral Nutrition
tTG	Tissue Trans Glutaminase
UTI	Urinary Tract Infection
WC	Waist Circumference

Contents

Introduction

Introduction

Diabetes is a major health issue that has reached a pandemic level. In Bangladesh, the treatment of diabetes is mainly provided by general physicians and specialist physicians, including endocrinologists and diabetologists, through government and private healthcare facilities. However, in some union-level government facilities, medical assistants detect high blood glucose and refer for treatment to physicians. Compliance with diabetes treatment is low mainly due to insufficient knowledge about disease control and prevention of complications, and the long-term cost of drugs in the case of poor patients. Lack of updated information and current recommendations on diabetes management for physicians are also important barriers to providing proper care. Although several international guidelines for diabetes management are now available, a guideline specific to the Bangladeshi population is required for the appropriate management of diabetes by physicians and healthcare providers working at various levels of the healthcare system in Bangladesh.

Objective

The objective of this national diabetes guideline is to provide clear and concise evidence to all healthcare providers on the current concepts in the management of diabetes. Since diabetes is managed by various levels of healthcare providers in Bangladesh, attempts are made to ensure that different stakeholders will benefit from this guideline.

Methods

To develop the guideline, the Noncommunicable Disease Control (NCDC) Program of the Directorate General of Health Services (DGHS) set up three groups – a working group, a task force group, and an advisory group. Both working and task force groups comprised leading experts from endocrinology, diabetology, internal medicine, nephrology, primary care medicine, and public health in Bangladesh. The advisory group consists of both renowned clinicians and government policymakers. Centre for Global Health Research, the Diabetic Association of Bangladesh (BADAS), and the Japan International Cooperation Agency (JICA) provided technical support. 'Diabetes Care BADAS Guideline 2019', a joint initiative of NCDC and BADAS, was a baseline document for guideline development. In addition, members of the working group reviewed recent diabetes care and prevention guidelines published by various internationally authoritative scientific and professional bodies. Also, they examined the recent reports on newer studies related to diabetes management to formulate a 'zero draft.' After completing the zero draft presentation, the working group members conducted a series of consultations. A draft document comprising seven chapters with a summary was developed. Each reference that was used to formulate this guideline was critically reviewed. The task force group, consisting of eighteen members, worked on this document and finalized it after making necessary changes. A four-member independent review committee reviewed this document, which was then uploaded to the DGHS website for public comments. Finally, the guideline was approved by the advisory group members.

Duration

June 2022 to November 2022

Chapter-1

Epidemiology, Classification, Pathophysiology and Clinical Presentation of Diabetes Mellitus

CHAPTER - 1

Epidemiology, Classification, Pathophysiology, and Clinical Presentation of Diabetes Mellitus

Executive summary

- Diabetes mellitus (DM) is a metabolic disorder characterized and identified by the presence of persistent hyperglycemia.
- The etiopathology of DM includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat, and protein metabolism.
- Type 1 diabetes (T1DM), type 2 diabetes (T2DM), and Gestational Diabetes (GDM) are the common types of DM.
- T1DM usually presents with classical features of hyperglycemia including polyuria, polydipsia, polyphagia, weight loss and generalized weakness.
- T2DM and other forms of diabetes mellitus may remain asymptomatic for quite a long period resulting in late diagnosis and intervention.
- A significant proportion of T2DM cases may present with one or more chronic complications.

Diabetes mellitus (DM) is a metabolic disorder characterized and identified by the presence of persistent hyperglycemia. Varying degrees of etiopathologies include principally defects in insulin secretion, insulin action or both, and disturbances of carbohydrate, fat, and protein metabolism.[1] In recent times several other pathological pathways are recognized, especially in type 2 diabetes (T2DM).

1.1 Epidemiology

1.1.1 Global trend

DM is now one of the most common noncommunicable diseases globally. It is an epidemic in many developing and industrializing countries. At present, the total number of diabetic persons globally is nearly 537 million with a prevalence of 10.5% in the adult population (20 to 79 years). China and India hold the first and second positions respectively having 140.9 and 74.2 million of total cases of diabetes. It is estimated that this current number of diabetic persons is projected to reach 643 million by 2030, and 783 million by 2045.[2]

In addition to diabetes, prediabetes also constitutes a major public health problem because of its association with an increased risk of DM and cardiovascular diseases (CVD). A total of 541 million (1 in 9) people are estimated to have impaired glucose tolerance (IGT) and 319 million (1 in 18) people have impaired fasting glucose (IFG).[2]

1.1.2 Bangladesh Trend

At present, the total number of diabetic people is nearly 13.1 million, with a prevalence being 14.2% in the adult population (20 to 79 years). Almost all are T2DM. Bangladesh at present is in 8th position in the world by the total number of people with DM. By 2045, it is projected to move to the 7th position, with 22.3 million people with T2DM.[2] National Noncommunicable disease (NCD) Risk Factor Study 2022 reported 9.7% (15-69 years) DM in Bangladesh (Collected by personal Communication).[3]

1.2 Classification[1]

Diabetes mellitus is classified based on clinical care into six types (Table 1). However, type 1 diabetes (T1DM), T2DM, and gestational diabetes (GDM) are the common types of DM.

Table 1.1 Classification of DM

Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes
Slowly evolving immune-mediated diabetes of adults
Ketosis prone type 2 diabetes
Other specific types
Monogenic diabetes
Monogenic defects of β-cell function
Monogenic defects in insulin action
Diseases of the exocrine pancreas (fibrocalculus pancreatopathy, pancreatitis, trauma/pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis and others)
Endocrine disorders (Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma, hyperthyroidism, somatostatinoma and others)
Drug-or chemical-induced (glucocorticoids, thyroid hormone, thiazides, alpha-adrenergic agonists, beta-adrenergic agonists, dilantin, pentamidine, nicotinic acid, interferon-alpha etc.)
Infections (congenital rubella, cytomegalovirus)

Uncommon specific forms of immune-mediated diabetes (insulin autoimmune syndrome, anti-insulin receptor antibodies, stiff man syndrome)
Other genetic syndromes sometimes associated with diabetes (Down syndrome, Friedreich's ataxia, Huntington's chorea, Klinefelter's syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome, Turner's syndrome and others)
Unclassified diabetes
This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes
Hyperglycemia first detected during pregnancy
Diabetes mellitus in pregnancy
Gestational diabetes mellitus (GDM)

1.3 Criteria of different types of DM[1, 2, 4]

Table 1.2 Difference between T1DM, T2DM and GDM

Type 1 DM	Type 2 DM	GDM
• Markers of beta cell destruction may be present • Presents before 30 years of age • Body habitus - normal to wasted • Symptoms are sudden & classical • Less genetic link; maybe HLA linked • Ketoacidosis (DKA) is more common • Insulin reserve is very low; insulin is mandatory for treatment	• Markers of beta cell destruction usually absent • Presents after 30 years of age • Body habitus - obese/overweight • Symptoms are gradual & atypical • More genetic link • Hyperosmolar hyperglycemic state (HHS) is more common • Insulin reserve declines very slowly; can be treated with non-insulin agents	• Associated with pregnancy • Placental hormones antagonize maternal insulin • More common if maternal age is ≥25 years • Obesity/over-weight favors the development of GDM • Family history of T2DM is a risk factor • Ketosis may develop • Insulin is the treatment of choice

1.4 Initial steps for classifying DM[1]

1. Confirm diagnosis of DM
2. Exclude secondary causes
3. Consider the following which may assist in differentiating subtypes:
    a. Age at diagnosis
    b. Family history
    c. Physical findings, especially the presence of obesity
    d. Presence of features of metabolic syndrome
4. Note the presence or absence of ketosis or ketoacidosis
5. Perform diagnostic tests if available (β-cell autoantibodies, C-peptide)

1.5 Pathophysiology[1, 2, 4-6]

1.5.1 Type 1 diabetes

It is mostly caused by autoimmune destruction of the beta cells in the pancreas, resulting in a severe reduction in insulin production. Genetic susceptibility, an environmental factor like viral infection and autoimmunity, in combination, plays an important role in the development of T1DM. Some T1DM cases are idiopathic in nature.

1.5.2 Type 2 diabetes

Insulin resistance and beta cell failure represent the main pathophysiologic defects in T2DM. Subjects with T2DM are maximally insulin resistant and have lost approximately 50% of their beta cell function. The degree of insulin resistance and beta cell loss defer from one type to another type and that is why the presentation of T2DM is heterogeneous. Gradual loss of beta cell function is characteristic of T2DM over the course of time. In addition, muscle (impaired glucose disposal), liver (increased glucose production), beta cell (reduced insulin production), fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), alpha cell (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance) – all play important roles in the development of glucose intolerance in T2DM individuals. Collectively, these eight pathways comprise the ominous octet.

1.5.3 Gestational diabetes mellitus

This type of diabetes is caused by placental hormones, namely beta hCG, human placental lactogen, estrogen, progesterone, etc. antagonizing the action of insulin.

1.6 Clinical presentation[1, 2, 4, 6]

The spectrum of presentation ranges from asymptomatic to typical features.

- Asymptomatic cases are diagnosed by biochemical tests only. A vast majority of T2DM and other types remain asymptomatic over a prolonged period. Routine check-up usually picks up this form of DM. T1DM is always symptomatic and shows classical features of hyperglycemia.
- Typical features of DM start with glycosuria, which begins after the blood glucose level has gone above an individual's renal threshold for glucose. Features include polyuria, polydipsia, polyphagia, weight loss and generalized weakness. These are mostly seen in the presentation of T1DM, though not so common in other types.
- Atypical manifestations are non-specific, which include non-healing infection, infertility or repeated pregnancy loss, pruritus vulvae, undue fatigability etc. This is a common mode of presentation in T2DM.
- Specific complications of DM may be present at the time of diagnosis. In T2DM and other forms of diabetes mellitus, presentations may remain asymptomatic for quite a long period resulting in late diagnosis and intervention. So significant proportion of T2DM cases presents with one or more chronic complications. All T1DM cases are usually diagnosed before the development of chronic complications.

1.7 Prediabetes[1, 2, 4]

IGT (impaired glucose tolerance) and IFG (impaired fasting glucose) are referred to as 'Prediabetes'. Persons with prediabetes have a high risk of developing DM (25% of IFG and 30% of IGT cases become diabetic over time) and CVD. Any type of DM can pass through the stages of prediabetes, but it is most obvious in T2DM. These persons are treated by lifestyle modifications; drugs may be used where indicated. About 40% of IFG and 30% of IGT cases may revert to normal if the proper intervention can be given.

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Chapter-2

Screening and Diagnosis of Diabetes Mellitus

CHAPTER-2
Screening and Diagnosis of Diabetes Mellitus

Executive summary

- Procedures for documenting glucose intolerance includes: 2-sample oral glucose tolerance test (OGTT), fasting plasma glucose (FPG), HbA1c and random plasma glucose (RPG) with symptoms.
- Screening prediabetes/ diabetes should be considered in all asymptomatic adults ≥30 years of age, adults <30 years of age who are over-weight/obese (BMI ≥23 kg/m^2) and adults <30 years of age with BMI <23 kg/m^2 but have one or more risk factors.
- Screening should be considered after onset of puberty or after 10 years of age in all asymptomatic children and adolescents with BMI ≥85th percentile and before 10 years of age with BMI ≥85th percentile and who have additional risk factors for diabetes.
- If results are normal, testing should be repeated at 1-year interval or as relevant.
- Testing for prediabetes/ diabetes should be considered in all women planning pregnancy. All women should be screened at the first antenatal visit with 3 sample 75 gm OGTT, if negative, re-screen during 24-28 weeks of gestation.

Screening and diagnosis of glucose intolerance in various population can be made with different clinical scenario and laboratory tests.

2.1 Screening for prediabetes and diabetes

2.1.1 Screening for prediabetes and diabetes in adults

- Testing for prediabetes/ diabetes should be considered in all asymptomatic adults ≥ 30 years of age (even if without risk factors).[1]
- Testing for prediabetes/ diabetes should be considered in all asymptomatic adults <30 years of age who are over-weight/obese (BMI ≥23 kg/m^2).[1-3]
- Testing for prediabetes/ diabetes should be considered in all asymptomatic adults <30 years of age with a BMI <23 kg/m^2 and who have one or more of the following risk factors:[1]
  - First-degree relative with diabetes
  - History of GDM
  - History of CVD with Hypertension (140/90 mmHg or on therapy for hypertension)
  - HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
  - Women with polycystic ovary syndrome
  - Physical inactivity

- Immediate testing is required in symptomatic cases.[1]
- Testing is advised in all patients with HIV.[1]

If results are normal, testing should be repeated at 1 year interval, with consideration of more frequent testing depending on initial results, deteriorating risk status and appearance of symptoms. People with prediabetes (HbA1c >5.7-6.4%, IGT or IFG) and women who were diagnosed with GDM should be tested yearly.

2.1.2 Screening for prediabetes and diabetes in children

- Testing for prediabetes/diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in all asymptomatic children and adolescents who are over-weight (BMI ≥85th percentile) or obese (BMI ≥95th percentile).[1]
- Testing for prediabetes/diabetes should be considered before 10 years of age in asymptomatic children and adolescents who are over-weight (BMI ≥85th percentile) or obese (BMI ≥95th percentile) and who have additional risk factors for diabetes:[1]
    - History of diabetes or GDM during the child's gestation
    - Both parents with diabetes
    - Family history of type 2 diabetes in first- or second-degree relative
    - Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight)
- Immediate testing is required in symptomatic cases.[1]

If results are normal, testing should be repeated at 2-year intervals, with consideration of more frequent testing depending on initial results, deteriorating risk status or appearance of symptoms. Children with prediabetes should be tested yearly.

2.1.3 Screening for diabetes in women planning pregnancy and pregnant

- Testing for prediabetes/ diabetes should be considered in all women planning pregnancy.[1]
- If preconception test is negative, test all women at the first antenatal visit with 3 sample 75 gm OGTT.[1]

- If early screening is negative, screening should be done at 24-28 weeks of gestation with 3 sample 75 gm OGTT.[1]
- Women with GDM should be tested with 2 sample 75 gm OGTT and non-pregnant diagnostic criteria at 4-12 weeks postpartum, preferably at 6th week considering vaccination schedule of children in Bangladesh.[1]

2.1.4 Screening for T1DM

- Plasma glucose rather than HbA1c should be used to diagnose the acute onset of T1DM in individuals with symptoms of hyperglycemia.[1]
- Screening for T1DM risk with a panel of autoantibodies (autoantibodies to islet cell, insulin, GAD, Zinc transporter) can be done in first-degree family members of a proband with T1DM where facility is available.[1]

2.1.5 Screening in special populations

- In those with hemoglobinopathies, annual screening with standard OGTT should begin at 10 years of age. There is limited role of HbA1c in this setting.[4]
- After organ transplantation, testing with OGTT should be performed once the patient is stable on immunosuppressive therapy and there is no infection.[1]

2.2 Diagnosis of prediabetes and diabetes

Diagnosis is based on documentation of glucose intolerance in an individual. Procedures for documenting glucose intolerance include:

1. Oral glucose tolerance test (OGTT) – gold standard test
2. Fasting plasma glucose (FPG)
3. HbA1c (Glycated hemoglobin)
4. Random plasma glucose (RPG)

2.2.1 OGTT (gold standard test)

Plasma glucose level is determined at fasting and 2 hours after 75 grams (1.75-gram glucose/kg body weight, up to maximum 75-gram glucose for children) of oral glucose drink. It classifies a

person as a diabetic, IGT (impaired glucose tolerance), IFG (impaired fasting glucose) or normal.[1,5]

OGTT procedure[5]

- Person should take unrestricted diet containing at least 150 grams of carbohydrate daily for at least previous 3 days.
- The test should be done in the morning after 8-14 hours of overnight fast (Preferably before 9 am).
- A fasting blood sample prior to glucose drink is collected.
- An oral glucose load of 75-gram of anhydrous glucose for adult (1.75-gram glucose/kg body weight, up to maximum 75-gram glucose for children) is given in 250-300 ml of water. The drink must be completed within 5 minutes.
- A second blood sample is collected at 120th minute after the glucose drink.
- If glucose is not estimated immediately then the blood sample may be preserved with sodium fluoride (6 mg/ml whole blood), blood should be centrifuged, and plasma separated and frozen until estimation.
- Smoking, tea or physical stress is not allowed during the test.

2.2.2 FPG

By fasting plasma glucose level, a person can be labeled as a diabetic, but cannot exclude diabetes.[1,5]

2.2.3 HbA1c

HbA1c is now increasingly being used in diagnosis of diabetes. The test must be highly standardized for using it in this purpose.[1,5]

2.2.4 RPG

No preparation is required for this procedure. Plasma glucose levels are estimated from a sample irrespective of last meal. RPG, in presence of classical symptoms of hyperglycemia or hyperglycemic crisis can confirm diabetes.[1]

Table 2.1 Diagnostic criteria for prediabetes (IFG and IGT) and diabetes mellitus for non-pregnant adults and children[1,5]

	IFG	IGT	DM
Fasting plasma glucose	6.1-<7.0 mmol/L (110-<126 mg/dL)	<7.0 mmol/L (<126 mg/dL)	≥7.0 mmol/L (≥126 mg/dL)
	And	And	Or
2–h plasma glucose during OGTT	<7.8 mmol/L (<140 mg/dL)	7.8-<11.1 mmol/L (140-<200 mg/dL)	≥11.1 mmol/L (≥200 mg/dL)
	And/or		Or
HbA1c	5.7- 6.4% (39-47 mmol/mol)		≥6.5% (≥48 mmol/mol)
			Or
Random plasma glucose*	--	--	≥11.1 mmol/L

NB: *In presence of classical symptoms of hyperglycemia (polyuria, polydipsia, polyphagia, weight loss and generalized weakness) or hyperglycemic crisis.

Table 2.2 Diagnostic criteria for hyperglycemia in pregnancy[6]

	Gestational diabetes mellitus (GDM)	Diabetes in pregnancy (DIP)
FPG	5.1-<7.0 mmol/L (92-<126 mg/dL)	>7 mmol/L (126 mg/dL)
1-hr PG at OGTT	≥10.0 mmol/L (180 mg/dL)	--
2-hr PG at OGTT	8.5-<11.1 mmol/L (153-<200 mg/dL)	≥11.1 mmol/L (200 mg/dL)

NB: Diagnosis is made when any one of the plasma glucose values is met. Performed with a 3-step 75-gm OGTT at any time in pregnancy. All values are venous plasma glucose.

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Chapter-3

Treatment of Diabetes Mellitus

CHAPTER-3
Treatment of Diabetes Mellitus

Executive summary

- Comprehensive medical assessment is imperative for people with DM.
- In the management of diabetes diet and exercise are mandatory for all individuals.
- Insulin is the only pharmacotherapy for T1DM on the other hand various classes of medications including sulfonylureas, meglitinides (non-sulfonylureas), biguanides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, glucagon-like peptide-1 (GLP1) receptor agonists, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium glucose cotransporter-2 (SGLT2) inhibitors and insulin can be used in T2DM.
- The presence of complications or comorbidities such as ASCVD, CKD, and heart failure also has an important role in determining therapy.
- Monitoring of glycemic control by SMBG and CGM are important components of diabetes management.

Treatment of DM is always individualized. T1DM always requires insulin but the management of T2DM is of great challenge and require appropriate decision making. Not only the glycemic control but CVD risk, presence of comorbidities and complications need to be considered when choosing a particular antidiabetic agent.

Table 3.1 Factors to be considered before selection of antidiabetic agent[1,2]

• Type of DM • Age of the person • Body weight/BMI • Associated conditions, e.g. acute/chronic complications/illnesses, pregnancy/lactation, major surgery, life expectancy etc. • Socio-economic condition/cost of medication • Personal preference	• Degree of hyperglycemia • Job and occupation/lifestyle of the person • Previous antidiabetic agents (if on any) • Caregiver support • Potential for side effects like hypoglycemia risk

Table 3.2 Target of diabetes management (in non-pregnant adult)[2]

Blood (plasma) glucose	Fasting/pre-meal <7.0 mmol/L Post-meal <10.0 mmol/L (1-2 hr after beginning of meal)
HbA1c	<7% (Less stringent, e.g. 7-8% in elderly with multiple comorbidities)
Blood lipids	LDL cholesterol <100 mg/dL (<70 mg/dL in H/O CVD) HDL cholesterol >40 mg/dL (male) >50 mg/dL (female) Triglyceride <150 mg/dL
Blood pressure	Systolic <130 mm of Hg Diastolic <80 mm of Hg
BMI	BMI <23 kg/m^2
Waist circumference (WC)	WC <90 cm (male) <80 cm (female)
Education and empowerment regarding lifestyle changes, SMBG and treatment adjustment should also be targeted	

NB: Target of glycemic control may be individualized considering individual factors.

3.1 Treatment regimen and monitoring

3.1.1 Non-pharmacological

Lifestyle modification includes medical nutrition therapy and exercise.

Medical nutrition therapy

An individualized medical nutrition therapy preferably by a registered dietitian, is recommended for all people with diabetes and prediabetes. Typical composition of a balanced diet should be carbohydrate 50%, protein 10-20%, fat<30%. Meal plans should be individualized while keeping total calorie and metabolic goals in mind.

Table 3.3 Factors related to medical nutrition therapy

Points	Description
Weight loss	≥5% by combination of reduction of calorie intake and increased physical activity, benefits over-weight or obese adults with T2DM and prediabetes.
Nutrient-dense carbohydrate	Sources that are high in fiber, including vegetables, fruits, legumes, whole grains, as well as dairy products should be emphasized.
Sugar-sweetened beverages	People with DM and those at risk are advised to avoid sugar-sweetened beverages (including fruit juices) in order to control glycemia, weight. It also reduces their risk for cardiovascular disease and fatty liver.
Protein	Diet should contain sufficient protein from animal and plant sources.
Dietary fat	Diet rich in monounsaturated and polyunsaturated fats may be considered to improve glucose metabolism and lower cardiovascular disease risk. Foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA) are recommended to prevent or treat cardiovascular disease.
Salt consumption	As for the general population, people with diabetes should limit salt consumption to 5 gm/day.
Non-nutritive sweeteners	Non-nutritive sweeteners can reduce overall calorie and carbohydrate intake but overall, people are encouraged to decrease both sweetened and non-nutritive sweetened beverages and to use other alternatives, with an emphasis on water intake.
Dietary supplementation	There is no clear evidence that dietary supplementation with vitamins, minerals (such as chromium and vitamin D), herbs, or spices (such as cinnamon or aloe vera) can improve outcomes in profile with diabetes.
Meal frequency	Three main meal and 2 snacks with a bed time snack for those having multiple daily injection or have a tendency for midnight hypoglycemia.
Calorie allowance	Calorie Allowence = Ideal body weight x calorie factor Ideal body weight = height in cm - 100 Calorie factor varies from 20 to 45 according to BMI and physical activity status.

Exercise/physical activity[3]

- Adults with diabetes should perform150 minutes or more of moderate intensity aerobic activity per week, spread over at least 5 days/week, with no more than 2 consecutive days without activity.
- Shorter durations (minimum 75 min/week) of moderate intensity or interval training may be sufficient for younger and more physically fit individuals.
- Adults with diabetes should engage in 2-3 sessions/week of resistance exercise on non-consecutive days.
- All adults and particularly those with type 2 diabetes, should decrease the amount of time spent in daily sedentary behavior, prolonged sitting should be interrupted every 30 minutes.
- Physical activity or exercise is encouraged to do same time in a day.

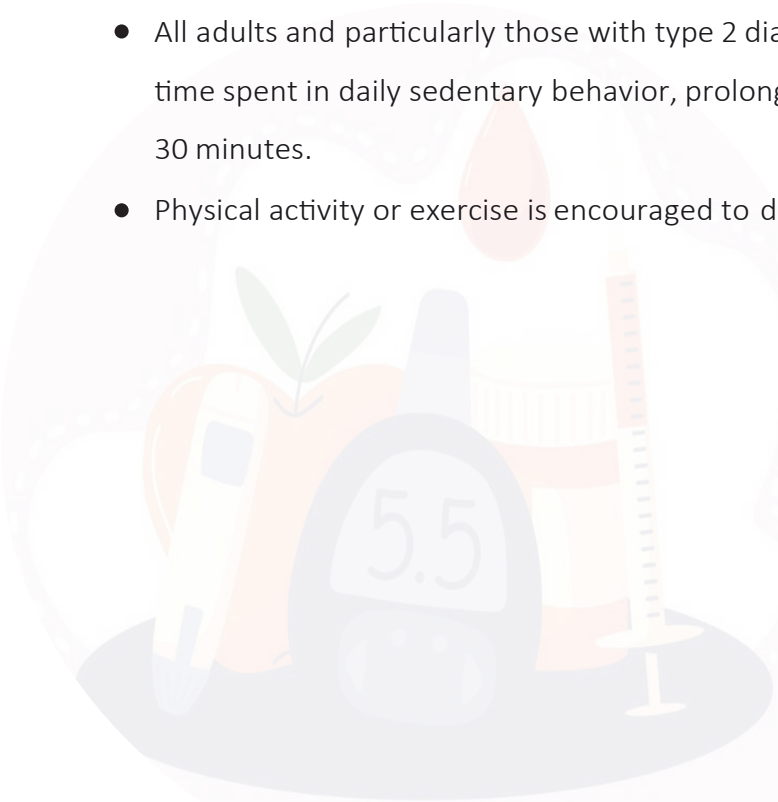


Table 3.4 Some practical points on exercise[2]

	Warm up	Muscle stretching	Main exercise	Cool down
Time	5-10 minutes	5-10 minutes	30 minutes	5-10 minutes
Type of exercise	Aerobic activity (e.g. walking) at low intensity	Gentle muscle stretching	Moderate to high intensity exercise	Low intensity activity

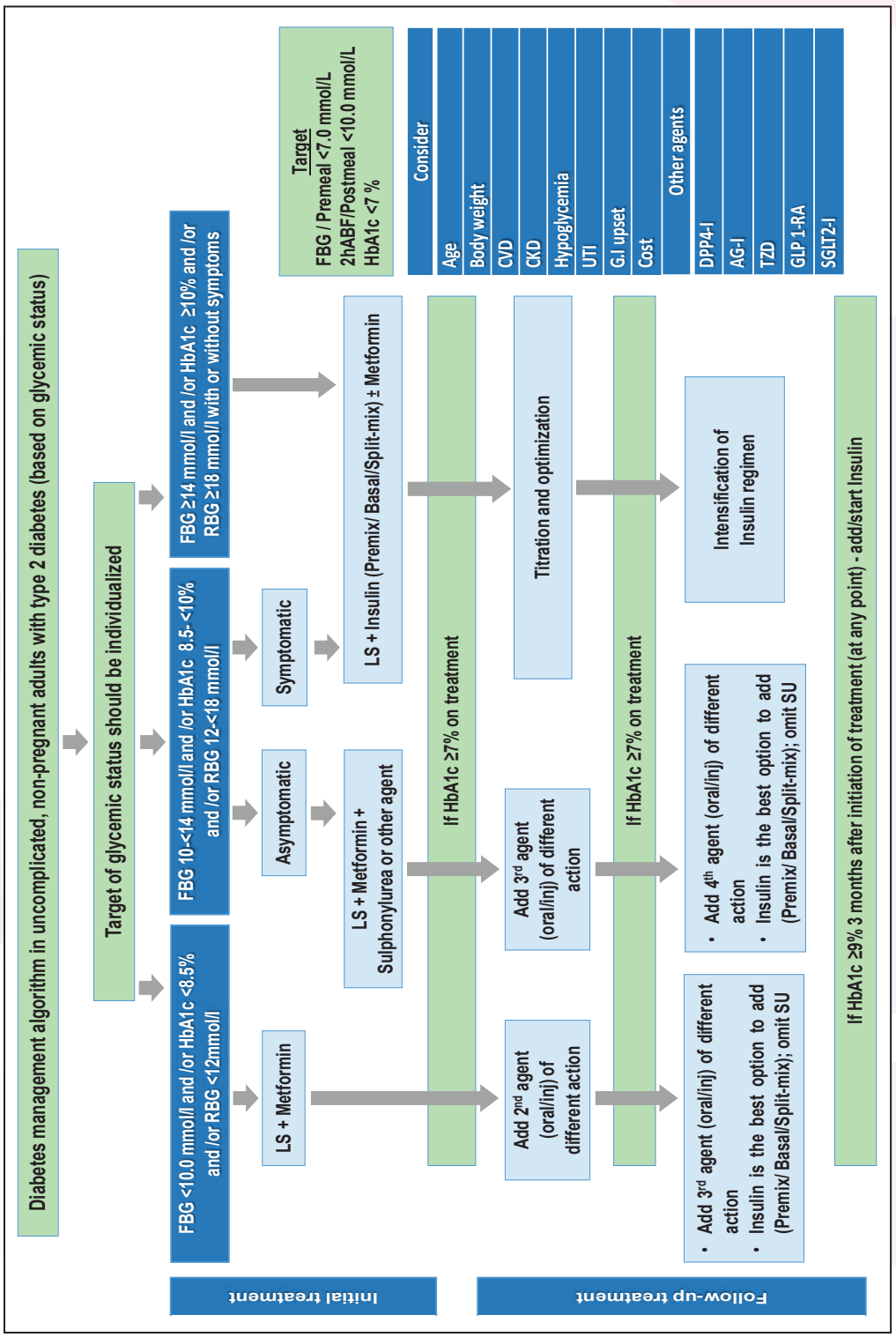
Type and duration of exercise may vary in some special instances as shown in the following table.

Table 3.5 Exercise in special situations[2]

Condition	Exercise recommendation
Peripheral neuropathy, loss of protective sensation, Charcot's joint and osteoarthritis of back and knee	Should not engage in repetitive weight bearing exercises, e.g. prolonged walking, treadmill, jogging etc. as these activities may result in blistering, ulceration and fracture. Non-weight-bearing exercises, e.g. swimming, cycling, rowing, etc. may be better.
Proliferative and moderate to severe non-proliferative diabetic retinopathy	Strenuous activity may precipitate vitreous hemorrhage or tractional retinal detachment; they should avoid anaerobic exercise and physical activity that involves straining, jarring or Valsalva-like maneuvers (e.g. weight lifting, boxing, heavy competitive sports etc). In these persons low impact exercises like swimming (but not diving), walking or stationary cycling may be recommended.
Stable coronary heart disease	Perform moderate intensity exercise.
Uncontrolled hypertension	Withhold exercise until control of blood pressure.
Symptomatic hyperglycemia/ketosis or hypoglycemia	Exercise should be postponed If blood glucose goes >16.7 mmol/L. If blood glucose is <3.9 mmol/L the person should take extra 15-30 grams carbohydrate before exercise.
Significant acute illness or uncompensated major chronic illnesses	Should not exercise during this illness.
During pregnancy	Moderate exercise (e.g. walking at moderate speed for 30 minutes a day at a time or in divided fashion) is advised if there is no obstetric contraindication.
Bed-ridden persons	Physiotherapy, passive movement and posture change.

3.1.2 Pharmacological therapy

Oral drugs, insulin and other injectable agents are used for management of diabetes. Several individual and drug factors are considered while choosing an antidiabetic agent. Selection of antidiabetic agent is always individualized and may vary in same person in different situation.



NB: LS - Lifestyle

Figure 3.1 Type 2 diabetes management algorithm
(Adapted from Diabetes Care, BADAS Guideline 2019)

3.2 Oral antidiabetic drugs (OADs)

Oral drugs are not recommended in type 1 DM, and during pregnancy and lactation.

Table 3.6 Different classes of OADs

Class	Drugs
Sulfonylureas (stimulate insulin secretion from beta cells)	Glibenclamide Glipizide Gliclazide Glimepiride
Non-sulfonylureas (stimulate insulin secretion from beta cells)	Repaglinide Nateglinide
Biguanides (reduce insulin resistance)	Metformin
Thiazolidinediones (insulin sensitizers, act via PPARγ receptor stimulation)	Pioglitazone Rosiglitazone
Alpha-glucosidase inhibitors (inhibit glucose absorption from intestinal brush border)	Acarbose Miglitol Voglibose
DPP4 inhibitors (inhibit DPP4 enzyme and increase half-life of GLP1)	Vildagliptin Sitagliptin Linagliptin Saxagliptin Alogliptin
SGLT2 inhibitors (inhibit glucose reabsorption from proximal convoluted tubule)	Dapagliflozin Canagliflozin Empagliflozin Ertugliflozin
Oral GLP1 receptor agonists (stimulate glucose dependent insulin secretion from beta cells, suppress glucagon secretion alpha cells and delay gastric emptying)	Semaglutide

Table 3.7 Selection issues of an oral agent

Drug	Advantages	Hazards	Limitations
Sulfonylureas	Potent Reduce pre- & post-prandial BG	Hypoglycemia, weight gain	Impaired hepatic, renal function Avoid long acting SU in CKD
Non-sulfonylureas	Less hypoglycemia Reduce post-prandial BG	Weight gain	Impaired hepatic, renal function
Biguanides	Improve insulin sensitivity Weight friendly Reduce pre- (mostly) & post-prandial BG Favorable effect on lipid & NAFLD	GI upset, lactic acidosis	Impaired renal function eGFR <45 - Do not initiate eGFR <30 - contraindicated
Thiazolidinedi-ones	Improve insulin sensitivity Reduce pre- (mostly) & post-prandial BG Favorable effect on lipid & NAFLD	Weight gain, fluid retention	Heart failure Risk of bone fractures Bladder cancer
Alpha-glucosidase inhibitors	Weight friendly Reduce post-prandial BG	GI upset	Impaired hepatic function Inflammatory. bowel disease Malabsorption states
DPP4 inhibitors	Weight friendly Reduce pre- & post-prandial (mostly) BG	GI upset, upper RTI, pancreatitis	Impaired renal function Vildagliptin: eGFR <50 - 50% of max. dose eGFR >50 - normal dose Sitagliptin: eGFR <30 - 25% of max. dose eGFR 30-60 - 50% of max. dose
SGLT2 inhibitors	Weight friendly Reduce pre- & post-prandial BG	UTI, genital fungal infection	Impaired renal function eGFR <30 - contraindicated
GLP1-RAs	Weight reduction Cardiovascular safety	GI upset, pancreatitis	Personal or family history of MTC, & in MEN-2

NB: NAFLD - Non-alcoholic fatty liver. eGFR ml/min/1.73m^2. MTC - medullary thyroid cancer. MEN-2 - multiple endocrine neoplasia syndrome type 2.

Special note

- Two secretagogues cannot be prescribed together.
- One secretagogue cannot be replaced by other in case of failure of one secretagogue to achieve glycemic target.
- Secretagogue needs to be discontinued when twice daily insulin is started.

Table 3.8 Initiation and dose titration of OADs[2,4,5]

Drug	Starting daily dose	Maximum daily dose	Time required for reasonable effect
Glibenclamide	1.25-2.5 mg x 1; 30 min ac	20 mg (in 1-2 doses)	2 weeks
Glipizide	2.5 mg x 1; 30 min ac	40 mg (in 1-2 doses)	
Gliclazide	40 mg x 1;30 min ac	320 mg (in 1-2 doses) MR/ExR-120 mg (in 1 dose)	
Glimepiride	1 mg x 1	6 mg (in 1 dose)	
Repaglinide	0.5 mg x 3; 15 min ac	12 mg (in 3 doses)	1-2 weeks
Nateglinide	60 mg x 3; 15 min ac	360 mg (in 3 doses)	
Metformin	500 mg x 1; pc; build up dose weekly	2500 mg (in 2-3 doses) ExR-2000 mg (in 1 dose)	4 weeks
Pioglitazone	15 mg x 1; morning	45 mg (in 1 dose)	4-6 weeks
Rosiglitazone	4 mg x 1 (or 2 mg x 2)	8 mg (in 1-2 doses)	
Acarbose Miglitol	25-50 mg X 1-3; within meal; build up dose weekly	300 mg (in 3 doses)	6 weeks
Voglibose	0.2 mg x 1-3; pc	0.9 mg (in 3 doses)	
Sitagliptin	100 mg x 1	100 mg (in 1 dose)	12 weeks
Vildagliptin	50 mg x 2	100 mg (in 2 doses)	
Linagliptin	5 mg x 1	5 mg (in 1 dose)	
Saxagliptin	2.5 mg x 1	5 mg (in 1 dose)	
Alogliptin	25 mg x 1	25 mg (in 1 dose)	
Dapagliflozin	5 mg x 1, morning	10 mg (in 1 dose)	4-12 weeks
Canagliflozin	100 mg x 1, morning	300 mg (in 1 dose)	
Empagliflozin	10 mg x 1, morning	25 mg (in 1 dose)	
Ertugliflozin	5 mg x 1, morning	15 mg (in 1 dose)	
Semaglutide	3 mg daily	14 mg (once daily)	4 weeks

NB: ac - before meal. pc - after meal.

3.3 Insulin and other injectable agents

Insulin is the most potent pharmacological agent in the management of all types of diabetes.

Table 3.9 Classification of insulin

Insulin type	Onset of action	Peak	Duration of action	Appearance
Bolus (prandial) insulin				
Short-acting (Regular) insulin	30 min	2-3 hr	6.5 hr	Clear
Rapid-acting insulin analogue				
Insulin Lispro	10-15 min	1-2 hr	3.5-4.75 hr	Clear
Insulin Faster Aspart	<5 min	1 hr	3-5 hr	Clear
Insulin Aspart	10-15 min	1-1.5 hr	3-5 hr	Clear
Insulin Glulisine	10-15 min	1-1.5 hr	3-5 hr	Clear
Basal insulin				
Intermediate-acting (NPH)	1-3 hr	5-8 hr	Upto 18 hr	Cloudy
Long-acting insulin analogue				
Insulin Detemir	90 min	No peak	24 hr	Clear
Insulin Glargine	90 min	No peak	24 hr	Clear
Insulin Degludec	90 min	No peak	42 hr	Clear
Premixed insulin (30/70,50/50,25/75)				
Biphasic Human Insulin	30 min	2-8 hr	Upto 24 hr	Cloudy
Biphasic Insulin Aspart	10-20 min	1-4 hr	Upto 24 hr	Cloudy
Biphasic Insulin Lispro	10-20 min	1-4 hr	Upto 24 hr	Cloudy
Coformulation (30/70)				
Insulin Degludec + Insulin Aspart	30-90 min 10-20 min	No peak 40-90 min	Beyond 24 hr	Clear

Table 3.10 Dose adjustment of injectable GLP1-RAs

Drug	Dose
Liraglutide	0.6 mg daily, increase to 1.2 mg after 1 week; max. dose 1.8 mg
Dulaglutide	0.75 mg daily, increase to 1.5 mg after 4 week; max. dose 4.5 mg
Semaglutide	0.25 mg daily, increase to 0.5 mg after 4 week; max. dose 1.0 mg

Table 3.11 Insulin regimens[4,5]

Regimen	Description
Basal only regimen	• NPH given once or twice daily or basal analogue given once daily • Common regimen of initiation of insulin therapy • To make the person confident about self injection of insulin
Twice daily injections	
Premixed	• Most commonly prescribed insulin regimen • Convenient • Difficult to achieve glycemic control at all points of day • Risk of hypoglycemia when meal time is irregular
Coformulation	Convenient and allows flexibility in regard to meal
Split-mixed	• Two/three times short acting added to twice daily intermediate acting insulin • Easier to achieve glycemic control at all points of day • Need for multiple injections • Dose adjustment is sometimes difficult for some persons
Multiple daily injections	
Basal Plus	• Combination of basal insulin with one or more doses of short acting insulin as needed • Offers more meal time flexibility
Basal-bolus	• Long acting insulin analogue given at bedtime as basal dose and rapid acting insulin analogue given before each meal as bolus doses • Ideal insulin regimen as it mimics normal physiological insulin secretion pattern • This is very flexible and ideal for those who are very active and meal time is irregular • Need for multiple injections
Continuous subcutaneous insulin infusion (CSII)	Insulin pump, delivering insulin continuously as basal, with person activated boluses with meals
Intravenous insulin infusion	DKA, HHS, critical illness, prolonged NPO, TPN, perioperative period, during delivery etc.

3.3.1 Indications of insulin

- Type 1 DM
- Severe acute complication/illness e.g. MI, acute infection
- Uncompensated chronic complication or illness
- Pregnancy and lactation

- At least 3-5 months prior to planned conception
- Major surgery
- OAD failure
- Poor glycemic status
    - HbA1c ≥10%
    - FBS ≥14 mmol/L, RPG ≥18 mmol/L (with or without symptom)
    - HbA1c ≥7% in spite of 50% of maximum dose of SU and maximum tolerable dose of sensitizer
    - Symptomatic hyperglycemia

3.3.2 How to start and adjust insulin[3,4]

1. Start with 0.2-0.5 unit/kg/day.
2. Premixed or coformulation: Start with two third of the total calculated dose in the morning and one-third at the evening (To start at a low dose with gradual up or down titration).
3. Split-mixed: Two third of the total dose will be intermediate acting and one third short acting. Among this two third dose in morning and one third dose at evening.
4. Basal insulin of 10 unit/day or 0.1-0.2 unit/kg/day. Fixing the fasting first. If postprandial still not within target, add bolus insulin 4 unit/day or 10% of basal dose.
5. Increase dose by 2-4 units every 3 days to reach the target.
6. Decrease dose by 2-4 units if blood sugar is below the target.

3.3.3 Continuous subcutaneous insulin infusion (CSII) pump

Continuous subcutaneous insulin infusion is a mode of delivering intensive insulin therapy, which usually leads to improved glycemic control and reduced glycemic fluctuation. It is a battery operated, portable, programmable pump to continuously deliver rapid-acting insulin via an infusion set inserted subcutaneously. Insulin pump is an alternative to treatment with multiple daily injection. Children with T1DM having multiple episodes of hypoglycemia or uncontrolled diabetes requiring multiple daily injection and T2 DM requiring high dose of insulin (>10 unit/kg) and not achieving glycemic target are candidates for CSII.

3.3.4 Insulin injection technique[1]

- Injections are given into the deep subcutaneous tissue at 45-90^0 angle by two-finger pinch of skin. The pinch is recommended to ensure a strict subcutaneous injection; avoiding intramuscular injection. Injections can be given perpendicularly without lifting a skin fold when needles are smaller and there is enough subcutaneous fat. Needles should be inserted full, otherwise there is a risk of intradermal injections. A wait of 15 seconds after pushing the plunger helps to ensure complete expulsion of insulin through the needle, especially in pens. Cleaning or disinfection of skin is advisable, but may not be necessary unless hygiene is a real problem.
- Vials (also the pen devices) of cloudy insulin must always be gently rolled (not shaken) 10-20 times, to mix the insulin suspension. When two insulins are drawn (e.g. regular insulin is mixed with NPH), the regular insulin is to be drawn before the intermediate acting one. The mixture must be administered immediately.
- Abdomen is the preferred site when faster and uniform absorption is required; it is less affected by muscle activity or exercise. Front and lateral aspects of thigh is the preferred site for slower absorption of longer acting insulin. Lateral aspect of upper arm is another site, but assistance is required for injection. The lateral upper quadrant of the buttocks is used less often. Rotation of injection sites are important within the same area of injection.

3.3.5 Storage of insulin[1]

Insulin must never be frozen. Direct sunlight or warming (e.g. in hot climates) damages insulin. Insulin should not be used if there is change in appearance (clumping, frosting, precipitation or discoloration). Unused insulin should be stored in a refrigerator (4-8^0 C) to retain its potency up to expiry date. When in use, the insulin can be kept in room temperature (if not too hot) without much loss of efficacy. But it retains its potency much better if kept in refrigerator. In hot climates where refrigeration is not available, cooling jars, earthenware pitcher or cool wet cloth around the insulin container will help to preserve activity.

3.4 Glycemic monitoring

3.4.1 Self blood glucose testing (SMBG)

To be done frequently (preferably once /twice weekly covering pre-meal, post-meal) in persons who are on multiple dose insulin regimen or insulin pump, especially in T1DM and pregnancy. For others it is to be done as required according to clinical situations.

3.4.2 HbA1c

- Glycated hemoglobin is formed by non-enzymatic condensation of glucose with the globin component of hemoglobin. This generally reflects glycemic status over the preceding 2-3 months. The target of HbA1c is <7%. HbA1c guides change in the therapeutic regimen.
- HbA1c test should be done at least two times a year in those who are meeting treatment goals (and who have stable glycemic control) and quarterly in persons whose therapy has changed or who are not meeting glycemic goals.
- RBC turnover (blood loss, hemolysis, blood transfusion, pregnancy, etc.) and hemoglobin variants must be considered while testing HbA1c.
- Result may vary if not done from a standardized lab.

3.4.3 Continuous glucose monitoring (CGM)

Continuous glucose monitoring automatically monitors blood glucose throughout the day and night. A CGM works through a tiny sensor inserted in skin, usually on abdomen or arm. The sensor measures interstitial glucose level. It measures glucose every few minutes and gives real time update. While calculating the report of CGM the percentage of time a person's blood sugar is found between 4.0-10.0 mmol/L is measured and this measured time is designated as Time in Range. The target of time in range to keep >70% (17hours).

3.5 Comprehensive medical evaluation for people with DM

Components of comprehensive diabetes medical evaluation at initial, follow up and annual visits includes: a) past medical and family history, b) social history, c) medication and vaccination, d) screening of psychosocial conditions, educational supports, nutritional support, pregnancy planning, e) physical examination, f) laboratory and imaging investigations and g) planning for achieving glycemic and other metabolic targets.

Table 3.12 Components of comprehensive medical evaluation[3]

Past medical, personal and family history	age and onset of symptoms, personal history, history of diabetes of first-degree family members, family history of autoimmune disorders, history of comorbidities, presence of macrovascular and microvascular complications, hemoglobinopathies, anemia, hypertension, dyslipidemia, hyperuricemia, PCOS, subfertility etc.
Social history	assessment of eating pattern, weight changes, physical activity, sleep pattern, use of tobacco, alcohol and substance use and social circumstances etc.
Medication and vaccination	history of medication adverse effects/ allergy, use of complementary and alternative medicines, vaccination history and need, assessment of use of health apps, education portals, glucose monitoring devices etc.
Education supports	Assessing diabetes self-management education and supports, identifying need to implement education support and to overcome barriers.
Screening of psychosocial conditions, nutritional support, pregnancy planning	Screening for anxiety, depression, cognitive function, pre-pregnancy and pregnancy planning.
Physical examination	Height, weight, BMI, pubertal development, blood pressure (BP), skin, thyroid examination, fundoscopy, foot examination, others as relevant.
Laboratory and imaging investigations	HbA1c, if not performed within past 3 months, If not performed within past year: fasting lipid profile, liver function test, spot albumin-to-creatinine ratio, serum creatinine and eGFR, thyroid function test, serum electrolyte, serum vitamin B12 level (if on metformin), others as relevant.
Referral	Referral to specialist when indicated: e.g. eye care annually, dietitian for MNT, dentist for comprehensive dental care, mental health specialist if indicated.

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Chapter-4

Acute Complications of Diabetes Mellitus

CHAPTER-4

Acute Complications of Diabetes Mellitus

Executive summary

- Hypoglycemia is defined biochemically with blood glucose level below 3.9 mmol/L (70 mg/dL). In level 1 hypoglycemia blood glucose is between <3.9 and 3.0 mmol/L; in level 2, <3.0 mmol/L, and in level 3 there is altered mental and/or physical status requiring assistance.
- Hypoglycemia should be promptly treated with oral carbohydrate in level 1 and level 2 hypoglycemia, and by parenteral glucose in level 3.
- Hyperglycemic acute complications demand prompt diagnosis, urgent hospitalization and management with I/V fluids, insulin etc. frequent clinical and lab monitoring.

Spectrum of acute complications vary from hypoglycemia at one end to hyperglycemic complications at the other, which include diabetic ketoacidosis, hyperosmolar hyperglycemic state, and also lactic acidosis.

4.1 Hypoglycemia

It is defined biochemically with blood glucose level below 3.9 mmol/L (70 mg/dL) with clinical features of autonomic over activity and neuroglycopenia.

Some people with DM, especially those with persistent high blood glucose, may develop clinical features (particularly autonomic) of hypoglycemia at a higher blood glucose level. Hypoglycemia is more common in T1DM than in T2DM.

4.1.1 Levels of hypoglycemia[1]

Level 1: blood glucose <3.9-3.0 mmol/L

Level 2: blood glucose <3.0 mmol/L

Level 3: a severe event characterized by altered mental and/or physical status requiring assistance

4.1.2 Causes of hypoglycemia

- Taking excess dose of insulin
- Excess intake of antidiabetic medications, specially insulin secretagogues
- Delay, omission or undue reduction of a meal
- Unusual exercise
- Severe renal or hepatic impairment
- Over intake of alcohol

4.1.3 Consequences of hypoglycemia[2]

Recurrent hypoglycemia may cause behavioral change and cognitive impairment

Increased incidence of life-threatening cardiovascular events due to severe hypoglycemia

4.1.4 Hypoglycemia unawareness and nocturnal hypoglycemia

Occurs in individuals with long standing T1DM, autonomic neuropathy, medications (like non-selective beta-blockers), or very tight glycemic control. Frequent blood glucose should be monitored to prevent hypoglycemia.

Nocturnal hypoglycemia occurs any time during night, usually between 2 and 4 am.

Table 4.1 Clinical features of hypoglycemia[1]

Level	Types of feature	Symptoms
Level-1	Autonomic	Palpitation, tremor, sweating, hunger
Level-2	Neuroglycopenic	Irritability, headache, visual disturbance
Level-3	Neuroglycopenic	Drowsiness, confusion, behavioral abnormality, convulsion, coma

4.1.5 Treatment of hypoglycemia[1,2]

Level 1 and 2 hypoglycemia

- Treated by the person him/herself or by a family member.
- It is usually relieved by 15 gm glucose or equivalent food, e.g. a glass of soft drink or fruit juice or snacks or meal (if it is due). These measures are usually adequate to raise blood glucose to reasonably safe limit (5.5 mmol/L).
- The food/drink is repeated every 15 minutes, and blood glucose should be checked every 15 minutes until the person is stable.
- Modification in ongoing treatment should be considered. Not to omit insulin/OAD altogether; dose may be reduced according to the condition.
- Glucagon 1 mg intramuscularly or subcutaneously can be given in those at increased risk of level 2 hypoglycemia if it is available.

Level 3 hypoglycemia

- 100 ml of 25% dextrose is given intravenously under medical supervision.
- If hypoglycemia is due to longer acting antidiabetic medications then 10% dextrose infusion should be started and may need to be continued for some time to prevent recurrent hypoglycemia.
- Ongoing activity of the antidiabetic medication may lead to recurrence of hypoglycemia. Hence, food ingestion is to be ensured after initial recovery.
- If recovery does not occur, addressing additional causes, modification in treatment and keeping the person under supervision in hospital may be required.
- Glucagon 1 mg intramuscularly or subcutaneously can be given if it is available.

Hospitalization criteria

Level 3 hypoglycemia

Recurrent hypoglycemia

Hypoglycemia in people on long acting antidiabetic agents

Nocturnal hypoglycemia

- Reduction of evening dose of insulin
- Changing time of evening insulin dose with dinner time
- Taking bed time snacks may be considered
- These adjustments are made in conjunction with blood glucose monitoring

4.1.6 Prevention of 'hypo'

- Frequent monitoring of blood glucose
- Proper meal timing and amount
- Avoid unaccustomed exercise
- Setting higher target for some people, e.g. older people, children, hypoglycemia unawareness

4.2 Diabetic ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a medical emergency in persons with diabetes. It is commonly found in T1DM but it also occurs in other types of diabetes during stressful situations. It results from lack of insulin and an increase in counter-regulatory hormones that lead to hyperglycemia and subsequent lipolysis.

4.2.1 Precipitating factors

- Intercurrent Infection
- Discontinuation of insulin therapy
- Inadequate insulin therapy
- Pancreatitis, myocardial infarction, cerebrovascular accident, pulmonary embolism
- Stressful conditions like trauma, pregnancy

  New-onset T1DM

4.2.2 Clinical features

- Develops rapidly (hours to days).
- Symptoms of uncontrolled diabetes precedes.

- Dehydration is the most obvious clinical feature with dry skin and tongue, low BP, rapid weak pulse.
- Acidotic breathing is characteristic; there may be acetone smell in breath.
- Weakness, vomiting, impairment of level of consciousness, acute abdomen.

4.3 Hyperosmolar hyperglycemic state (HHS)

HHS is a combination of severe degree of hyperglycemia, dehydration and hyperosmolality without significant ketonuria, usually seen as complication of elderly T2DM persons. Here, residual insulin reserve prevents ketosis.

4.3.1 Precipitating factors

Similar as DKA; also there may be:

- Compromised fluid intake
- Drugs e.g. glucocorticoids, diuretics etc.

4.3.2 Clinical features

- Develops slowly (days to weeks)
- Symptoms of uncontrolled diabetes precede
- Dehydration is profound
- Impaired consciousness

Table 4.2 Diagnostic criteria for DKA and HHS[3]

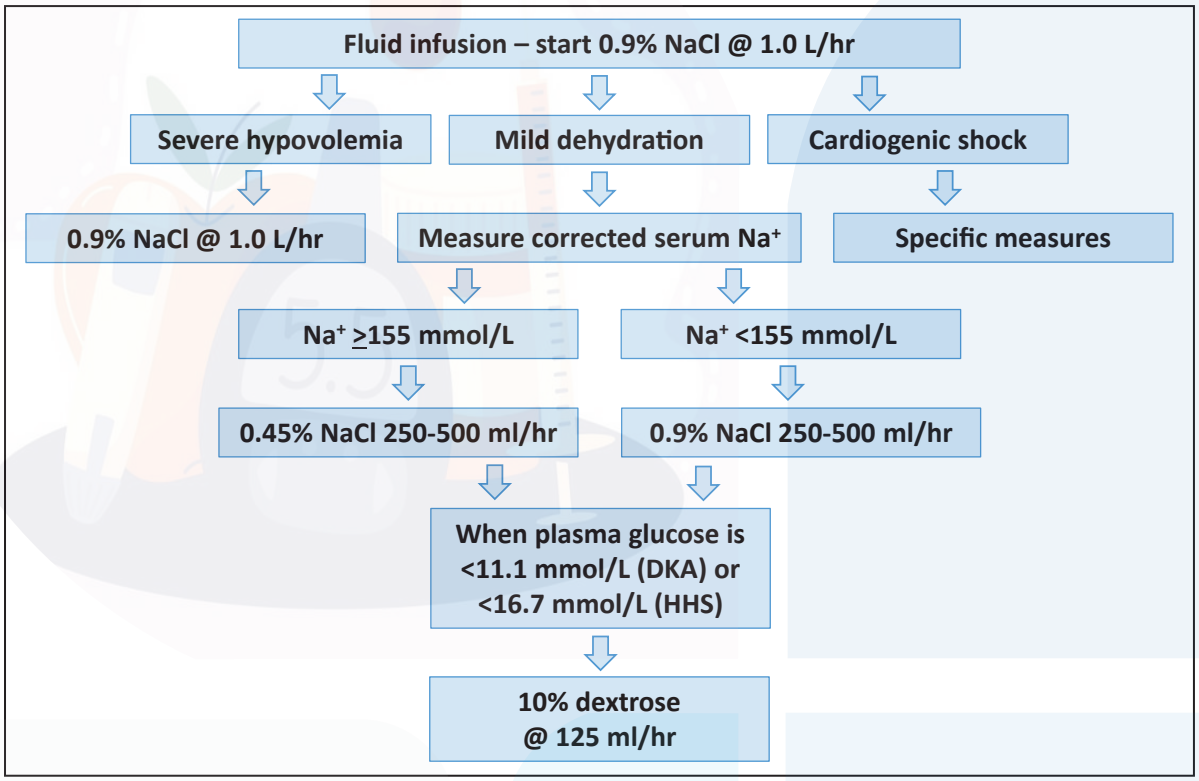
	DKA			HHS
	Mild	Moderate	Severe	
BG	>13.8 mmol/L	>13.8 mmol/L	>13.8 mmol/L	>33.3 mmol/L
Arterial PH	7.25-7.30	7.00-<7.24	<7.00	>7.30
S. bicarbonate mEq/L	15-18	10-<15	<10	>18
Urine ketone	Positive	Positive	Positive	Small
Effective serum osmolality	Variable	Variable	Variable	>320 mOsm/kg
Anion gap	>10	>12	>12	Variable
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma

NB: Effective serum osmolality: 2[Measured Na^+ (mEq/L)] + Glucose (mmol/L). Anion Gap: Na^+ - [Cl^- + HCO_3^- (mEq/L)].

4.3.3 Protocol for management of adult persons with DKA or HHS

Initial evaluation

- Immediate hospitalization
- Check blood glucose/capillary glucose, serum/urine ketones: to confirm hyperglycemia and ketonemia/ketonuria
- Test for blood pH, electrolytes, urea, creatinine, CBC
- Start IV fluid as per protocol



NB: Corrected Na^+ for hyperglycemia = Measured Na^+ + [1.6 (glucose in mg/dL - 100)/100].

Figure 4.1 Fluid infusion protocol (DKA, HHS)[3,4]

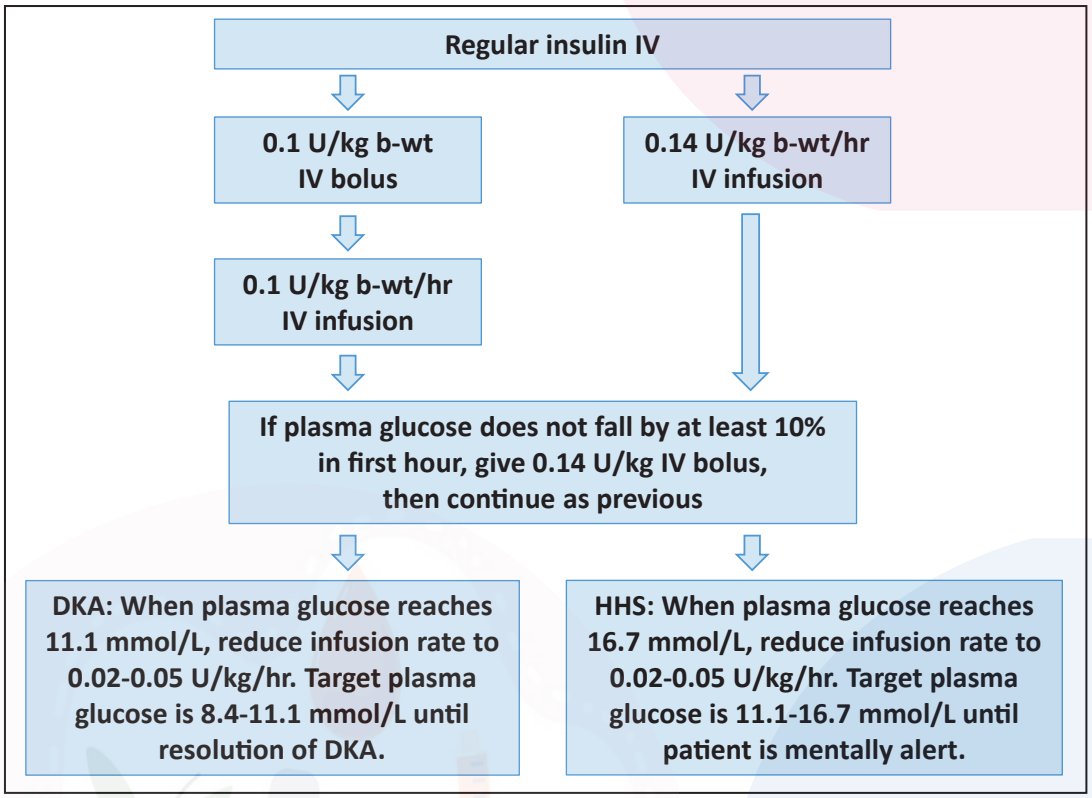


Figure 4.2 Insulin protocol (DKA, HHS)[3,5]

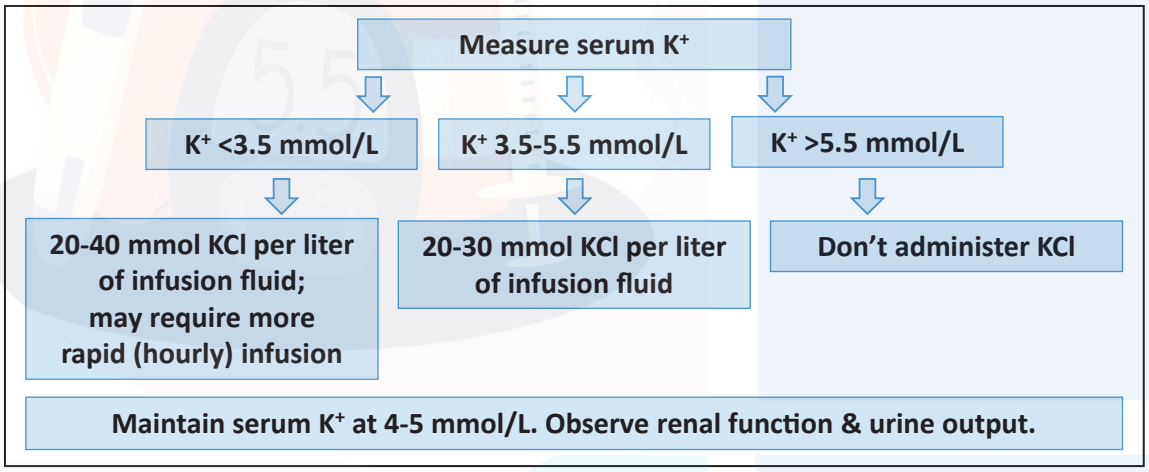


Figure 4.3 Potassium infusion (DKA, HHS)[3,4]

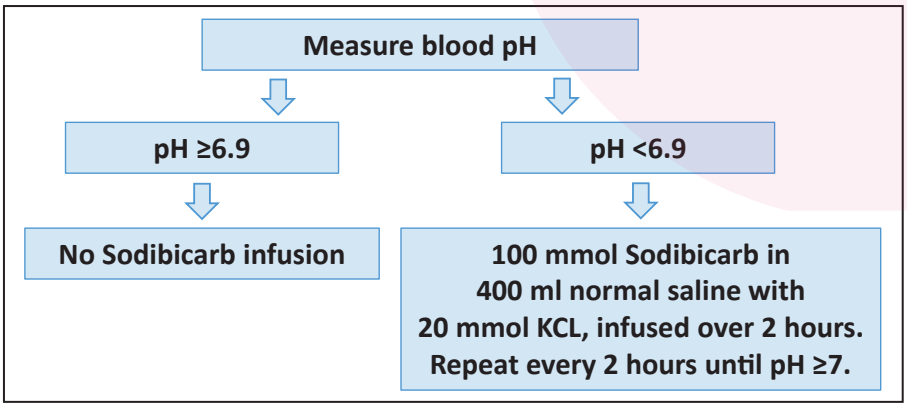


Figure 4.4 Bicarbonate infusion (DKA)[3]

4.3.4 Other evaluations

- Blood glucose should be checked hourly initially.
- Blood pH, electrolytes, urea, creatinine should be rechecked frequently as required.
- After resolution of DKA/HHS and person is able to eat, SC insulin should be initiated. SC insulin should be started at least 1-2 hour before stopping intravenous insulin.
- During transition to SC insulin, multiply last 6 hours' insulin dose by 4 to get 24 hours' dose (TDD); from this initiate split-mixed or basal-bolus insulin regimen.
- Precipitating cause should be addressed.

4.3.5 Criteria for improvement of DKA/HHS[3]

1. No dehydration
2. No vomiting; able to take food
3. Person is well oriented and hemodynamically stable
4. No ketone in urine and anion gap normal (in DKA)
5. Effective serum osmolality <315 mOsmol/kg (in HHS)

4.3.6 Complications of DKA/HHS[2]

- Cerebral oedema
- Circulatory failure
- Thromboembolism
- DIC

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Chapter-5

Chronic Complications of Diabetes: Prevention and Management

CHAPTER-5

Chronic Complication of Diabetes: Prevention and Management

Executive summary

- Every person with diabetes should be screened periodically for chronic complications.
- Control of blood glucose, blood pressure and blood lipids along with other factors, form the cornerstone of prevention and control of diabetic complications.
- Serum creatinine, eGFR and urine albumin excretion should be used for screening diabetic nephropathy.
- Ophthalmoscopy of dilated eyes should be performed yearly to screen for retinopathy, with color fundus photography if needed.
- Every person with diabetes should receive preventive foot care advices.

Chronic complications of diabetes encompass a wide spectrum of microvascular (nephropathy, retinopathy and neuropathy) and macrovascular (coronary artery disease, cerebrovascular disease and peripheral vascular disease) disorders. More than 50% people with diabetes have one or more complications at the time of presentation, and all are treatable and preventable. A study in 2019 found that among macrovascular complications, the prevalence of coronary artery disease was 30.5%, 10.1% for stroke and 12.0% for diabetic foot. Among microvascular complications, prevalence of nephropathy was 34.2%, retinopathy was 25.1% and neuropathy was 5.8% in people with diabetes.[1]

5.1 Diabetic nephropathy

It is a specific form of microangiopathy of the kidney which is characterized by:

- Persistent albuminuria
- Progressive renal insufficiency (declining eGFR) with or without hypertension[2]

5.1.1 Albuminuria

- Albumin-to-creatinine ratio (ACR) is the preferred method to detect elevated protein in urine. The recommended method to evaluate albuminuria is to measure urinary ACR in a spot urine sample (preferably morning fasting sample before exercise).
- ACR is calculated by dividing albumin concentration in milligrams by creatinine concentration in grams.

- Normal: ACR <30 mg/g, normal to mildly increased albuminuria.
- Microalbuminuria: ACR 30-<300 mg/g, moderately increased albuminuria.
- Macroalbuminuria: ACR ≥300 mg/g, severely increased albuminuria.[2]

Table 5.1 Stages of CKD by eGFR[3]

Stages	eGFR (ml/minute/1.73m^2)	Description
1	≥90	Renal damage + normal or raised GFR
2	60 to 89	Renal damage + mildly decreased GFR
3	30 to 59	Moderately decreased GFR
4	15 to 29	Severely decreased GFR
5	<15 or on dialysis	Kidney failure

Markers of renal damage (one or more)[4]

- Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol])
- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

5.1.2 Screening and follow up[2]

- Full clinical check-up during each visit, especially anemia, blood pressure, pedal edema etc.
- AER (albumin excretion rate) and eGFR or CCr estimation. Two of three samples of AER should be abnormal in 3-6 months.
- Blood urea, creatinine, total protein, albumin, electrolytes, uric acid, calcium and phosphate estimation.
- Serum creatinine and eGFR should be assessed at least annually.
- Monitoring of other urinary complications e.g. UTI (including asymptomatic), bladder dysfunction (autonomic bladder) etc.
- Monitoring by sonography – kidney size, progressive increase in echogenicity of cortex.
- Renal biopsy may be required in nephropathy in absence of retinopathy, heavy proteinuria, rapid unexplained deterioration of renal function etc.

5.1.3 Treatment[2]

- Good glycemic control reduces the incidence of diabetic nephropathy and delays its progression, evidence suggests that SGLT2 inhibitors and GLP1-RA are beneficial, if not contraindicated.
- Control of hypertension is very important because uncontrolled hypertension causes rapid progression of diabetic nephropathy. Target of BP is <130/80 mm of Hg.
- ACE inhibitors and ARBs are preferred drugs to reduce or revert early nephropathy. But these two drugs must not be combined. Check electrolytes and creatinine 2 weeks after starting and stop if >30% increase of baseline serum creatinine or hyperkalemia.
- Protein intake up to 0.8 gm/kg/day of body weight is allowed.
- Correct high phosphate and uric acid. Restrict high uric acid and phosphate-containing foods if necessary.
- Fluid and electrolyte balance should be maintained.
- Iron supplementation often fails to correct anemia in renal failure. Iron along with erythropoietin provides the optimum response.
- Renal replacement therapy (dialysis and renal transplantation) is done when indicated.

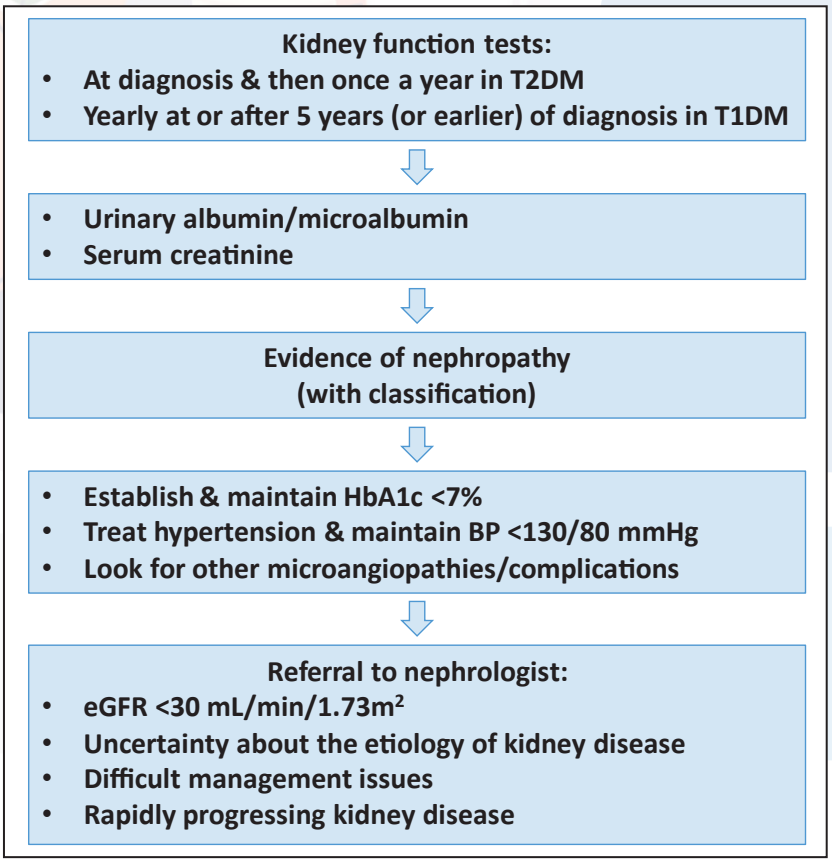

Figure 5.1 Decision making path: nephropathy[2]

5.2 Diabetic retinopathy

Diabetic retinopathy is the most frequent cause of new cases of blindness in our country. Glaucoma, cataract, and other disorder of the eye occur earlier in persons with diabetic.

5.2.1 Screening and follow-up

In T1DM

An initial dilated, comprehensive eye examination by an ophthalmologist or optometrist within 5 years of diagnosis and then annually. If retinopathy is progressing or sight-threatening, then an examination should be done frequently.

In T2DM

An initial dilated, comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis and then annually. If retinopathy is progressing or sight-threatening, then examinations should be done frequently.

In women with T1DM or T2DM

If planning pregnancy, should have screening for retinopathy before pregnancy. During pregnancy, a repeat eye examination should be done.

Table 5.2 Classification of diabetic retinopathy[2]

Stage	Characteristic lesions
Early non-proliferative diabetic retinopathy (NPDR)	Microaneurysm, dot and blot hemorrhage, hard exudate.
Moderate to severe non-proliferative diabetic retinopathy (NPDR)	Cotton wool spots/soft exudate, venous beads and loops, intraretinal microvascular abnormalities (IRMA)
Proliferative diabetic retinopathy (PDR)	Neovascularization of disc (NVD), Neovascularization elsewhere (NVE), vitreous hemorrhage, tractional retinal detachment
Maculopathy	Edema, exudate or hemorrhage in and around macula

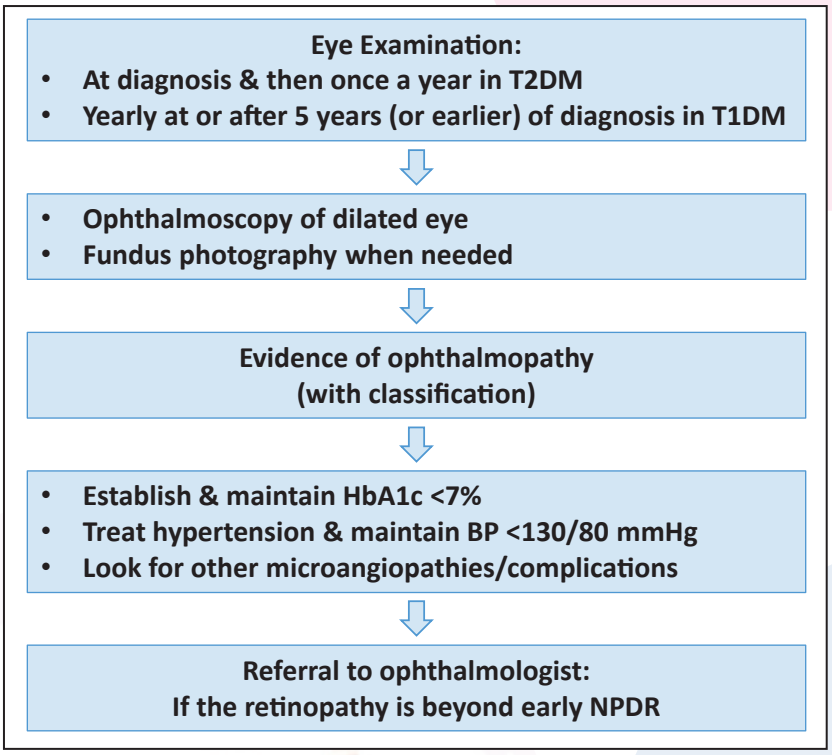

Figure 5.2 Decision making path: retinopathy[2]

5.3 Diabetic neuropathy

5.3.1 Types

1. Somatic – sensory, motor, cranial (focal neuropathy)
2. Autonomic – gastroparesis, hypoglycemia unawareness, postural hypotension, erectile dysfunction etc.

5.3.2 Screening

- Starting at diagnosis of T2DM, then annually.
- 5 years after the diagnosis of T1DM, then annually.
- Testing sensory neuropathy by 10-g monofilament.
- Assessment of either temperature or pinprick sensation (small fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function).
- Symptoms and signs of cranial and autonomic neuropathy should also be assessed.

5.3.3 Treatment[2]

- Treatment of painful diabetic peripheral neuropathy
  - Metabolic control: optimum glycemic control.
  - For burning pain: antidepressants e.g. duloxetine, tricyclic antidepressants etc. or anticonvulsants e.g. gabapentin, pregabalin, or topical capsaicin etc. are used.
  - For lancinating pain: anticonvulsants e.g. carbamazepine, phenytoin or valproate are used.
  - For painful cramps: quinine sulfate. Aldose reductase inhibitors may be used.
  - Other contributing factors e.g. alcohol, cord lesions, vitamin deficiency, renal failure etc. should be addressed.
- Treatment of autonomic neuropathy
  - Metabolic control: good metabolic control may halt its progression
  - For gastroparesis: erythromycin, metoclopramide, domperidone
  - For diarrhoea: antibiotics, loperamide
  - For impotence: PDE5 inhibitors
  - For neurogenic bladder: intermittent catheterization, surgery, drug (rarely)
  - For orthostatic hypotension: midodrine, mineralocorticoids, elastic stockings, fluid and salt intake, positional adjustments etc.
  - Supportive measures e.g. physiotherapy

5.4 Diabetic Foot

- Most common cause of non-traumatic amputation is diabetic foot, which is preventable and treatable.
- Comprehensive foot evaluation should be done initially and at least annually to identify risk factors for ulcers and amputations.
- Individuals with sensory loss or prior ulceration or amputation should have their feet examined at every visit.

5.4.1 History

- Prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette smoking, retinopathy.

- Current symptoms of neuropathy (pain, burning, numbness) and vascular disease (fatigue, claudication).

5.4.2 Examination

- Inspection of the skin
- Assessment of foot deformities
- Neurological assessment: 10-g monofilament testing with at least one other assessment: pinprick, temperature, vibration
- Vascular assessment: pulses in the legs and feet. With symptoms of claudication or decreased or absent pedal pulses: ankle-brachial index, further vascular assessment as appropriate e.g. doppler study

Table 5.3 Risk categories of diabetic foot:[5]

Normal plantar sensation	Loss of protective sensation (LOPS)	LOPS with either high pressure or poor circulation or structural foot deformities or onychomycosis	History of ulceration, amputation or neuropathic fracture
LOW RISK	MODERATE RISK	HIGH RISK	VERY HIGH RISK

5.4.3 Management

- A multidisciplinary approach is recommended.
- Provide general preventive foot self-care education to all individuals with diabetes.
- Specialized therapeutic footwear is recommended for high-risk persons with diabetes
- including those with severe neuropathy, foot deformities, or history of amputation.

Do's and don'ts for people at risk of diabetic foot

Do's

- Check feet daily for cuts, blisters, colour changes, swelling, ingrown toe nails. Use a mirror or take someone's help if required
- Always protect feet with appropriate footwear
- Before wearing shoes check inside for nails, stones or any other sharp object

- Wear socks with shoes; use cotton socks
- Wash socks daily; make sure they have no holes
- Buy new shoes at the end of the day
- After washing, dry feet carefully especially between toes
- Cut nails straight across and file the sharp edges
- Annual foot examination by healthcare professional

Don'ts

- Avoid barefoot walking
- Avoid tight or torn shoes with rough and uneven edges
- Avoid shoes with narrow toe box, high heels or footwear that have no back supports
- Don't use socks with tight top or rough sim
- Don't use hot water to wash feet
- Don't let the feet dry and cracked
- Don't use corn medicine or blades to remove it by self

5.4.4 Referral criteria to foot care specialists

- History of prior lower-extremity complications
- Loss of protective sensation
- Structural abnormalities of foot
- Peripheral arterial disease
- Presence of ulcer, gangrene or infection

5.5 Cardiovascular diseases

More than 70% people with DM die due to cardiovascular causes.

5.5.1 Screening

Screening for coronary artery disease should be done in symptomatic persons and people with risk for cardiovascular disease.

5.5.2 Treatment

- ACE inhibitor or angiotensin receptor blocker
- SGLT2 inhibitors and GLP1-RA
- Statins
- Aspirin and/or clopidogrel
- Selective beta-blockers should be continued for at least 2 years after the event

5.5.3 Hypertension

Hypertension is a common comorbidity of DM.

- Blood pressure should be measured in every follow-up.
- Target is <130/80 mmHg for non-pregnant adult.
- If blood pressure is ≥130/80 mmHg but <140/90mmHg, then lifestyle modification.
- If blood pressure is ≥140/90 mmHg, recheck after 1week. If still high then lifestyle modification and monotherapy.
- If blood pressure is ≥160/100 mmHg, start dual antihypertensive.
- The choice can be ACE inhibitor or ARB, Calcium channel blocker and diuretics.
- Selective beta blocker or alpha blocker can be used in special situation.

5.5.4 Dyslipidemia

Diabetic dyslipidemia is very common. Screening and Monitoring of lipid profile should be done at the time of diabetes diagnosis, at an initial medical evaluation, yearly and more frequently if indicated.

Table 5.4 Targets of blood lipids in person with DM[6]

Lipid	Target level
LDL cholesterol	<70mg/dL
Triglyceride	<150 mg/dL
HDL cholesterol	>40 mg/dL (male), >50 mg/dL (female)

Treatment

Lifestyle modification:

- Maintain ideal body weight
- Avoid saturated and trans fats
- Increase dietary omega-3 fatty acids, fibers, and green leafy vegetables and fresh fruits
- Increased physical activity

Table 5.5 Pharmacological therapy based on age, ASCVD or ASCVD risk factors[6,7]

Age in years	ASCVD or 10-year ASCVD risk >20%	Recommended pharmacological therapy, along with lifestyle modification
<40	No	None or moderate intensity statin may be considered based on risk-benefit profile or presence of ASCVD risk.
<40	Yes	High-intensity statin; if LDL cholesterol ≥70 mg/dL despite of therapy consider combining with ezetimibe.
≥40	No	Moderate-intensity statin or high-intensity statin may be considered based on risk-benefit profile or presence of ASCVD risk.
≥40	Yes	High-intensity statin; if LDL cholesterol ≥70 mg/dL despite of therapy, consider combining with ezetimibe.

NB: Intensity of statin therapy may need to be adjusted according to individual response to medication (e.g. side effects, tolerability, LDL cholesterol levels, etc).

5.5.5 Antiplatelet agents[6]

- Aspirin therapy (75–150 mg/day) as a secondary prevention strategy in those with diabetes
- and a history of atherosclerotic cardiovascular disease.
- Persons with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used.
- Dual antiplatelet therapy is reasonable for a year after an acute coronary syndrome.
- For primary prevention of ASCVD, aspirin is recommended for those with diabetes and age ≥50 years, having at least one major risk factor for ASCVD.

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Chapter- 6

Special Situations in Diabetes Mellitus

CHAPTER-6

Special Situations in Diabetes Mellitus

Executive summary

- All women planning for pregnancy or conceived should be screened for diabetes. Only insulin is recommended for use in pregnancy and lactation period.
- Insulin is the only therapy in children <10 years of age. Metformin can be given after 10 years.
- In hospital admitted patients, insulin therapy should be initiated in persistent hyperglycemia >10 mmol/L, checked on two occasions. Target blood glucose is to be maintained between 7.8 and 10 mmol/L. In critical setting intravenous insulin infusion is preferred.
- During sick days, the person should be advised to check blood glucose at home frequently and take plenty water and fluid.
- Diabetes education and counselling should be given prior to Ramadan and Hajj.

6.1 Hyperglycemia in pregnancy

Hyperglycemia in pregnancy may be due to GDM (diabetes that is first time detected during gestation who is not known to have it before) or preexisting prediabetes or diabetes in a pregnant woman. Hyperglycemia in pregnancy is caused by placental hormones, namely beta HCG, human placental lactogen, estrogen, progesterone etc. antagonizing the action of insulin.[1] The incidence of GDM is rising in all South East Asian countries and the prevalence in Bangladesh has been reported to be around 10%.[2]

6.1.1 Risk factors[3]

- BMI ≥23 kg/m^2
- Age ≥25 years
- First degree relative with DM
- History of delivery of baby >9lb or LGA or bad obstetric history
- Previous history of GDM, HbA1c ≥5.7%, IGT or IFG
- Physical inactivity
- HTN or therapy for HTN, HDL <35 mg/dL and or TG >250 mg/dL, PCOS, acanthosis nigricans, history of CVD

6.1.2 Screening and diagnostic criteria for GDM

See Chapter 2.

6.1.3 Preconception care[1]

- Preconception HbA1c should be below 6.5%
- Women receiving non-insulin antihyperglycemic agents should shift to insulin before conception
- Review of medication list for potential harmful drugs like ACEI, ARBs or statins should be done

6.1.4 Management

Medical nutrition therapy

- MNT Should be started soon after diagnosis of GDM preferably by dietitian and reviewed in each trimester.
- The aim is to achieve normoglycemia, adequate maternal weight gain, adequate fetal growth, prevention of ketosis.

Table 6.1 Recommended weight gain during pregnancy based on pre-pregnancy BMI[3]

BMI [kg/m2]	Recommended wt gain [lbs (kg)]
Singleton pregnancy	
<18.5 18.5-24.9 25.0-29.9 ≥30.0	28-40 (12.5-18.0) 25-35 (11.5-16.0) 15-25 (7.0-11.5) 11-20 (5-9.0)
Twin pregnancy	
<18.5 18.5-24.9 25.0-29.9 ≥30.0	No recommendation 37-54 (16.8-24.5) 31-50 (14.1-22.7) 25-42 11.4-19.1)

Table 6.2 Daily calorie allocation according to pre-pregnancy weight[3]

Pre-pregnancy weight (BMI in kg/m^2)	During first trimester (kcal/kg/day)	During 2nd and 3rd trimester (kcal/kg/day)
<18.5	35	40
18.5 to 22.9	30	35
23 to 27.4	25	30
> 27.5	30-33% calorie restriction	

Meal pattern

3 main meals and 3 snacks should be taken including 1 snack at bed time.

Recommended overall total caloric distribution[3]

- Carbohydrate: 33-40% with low glycemic index
- Protein: ~ 20%
- Fat: <40%, saturated fat <7% and transfat <1%
- Simple sugars should be avoided. Food containing complex carbohydrate is recommended
- High dietary fiber and whole grain containing foods should be encouraged
- Non-calorie sweeteners (aspartame) may be used safely
- Lean protein, oily fish and vegetable consumption should be increased
- Recommended daily requirement of iron- 30 mg, calcium- 1000 mg and folate- 0.6 mg

Physical activity[1]

- Moderate exercise, aerobic, resistance or both are effective. Duration of exercise can be 20-50 minutes/day, 2-7 days/week of moderate intensity.
- While doing exercise excessive abdominal muscular contracture should be avoided.

Pharmacological management

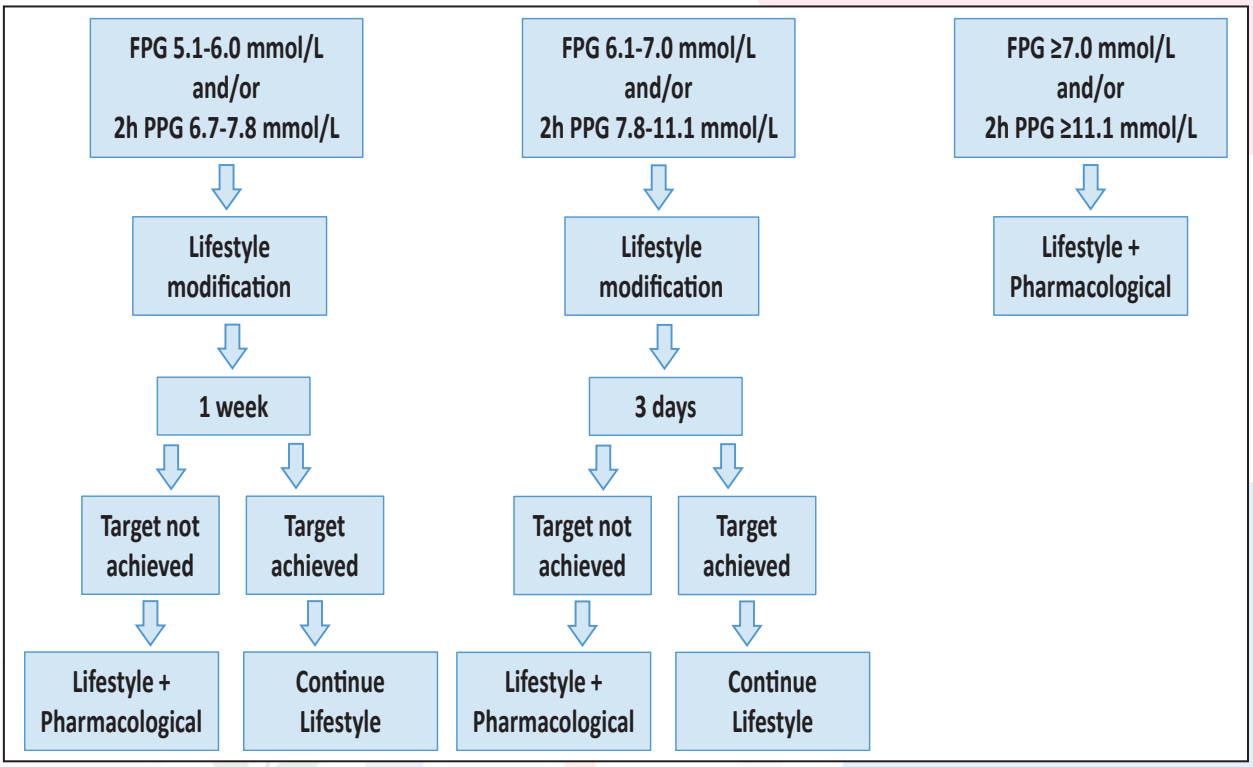

Figure 6.1 Diabetes management during first and third trimester[3]

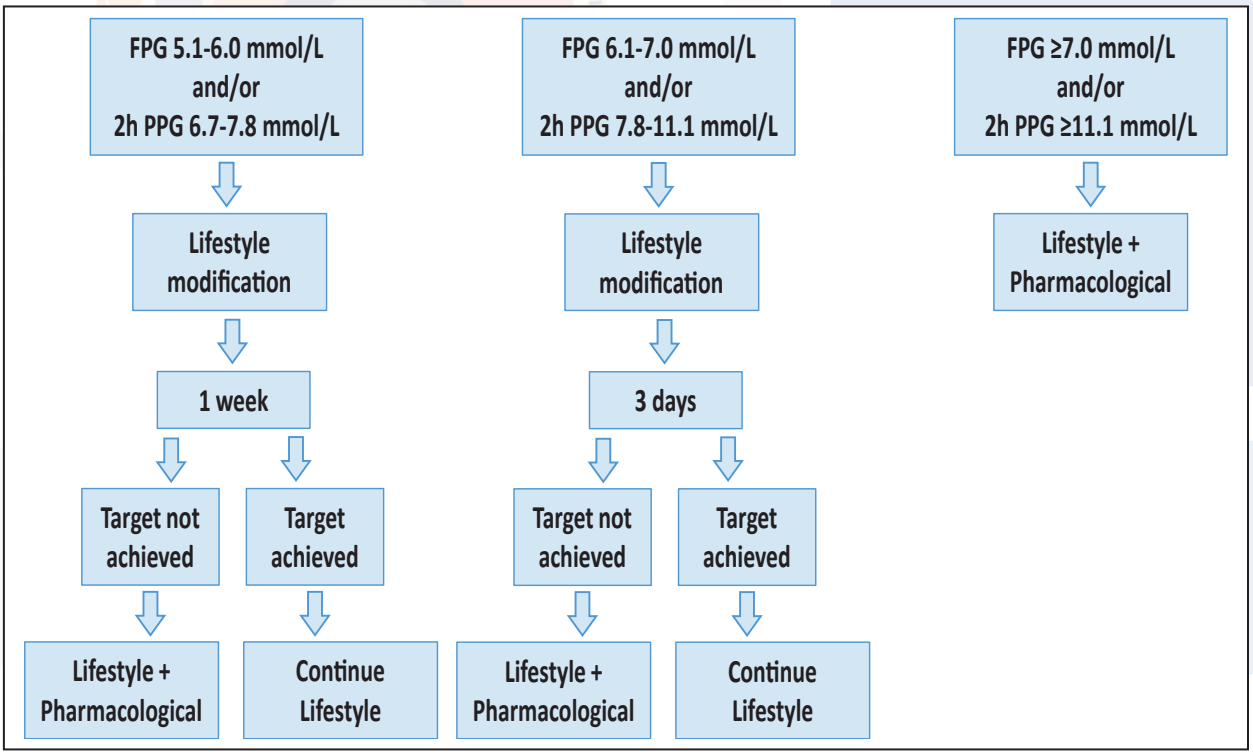

Figure 6.2 Diabetes management during second trimester[3]

Recommended insulins

- Recombinant human short and intermediate (NPH) acting insulin
- Rapid acting analogue aspart and lispro
- Long-acting analogue detemir
- Required initial daily dose is 0.2 to 0.5 unit/kg body weight. Obese women may need higher dose Treatment should be graded to reach the targets

Approach to start insulin

Step 1: Raised post meal blood glucose should be controlled by bolus insulin – either by regular/short acting human insulin or by short/ultra-short acting analogue with meal(s) and titrated frequently to reach the post-meal targets.

Step 2: High FPG should be controlled with intermediate acting human insulin (NPH) or basal analogue insulin in a lower dose then titrated to reach the target.[3]

- Only bolus insulin may be needed in some cases of GDM when FPG is well controlled
- Pre-mixed insulin is usually not preferred
- Non-insulin antihyperglycemic agents are not recommended

Target [1]

- Fasting blood glucose <5.3 mmol/L (95 mg/dL)
- 2-hour post-prandial glucose <6.7 mmol/L (120 mg/dL)

Glucose monitoring

- Every woman should be offered education and encouraged for self-monitoring of pre- and post-meal glucose at home, twice or thrice a week.
- HbA1c should be used as secondary measure of glycemic control, after blood glucose monitoring.

Management during labor[4]

- Hospital delivery is mandatory.
- Indications for C/S are the same for those with other women.
- Maternal glucose should be maintained between 4.0 to 7.0 mmol/L during labor.

- Most women who require <1.0 unit/kg/day insulin can simply be monitored without intravenous Insulin.
- If needed infusion of 5% Dextrose with short acting Insulin can be maintained but Glucose-Insulin infusion should be stopped immediately after delivery.
- Blood glucose of newborn should be seen by heel prick within half an hour.

6.1.5 Postpartum management[3]

- Mothers who were on low dose insulin (<0.5 unit/kg/day) can stop and monitor glucose levels. Mothers who were on insulin >1 unit/kg/day may reduce the dose to 50% and while those on 0.5-1 units need individualized clinical decision.
- If BG is normal, re-assessment should be done annually with 75-gm 2h OGTT or HbA1c. If prediabetes, should be put on MNT with standard protocol.
- After delivery at least 1 fasting and 1 post-meal PG before discharge should be measured in persons with GDM who were managed by MNT and FPG and PPG should be monitored for at least 24 hours who were managed with insulin. If blood glucose remains elevated, continued monitoring is warranted. If immediate post-delivery (1-3 days) BG is suggestive of DM, then should be confirmed by FPG (≥7 mmol/L) or post-prandial BG (≥11.1 mmol/L).
- As some case of GDM may represent preexisting undiagnosed type 2 diabetes and 50% women with GDM may develop type 2 DM within 5 to 10 years. Women with GDM (not requiring insulin after delivery) should be screened for diabetes 6 weeks post-partum (linked to child immunization) with 75g 2h OGTT using non-pregnant OGTT criteria.
- Contraception advice should be given. Low dose estrogen-progesterone can be offered for contraception. Progesterone only preparation increases risk of vascular complications.
- All types of insulins can be safely used in lactating women. Women with pre pregnancy diabetes who are breastfeeding should continue to avoid any drugs for the treatment of diabetes.
- All mothers with history of GDM should be counseled about screening for GDM during every subsequent pregnancy.

6.2 Diabetes in children and adolescent

Diabetes mellitus in childhood and adolescence is most often T1DM, but the incidence of T2DM is also increasing due to the rising rate of obesity among children, especially in Bangladesh.

6.2.1 Diagnosis and screening in children and adolescent

See Chapter 2.

6.2.2 Principles of management

In T1DM, insulin is the only choice. In T2DM, treatment modalities change according to age.

Table 6.3 Target level of glucose[5]

Plasma glucose	mmol/L
FBS/Pre-meal	5.0-7.2
Post-meal	5.0-10.0
Pre-bed	5.0-8.3
HbA1c %	<7.0

Table 6.4 Drug treatment of T2DM[6]

Age in years	Treatment option
<10	Insulin only
10-18	Insulin or metformin
>18	Insulin or metformin, or other antidiabetic agent, e.g. sulfoylureas, thiazolidindiione

Diabetes education[1]

- Diabetes education is very essential part for effective management diabetes in this age group especially insulin injection technique, dietary practice, home monitoring of blood glucose etc. are needed. Providing emotional support is also very important.
- Infants and toddlers: They are totally dependent on parents and care providers for injections, food and monitoring. Need to be educated on prevention, recognition and

management of acute complications, especially hypoglycemia, because it is very common complication in this age group.

- School going children: To be trained on Insulin injections and blood glucose monitoring,
- recognizing hypoglycemic symptoms, and understanding self-management, adapt to
- school programs, school meals, exercise and sports. Teacher/school authority should be
- involved in this learning process and parents are advised on the gradual development of the child's independence.
- Adolescents: Independent, responsible self-management appropriate to the level of maturity and understanding should be promoted.

Medical nutrition therapy (MNT)[1]

- All children with diabetes should be referred to a dietitian for counseling at diagnosis of
- diabetes and subsequently if they have problem with their diet adjustment.
- Age-specific calorie calculating charts are available for measuring diet allowance.

Sports and exercise[1]

- Children with T1DM with good blood glucose control can do all levels of exercise, including leisure activities, recreational sports and competitive professional performance. Exercise is more important for young T2DM, especially who are obese.
- Children between 3-5 years of age may take part in free play, walking, running etc.
- Children between 6-9 years of age may start learning to play team sports such as football, cricket etc.
- Children above 10 years of age and adolescents may be able to take part in all complex sports, like basketball, football, tennis, hockey etc.

6.2.3 Screening and treatment of complications and comorbidities[6]

Hypertension

- Blood pressure (BP) should be monitored at diagnosis and at every follow-up visit.
- Target BP (mmHg) < 90th percentile for age, sex, and height and if age $\geq$13 years old < 130/80.

- Lifestyle modification for elevated BP (90-95th percentile for age, sex, and height or if age ≥ 13 years 120-129/<80).
- Lifestyle modification and ACEI or ARB for hypertension (≥95th percentile for age, sex and height or if age ≥13 years old >130/80).

Dyslipidemia

- Lipid profile should be performed in children soon after diagnosis of DM (preferably after control of diabetes or age ≥2 year)).
- If lipids are abnormal, annual monitoring is recommended.
- If LDL cholesterol values are within the accepted risk levels (<100 mg/dL), a lipid profile should be repeated every 3-5 years.
- Initial therapy includes blood glucose control and MNT.
- After the age of 10 years, statin is recommended in those who do not reach target (who have LDL cholesterol >160 mg/dL or >130 mg/dL with a cardiovascular risk factor) with lifestyle changes.
- The goal of therapy is LDL cholesterol value <100 mg/dL.

Nephropathy

- Albumin creatinine ratio (ACR) should be measured at puberty or age >10 years old whichever is earlier and diabetes duration of > 5 years.
- If normal screen annually, if abnormal it should be confirmed by repeating the test from 2 out of 3 sample in 6 months.

Retinopathy

Dilated fundoscopy should be performed to screen for retinopathy at puberty or at age >11 years old whichever is earlier and diabetes duration of 3-5 years. If normal, every 2 years.

Neuropathy

Foot examination with foot pulse, pinprick, vibration test, ankle jerk and 10-gm monofilament sensation test (if possible) should be performed at puberty or at 11 years of age whichever is earlier and diabetes duration of 5 years. If normal, annually.

Other autoimmune disease

For those with type 1 diabetes advise for thyroid function test and IgA of tTG for celiac disease if possible soon after diagnosis.

6.3 Diabetes in elderly

- Prevalence of diabetes is high in older population. One fourth of older adult age >65-years old are diabetic and one half of older adult have prediabetes. Older adults with diabetes have high incidence of premature death, disability, muscle loss, and associated with other coexistent illness like hypertension, coronary heart disease and stroke, than those without diabetes.
- Assessment of medical and psychological factors, self-management abilities, social factors in older adults are necessary for better diabetes management, and to determine the target and therapeutic options.
- Screening for early detection of mild cognitive impairment or dementia should be performed for adults 65 years of age or older at the initial visit, annually and as appropriate.

6.3.1 Treatment goals[7]

- Older adults who are otherwise healthy with few coexisting chronic illnesses and intact cognitive function and functional status should have lower glycemic goals (such as HbA1c less than 7.5%, FPG <7.2 mmol/L, PPG <10.0 mmol/L).
- Those with multiple coexisting chronic illnesses, cognitive impairment or functional dependence should have less stringent glycemic goals (such as HbA1c 8.0-8.5%, FPG <10 mmol/L, PPG <11.1 mmol/L).
- Screening for diabetes complications should be individualized in older adults, particularly complications that would lead to functional impairment.
- Treatment of hypertension to individualized target levels is indicated in most older adults.
- Treatment of other cardiovascular risk factors should be individualized in older adults considering the time frame of benefit.
- Lipid lowering therapy and aspirin therapy may benefit those with life expectancies at least equal to the time frame of primary prevention or secondary intervention trials.

6.3.2 Management[7]

Lifestyle management

Optimal nutrition and protein intake is recommended for older adults; regular exercise, including aerobic activity, weight-bearing exercise, and/or resistance training should be encouraged in all older adults who can safely perform such activities.

Modest weight loss (e.g. 5-7%) should be considered for obese older adult with diabetes.

Pharmacologic therapy

- As increased risk of hypoglycemia in older diabetic people, medication classes with low risk of hypoglycemia are preferred.
- Avoid overtreatment of diabetes.
- Simplification of complex regimens is recommended to reduce the risk of hypoglycemia and polypharmacy.
- Consider costs of care when developing treatment plans to reduce risk of cost-related nonadherence.
- Oral drug Metformin is the first line therapy, but should be used cautiously.
- Those who are on short acing (prandial) insulin, with prandial insulin >10 units/dose, consider 50% reduction of dose and addition of non-insulin agent. If dose of prandial insulin <10 units/dose discontinue prandial insulin and no-insulin agent.
- SGLT2 inhibitors, GLP1-RA can be used if tolerated and not contraindicated.

6.4 Management of hyperglycemia in hospitalized patients[1]

- Hyperglycemia in hospitalized patients is defined as blood glucose levels >7.8 mmol/L.
- HbA1c should be measured in all patients with diabetes or hyperglycemia admitted to the hospital if the test has not been performed in the previous 3 months.
- An admission HbA1c value 6.5% or more suggests that the onset of diabetes preceded hospitalization.

6.4.1 Management

Insulin therapy should be initiated for treatment of persistent hyperglycemia at a threshold ≥10.0 mmol/L (checked on two occasions).

Once insulin therapy is started, a target glucose range of 7.8-10.0 mmol/L is recommended for the majority of critically ill and non-critically ill patients.[1]

Table 6.5 Insulin therapy in critical and noncritical setting[1]

Critical setting	Non-critical setting
● Continuous IV Insulin infusion is most preferred ● More frequent monitoring and adjustment needed	● Basal or basal plus/NPH or NPH plus short acting insulin for those who has poor oral intake ● Basal-bolus/split mixed + correctional for those who have good intake

Insulin therapy[1]

- Insulin therapy is preferred for treatment of hyperglycemia in all hospitalized individuals.
- In noncritical setting, scheduled insulin regimen is recommended.
- Use of sliding scale insulin regimen is strongly discouraged.
- Pre-mixed insulin is not preferred in hospitalized patients.
- If oral intake is poor, a safer procedure is to administer prandial insulin immediately after the person eats.

Glucose monitoring in hospital[1]

- Those who are on oral feeding: bedside glucose monitoring before meals and 2 hours after meals.
- Those who are on NG tube/NPO: bedside glucose monitoring every 4-6 hours.
- In critical setting, who are on IV insulin: more frequent monitoring from every 30 minutes to 2 hours may be needed.

6.4.2 Perioperative management

- Pre-operative assessment must be done in close consultation with the physician, surgeon and anesthetist.
- Metformin should be stopped 24 hours prior to or on the day of surgery.
- SGLT2 inhibitors must be discontinued 3-4 days before surgery.
- Withhold any other oral glucose lowering agents in the morning of surgery or procedure and give half of NPH dose or 75-80% doses of long acting analogue if scheduled in morning.
- The target blood glucose in perioperative period is 7.7-10.0 mmol/L.[9]
- In all major surgeries glucose-insulin infusion should be started. The unit of insulin to be added to 5 or 10% dextrose or dextrose saline needs to be individualized and adjusted as per the results of the glucometer readings.
- Blood glucose should be monitored 2 to 4 hourly. Glucose-insulin-potassium infusion may be considered according to situations. Best option I/V insulin syringe pump which can be practiced in long surgical procedure.
- During minor surgery glucose-insulin infusion may sometimes be required in uncontrolled diabetes, but not in stable state.

Table 6.6 Insulin dose adjustment prior and during surgery[10]

	Diet	Glargine/ detemir		NPH/pre-mixed		Regular/rapid acting	
		AM	PM	AM	PM	AM	PM
Day before surgery (Insulin)	Normal diet until midnight	Usual dose	80% of usual dose	80% of usual dose	80% of usual dose	Usual dose	Usual dose
	Only liquid 12-24 hrs prior surgery	Usual dose	80% of usual dose	80% of usual dose	80% of usual dose	Hold	Hold
Day of surgery (Insulin)	NPO	80% of usual dose if the person uses twice daily basal insulin		50% of usual dose Hold if BG<6.6 mmol/L		Hold	

Post-operative care[1]

- The glucose-insulin administration is continued (where required) till the person is able to take oral food.
- At this time, if the blood glucose is not under fair control, rapid acting insulin can be given in small doses (as correctional dose) subcutaneously.
- Once the person is back on his routine diet and is stable, he or she can be managed with the prior regimen to surgery.

6.4.3 Glucocorticoid therapy in hospitalized patients[1]

- The prevalence of Glucocorticoid use in hospitalized patients can be as high as 10%.
- Those on morning steroid regimens have disproportionate hyperglycemia during the day, but frequently reach normal blood glucose overnight.
- In individuals with once or twice daily steroids, administration of NPH insulin is a standard approach. As NPH action peaks at 4-6 hours after administration, it is best to give concomitantly with steroid.
- For long acting glucocorticoids like Dexamethasone and multidose or continuous steroid use, long acting insulin required to control fasting blood glucose.
- Insulin dose should be adjusted with anticipated change in steroid dosing.

6.4.4 Glucose management in enteral and parenteral feeing[11]

Enteral feeding

Enteral nutrition is started via nasogastric tube, or less frequently, percutaneous gastric tube. Diabetic specific formulas contain carbohydrates with monounsaturated fatty acids (up to 35 % of total calories), dietary fiber (10-15 g/L), and fructose. Low dose basal insulin in combination with supplemental regular insulin was shown to be effective in providing glycemic control in majority of patients receiving enteral feedings.

Parenteral feeding

Both subcutaneous and intravenous insulin have been shown to be effective in managing hyperglycemia in patients with TPN. In critically ill or hemodynamically compromised patients, treatment with intravenous continuous insulin infusion is preferred. Adding insulin to TPN mixture is clinically safe and effective in controlling hyperglycemia during TPN. Adding insulin

at the ratio of 1 unit of insulin per 11 g of dextrose in persons with diabetes receiving TPN containing 150-300 g of carbohydrates per day is an effective initial step to prevent and reduce hyperglycemia.

6.5 Sick day management[12]

Period of illnesses e.g. fever, vomiting or diarrhoea, often cause hyperglycemia and ketosis, and sometimes hypoglycemia. To prevent these, certain management principles are followed:

- The person needs to test his/her blood for glucose 4 hourly at home and if possible test urine Ketones. The blood glucose measurements should be written down in a diary.
- The aim or target to maintain between 6-10 mmol/L.
- Be aware of signs of hypoglycemia. Manage Hypoglycemia at home promptly and test more frequently.
- Fluid balance needs to be maintained; during illness sufficient intake is necessary. If the blood glucose is low, sweetened fluids, e.g. fruit juice can be given. If blood glucose is elevated, low calorie soft drinks, soup or broth may be given. Drink 120-180 ml of water or calorie free fluid each half hourly when awake. Try to eat normal meal schedule.
- Contact by telemedicine if required.
- The OADs should never be stopped altogether; dose may need to be reduced. If there is acute illness, specially in vomting and diarrhoea, stop Metformin temporarily. Stop SGLT2 inhibitor to avoid ketosis and dehydration. DPP4 inhibitors can be continued. SU should be used cautiously, dose may be readjusted.
- Do not stop insulin. Intermediate or basal insulin should be continued; the dose may need to be readjusted. If blood glucose remains above 10 mmol/L, increase insulin by 2 units. If decreased below 6 mmol/L, reduce insulin dose by 2 units. Shorter acting insulin should be adjusted according to blood glucose values and food intake. If necessary, short/rapid acting insulin can be given after meal, seeing the amount of intake or vomiting.
- Sometimes the OADs may need to be replaced by shorter acting ones or insulin. If OAD need to be discontinued, the alternative is insulin.
- These principles are to be followed until the blood glucose is <12 mmol/L and ketone diminishes or disappears.
- Regular exercise and physical activity should be postponed during sick days.

- Following conditions require hospitalization:
  - Vomiting or diarrhoea persisting for longer than 6 hours
  - Sick for 3 days and not getting better
  - Blood glucose remains above 14 mmol/L for 6 hours
  - Presence of ketonuria
  - Very young individual, individuals with T1DM and pregnant ones
  - Abdominal pain
  - Hyperventilation or breathing difficulties
  - Confusion or feeling drowsy
  - Co-existing serious diseases like ESRD, heart failure etc.

6.6 Ramadan fasting[13]

6.6.1 Pre-Ramadan assessment

- The persons with diabetes should receive a pre-Ramadan assessment ideally 6-8 weeks before the start of Ramadan.
- A detailed medical history on individuals should be obtained.
- Individual seeking to fast should be categorized as 'high', 'moderate' or 'low' risks based on the IDF-DAR Practical Guidelines 2021.
- Advice should be provided whether fasting is safe or not based on the risk category.
- Management plan should be individualized.
- To ensure safe fasting Ramadan-focused education is required consisting of:
  - Diet plan
  - Exercise pattern
  - The frequency of SMBG
  - When to break the fast
  - Ramadan-oriented medication adjustment

6.6.2 Ramadan nutrition plan (RNP)

- Should be individualized to an individual's lifestyle requirements, age, comorbidities and other medical needs.
- Adequate daily calories should be divided between suhoor and iftar and 1-2 healthy snacks.
- Meals should be well balanced, with around 40–50% carbohydrates, preferably of a low GI source; the protein content (legumes, pulses, fish, poultry, or lean meat) should comprise 20–30%; and fat should comprise 30-35% ; saturated fat should be limited to <10% of total calorie sugar-rich desserts should be avoided after iftar and between meals.
- Low GI carbohydrate should be selected, particularly those high in fibre (preferably whole grains). The consumption of carbohydrates from vegetables, whole fruits, yogurt, milk and dairy products are encouraged and from sugar and highly processed grains (wheat flour and starches like corn, white rice, and potatoes) should be avoided or minimized.
- Food rich in protein and good quality fat can better induce satiety than food rich in carbohydrates.[1]

Table 6.7 Calorie and carbohydrate distribution during Ramadan

	Calorie (%)	Carbohydrate distribution
Suhoor	30-40%	3-5 exchanges (45-75 g)
Iftar snack (before Margib prayer)	10-20%	1-2 exchanges (15-30 g)
Iftar meal (after Magrib prayer)	40-50%	3-6 exchanges (45-90 g)
Healthy snack (if required)	10-20%	1-2 exchanges (15-30 g)

6.6.3 Exercise during Ramadan

- Physical activity should be reduced during day time
- Exercise can be performed after iftar or after tarawih
- Increased prayer during Ramadan should be taken into account while making plan for exercise

Table 6.8 Non-insulin antidiabetic agent dose adjustment

Name of drugs	Dose modification during Ramadan
Metformin	• Once daily metformin: no dose modification, should be taken at iftar. • Twice daily metformin: no dose modification, should be taken at iftar and suhoor. • Thrice daily metformin: Morning dose to be taken at suhoor and afternoon and evening dose combinedly at iftar.
Sulfonylureas	• Once daily dosing: should be taken at iftar and if blood glucose level well-controlled dose reduction should be considered. • Twice daily dosing: iftar dose remains the same as morning dose and suhoor dose should be 50% of the evening dose.
Short acting insulin secretagogues (repaglinide)	• Can be taken before iftar and suhoor. • Dose may be reduced or redistributed to two doses based on meal size.
DPP4 inhibitors	• No dose adjustment needed.
SGLT2 inhibitors	• SGLT2 inhibitors to be taken at iftar. • Increased fluid intake is recommended. • Should be cautious when diuretics are concomitantly used. • Do not require any dose adjustment. • Should not be initiated just before or during Ramadan.
Alpha-glucosidase inhibitors (acarbose, voglibose, miglitol)	• No dose modification is required. • Can be taken at iftar or at suhoor.
Thiazolidinediones (pioglitazone)	• No dose modification is required.
GLP1-RA	• liraglutide and lixisenatide were found to be safe as an add-on treatment to pre-existing antidiabetic regimens including metformin and insulin during Ramadan. • Use of newer GLP1-RAs (such as dulaglutide and albiglutide) during Ramadan is yet not evidence-based. • If liraglutide, lixisenatide, exenatide have been appropriately dose-titrated at least 2–4 weeks prior to Ramadan, no further treatment modifications are required.

Table 6.9 Insulin dose modification during Ramadan

Name of drugs	Dose modification during Ramadan
Basal insulin	There is an increasing body of evidence supporting the safety of basal insulin during Ramadan. Glycemic control can be successfully intensified with newer basal insulin analogue like glargine in the Ramadan without risk of hypoglycemia. The dose of once daily NPH should be reduced by 15-30% and should be taken at iftar. In case of twice daily NPH/detemir/glargine, usual morning dose should be taken at iftar and 50 % reduced evening dose should be taken at suhoor.
Short acting insulin	Normal dose should be taken at iftar. Lunch-time dose can be omitted. Evening dose should be reduced to 50% at suhoor.
Pre-mixed insulin	Once daily pre-mixed insulin should be taken at usual dose at iftar. In case of twice daily pre-mixed insulin, usual morning dose should be taken at iftar and suhoor dose should be reduced by 50% of evening dose.

6.6.4 SMBG

- Before iftar, 2 hours after iftar, mid-day and during any illness or symptoms of hypoglycemia.
- Frequency of SMBG should be daily for first 3 days, every 3rd day from next week onwards and every alternate day in the last week.

6.6.5 When to break the fast

All individuals willing to fast should be advised to break the fast if:

- Blood glucose 3.9 mmol/L
- Blood glucose levels 16.6 mmol/L (for those with sudden rise of blood glucose level)
- Symptoms of hypoglycemia or acute illness occur

6.7 Hajj and Travel[14,15]

Risk stratification, medication adjustments, proper clinical assessment, and education before doing the Hajj are crucial.

6.7.1 Health risks

- Hypoglycemia
- Dehydration
- Foot injuries and infection
- Hyperglycemia
- Heat stroke and heat exhaustion
- Infection
- Cardiac problems

6.7.2 General recommendations

Before travel

- To consult physician 1-2 months before the Hajj.
- To complete recommended vaccinations.
- It is preferable to pack diabetes medications in carry-on bags, not in the checked luggage. This will protect the medicines from temperature changes in luggage stored in cargoes, which may affect the potency of insulin and other medications.
- To choose shoes, sandals, and flip-flops with appropriate shapes and sizes (wide-front shoe to avoid extra pressure on the feet and the toes during long walking). Use socks while barefoot walking is required.

During travel and Hajj

- Some carbohydrates to be carried for use during hypoglycemia. Meals should not be skipped.
- Should drink plenty of water.

- If using insulin, before Ihram should check blood glucose using glucometer and urine ketone using dipstick (for T1DM). If needed, a small dose of insulin to cover for hyperglycemia and/or small meal to avoid hypoglycemia should be kept always.
- If using insulin before and during long walking, decrease the dose of short and intermediate insulin about 20% or more depending on the distance and effort. For those on sulfonylurea drugs, this adjustment of daily dose (up to 50% decrease in the corresponding drug dose of previous dose) can be applied.
- Before tawaf (circumambulation around Ka'bah) and saee (walking between Safa and Marwah), should consume some additional carbohydrates (Complex carbohydrate is preferred) if the blood sugar within target.
- Should check feet daily before going to bed.

6.7.3 Medication adjustment

- Metformin, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DPP4) inhibitors, glucagon-like peptide-1 (GLP1) receptor agonists and SGLT2 inhibitors require no dose adjustment.
- Sulfonylureas should be used with caution. The dose may be adjusted before doing the Hajj physical activity, and newer generations are preferred.
- Insulin treatment is usually linked to increased risk of hypoglycemia, especially during the Hajj and its prolonged walking.

6.8 Diabetes and infection[16,17]

- There is increased risk of infection in persons with diabetes. However, infection may worsen diabetes control. Hyperglycemia impairs humoral immunity and leukocyte functions. Persons with long-standing diabetes tend to have vasculopathy with resultant poor tissue perfusion. Moreover, diabetic neuropathy results in unnoticed injury – all of which can precipitate infection.
- The most common sites of infection in diabetes are the skin and urinary tract. Spread of infection bone causing osteomyelitis is common in diabetes. Lower urinary tract infections and acute pyelonephritis are seen with greater frequency.

- A few infections, such as malignant otitis externa, rhinocerebral mucormycosis, emphysematous pyelonephritis and emphysematous cholecystitis occur almost exclusively in persons with diabetes. Infection at insulin injection site, sometimes leading to abscess formation, though not common, may add to the suffering of the person. Some antidiabetic drugs may precipitate infection – SGLT2 inhibitors can precipitate UTI and genital fungal infection; DPP4 inhibitors, GLP1 receptor agonists and thiazolidinediones can precipitate nasopharyngeal infections.
- Management of hyperglycemia is crucial not only to contain the infection, but also to prevent fatal acute complications of diabetes. Insulin is the best option to control diabetes in presence of infection. In case of very minor infection non-insulin agents may be continued with cautious supervision. At the same time aggressive management of the particular infection with appropriate antibiotic should be ensured.

6.8.1 Tuberculosis[18]

Subjects with diabetes are three to five times at higher risk of getting active tuberculosis compared to those without diabetes. Often they do not have classical features, are associated with increased morbidity, drug resistance and relapse. On the other hand, tuberculosis can cause glucose intolerance and lead to increased incidence of diabetes mellitus. Insulin is the best option, specially during early phase, severe infection (like disseminated or military TB, tubercular meningitis), lean and thin patients, while using steroid etc. Moreover, some anti-TB drugs have interaction with some OADs.

6.8.2 COVID-19[19]

People with diabetes have increased risk of getting more severe form of COVID-19, though there is no sufficient proof of increased incidence of, or death from, the disease. There is increased risk of diabetes in individuals who have suffered from COVID-19. For control of blood glucose insulin is the best choice in case of moderate to severe disease. For critically ill COVID-19 patients, specific protocol should be followed for glycemic control. For mild cases non-insulin agents may be used with close monitoring.

6.9 Vaccination for people with diabetes[20,21]

As individuals with diabetes represent a vulnerable subgroup of the population with respect to susceptibility to infection, preventing these infections by means of vaccination assumes paramount importance and is recommended by many international organizations.

Table 6.10 Highly recommended immunizations for individuals with diabetes

Vaccine	Recommendations in diabetes
Pneumonia	Children should be vaccinated with 13-valent pneumococcal conjugate vaccine (PCV13) before the age of 2 years. People with diabetes aged 2-64 years should receive 23-valent pneumococcal polysaccharide vaccine (PPSV23). Booster dose is needed after age 65.
Influenza	Annual vaccination with influenza vaccine (preferably quadrivalent vaccine) is recommended for all people 6 months of age and above.
Hepatitis B	Administer a 2- or 3-dose series of hepatitis B vaccine, depending on the vaccine, to unvaccinated adults with diabetes ages 18 through 59 years. Consider administering a 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ≥60 years of age.
Human Papilloma Virus (HPV)	3 doses over 6 months, for <26 years of age; 27-45 years of age may also be vaccinated against HPV after a discussion with health care provider.
Tetanus, Diphtheria, Pertussis (TDAP)	Booster every 10 years for all adults; pregnant women should have an extra dose.

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Chapter -7

Prevention of Diabetes Mellitus

CHAPTER-7

Prevention of Diabetes Mellitus

Executive summary

- Type 2 diabetes is a preventable disease.
- Preventions applicable in T2DM are primordial, primary, secondary and tertiary prevention.
- Primary prevention is very much feasible and cost effective.

T2DM is a preventable disease. Its complications can also be prevented or delayed. And outcome of these preventive measures are immense on individual and also on the society. Still now T1DM is not preventable.

7.1 Goals of diabetes prevention

- Preventing or delaying the onset of diabetes by risk reduction
- Preventing or delaying microvascular and macrovascular complications
- Ultimately, ensuring socially productive life and reducing economic burden of diabetes care

7.2 Types of prevention of diabetes

- Primordial prevention: focuses on strategies to stop the emergence of the risk factors during the phase of normal glucose tolerance.
- Primary prevention: refers to avoiding the onset of the disease (diabetes).
- Secondary prevention: means early detection of diabetes and prompt initiation of treatment to prevent complications of diabetes.
- Tertiary prevention: aims to delay and/or prevent further progression of the diabetic complications.

7.3 Primary prevention of T2DM

Interventions in high risk individuals is a very effective strategy, and more cost effective than approaches in general population.

7.3.1 Identification of high risk individuals

Several risk factors that put a person vulnerable to T2DM:

- Family history of diabetes (in 1st degree relatives)
- Over-weight and obesity
- Unhealthy diet
- Physical inactivity
- Increasing age (male>female)
- High blood pressure
- Dyslipidemia
- Prediabetes
- Polycystic Ovary Syndrome (PCOS)
- Persons with features of insulin resistance i.e. acanthosis nigricans, severe obesity
- History of gestational diabetes
- History of poor nutrition during pregnancy

It is possible to measure quantitative risk core from these to predict future diabetes.

7.3.2 Interventions for primary prevention

An intensive lifestyle intervention could reduce the risk of incident T2DM by 58% over 3 years.[1]

Nutritional strategy

- Healthy eating in terms of type and calorie content needs to be ensured.
- Vegetables, fresh fruits, whole-grain bread and rice, lean cuts of white meat, poultry, seafood and unsaturated fats should be chosen.
- Personal and cultural preferences, willingness and ability should be emphasized; maintaining the pleasure of eating is important.

Physical activity

- The goal for physical activity is at least 150 minutes of moderate-intensity physical activity per week similar in intensity to brisk walking. Around 30 minutes walking for 5 days a week can serve the purpose.
- In addition to aerobic activity, an exercise regimen designed to prevent diabetes may include resistance training.
- Breaking up prolonged sedentary time may also be encouraged.
- The preventive effects of exercise appear to extend to the prevention of gestational diabetes mellitus.[2]

Weight management

- Over-weight/obesity is a well-known notorious factor in diabetogenesis.
- Maintaining desirable body weight can be achieved through healthy meal plan and proper exercise program.

Pharmacologic interventions

Metformin therapy for prevention of T2DM should be considered in adults with prediabetes, especially those aged 25-59 years with BMI ≥30 kg/m^2, higher fasting plasma glucose (e.g. ≥110 mg/dL), and higher HbA1c (e.g. ≥6.0%), and in women with prior gestational diabetes mellitus.

7.4 Secondary prevention

This encompasses early detection and prompt adequate treatment of diabetes. Early detection of diabetes is important because control of hyperglycemia early in the course of the disease may be crucial in preventing or delaying chronic complications. Majority of people with T2DM are asymptomatic, and may remain so for many years. Many persons with T2DM present with complications. For early detection regular and proper screening tests should be carried out. If found normal, test should be repeated every 3 years. In case of prediabetes and previous GDM, testing should be done every year. If found diabetic, interventions to prevent complications are to be undertaken.

7.4.1 Interventions for secondary prevention

These are actually target based treatment of diabetes. Intensive management of blood glucose and blood pressure reduces the risk of developing complications of diabetes;[3] lipid lowering reduces risk of coronary events. Foot care education reduces risk of ulceration. Cessation of smoking and weight control are also beneficial components in secondary prevention.

7.5 Tertiary prevention

In epidemiological terms, tertiary prevention aims to reduce the number and/or impact of complications. Strategies for tertiary prevention include regular screening for complications and then taking aggressive measures, e.g. laser therapy for diabetic retinopathy to prevent progression to blindness; treatment with ACE inhibitors to slow down the progression of nephropathy;[4] treatment of foot ulcer to prevent amputation etc.

7.6 Prevention of GDM

It is well known that women with GDM as well as their infants are at increased risk of developing T2DM and other cardio-metabolic diseases like obesity, hypertension and coronary artery diseases.[5] Again, GDM is a potentially preventable condition. Weight management, healthy eating and adequate exercise are effective ways to reduce the risk of GDM.

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5.5

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