Republic of Ghana

NATIONAL GUIDELINES FOR THE MANAGEMENT OF DIABETES MELLITUS

MINISTRY OF HEALTH
FIRST EDITION 2023

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FOREWORD

Since the first published reports on diabetes mellitus in Ghana in the 1950s and 1960s, its prevalence in urban areas has increased over twenty-fold in nearly 60 years. The writing of this guideline is, therefore, timely and sets the tone for beginning the search for appropriate local solutions to the many issues around diabetes in Ghana. Diabetes mellitus, a cardiometabolic disease, is a major cause of morbidity and mortality in Ghana. It causes microvascular and macrovascular complications such as stroke, heart attack, heart failure, nerve damage and kidney failure.

The Ministry of Health has rolled out policies aimed at attaining the highest possible standard of health peculiar to the health needs of our population. These policies aim to halt and reverse the rising burden of non-communicable diseases. Diabetes and other non-communicable diseases impose significant economic burden on healthcare needs resulting in loss of productivity, ultimately impacting economic and health indicators negatively .

This guideline has covered all the basics and more, making it very useful for health professionals with an interest in diabetes. It has also suggested the best ways to ensure treatment success for patients at all health facility levels in Ghana.

The relevance of this guideline and its future revisions cannot be underrated, considering the increasing numbers of diabetes patients attending health facilities around the country with various presentations, including complications. The guideline would be a useful companion for healthcare trainees, trainers, practitioners, and researchers, just as it would be for diabetes policymakers and agencies involved in procuring diabetes-related medications and products.

The Ministry of Health expresses its sincere appreciation to all individuals and stakeholders involved in developing this ground-breaking document. It is our hope that the provisions in the guidelines will be applied to reduce the morbidity and mortalities associated with diabetes and ultimately improve the quality of life of persons living with diabetes in Ghana.

Hon. Kwaku Agyeman-Manu (MP)
Minister of Health
Ghana

July 2023

PREFACE

Diabetes Mellitus is a medical condition that has attracted global attention not only for its relatively high and rising prevalence but also for its implications on social and national development, mainly owing to the high cost of routine care and that for complications that may arise from its improper management.

This document is, in several ways, the first of its kind in Ghana; a guideline on diabetes mellitus designed not only to influence clinical and policy decisions on the handling of a common non-communicable disease but also to educate and, at the same time, direct healthcare practitioners on the right approaches to its recognition and management.

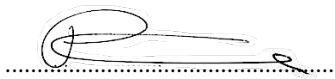
The writing of this document has been made possible by the collaborative effort of the Ministry of Health of Ghana, the Ghana Health Service through the Non-Communicable Disease Control Programme, the Diabetes Endocrine and Metabolic Society of Ghana (DEMSoG), along with invaluable support from international pharmaceutical company collaborators - Astra Zeneca and Servier Laboratories.

The idea to develop these guidelines was occasioned by the unavailability of a document written by local experts that comprehensively covered all aspects of diabetes mellitus. For many years, healthcare practitioners in Ghana had to rely largely on clinical guidelines authored by experts from other geographic regions of the world, especially Europe and North America. This document provides a country-specific context for practitioners in Ghana and other African countries.

The arrangement of the chapters in this guideline speaks for itself. It provides the reader, and indeed all healthcare practitioners and policymakers for

whom it is designed, an opportunity to grasp the basics of diabetes suited to their respective backgrounds. It begins with the classification and categorization of the condition, through its identification from clinical features and screening at-risk individuals to the use and interpretation of diagnostic tests. Readers have also been provided with an update on the appropriate dietary and lifestyle measures and the pharmacological management of the various forms of diabetes. Some chapters are dedicated to discussions on acute and chronic complications and the comorbidities associated with diabetes. The peculiar presentations of diabetes and its management in children and other special situations, such as in the hospital setting, have all been addressed in this guideline.

By producing this guideline, the authors, editors, governance committee members and sponsoring agencies have played a seminal role towards improving diabetes-related health outcomes in the country. It is now the turn of those who access this document to use the information provided to generate the expected results within their various fields of endeavour. Their contributions should ultimately help in several ways, including preventing new cases, of diabetes mellitus, improving clinical management of established cases or improving health outcomes for persons with the condition to enable them to attain an acceptable quality of life.



Dr Patrick Kuma-Aboagye
Director General
Ghana Health Service

July 2023

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- Society of Private Medical & Dental Practitioners (SMDP)
- Christian Health Association of Ghana (CHAG)
- Ahmadiyya Moslem Health Group
- Ghana Association of Quasi-Government Health Institutions of Ghana (GAQHI)
- Ghana Medical Association
- Ghana Association of Internal Medicine
- Society of Family Physicians of Ghana (SOFPOG)
- Diabetes Patients' Groups (Diabetes Youth Care, Kafui Foundation)
- Traditional Medicines Group/Herbal Pharmacists
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Greater Accra Regional Hospital (Ridge), Princess Marie Louis Hospital, University of Ghana Medical Centre
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- Coalition of NGOs in Health
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- Dietetics Association of Ghana
- Ghana College of Pharmacists
- Paediatric Society of Ghana
- Ghana College of Physicians & Surgeons
- NCD Alliance
- Ghanaian Society of Cardiology

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Chapter 1

INTRODUCTION

LIST OF ABBREVIATIONS

CHPS	Community-Based Health Planning and Services
EML	Essential Medicines List
NCD	Non-Communicable Diseases
DEMSoG	Diabetes Endocrine & Metabolic Society of Ghana
MoH	Ministry of Health
TWG	Technical Working Group

Background and Rationale

The prevalence of diabetes mellitus and associated complications are on the rise globally. Whilst the figures from Africa mirror the global picture, the continent is projected to suffer the largest increases, driven mainly by Type 2 diabetes and sedentary lifestyles.[1]

Many gaps have been identified that militate against the comprehensive management of diabetes in Ghana. These gaps include, among others, the lack of facilities, trained personnel, morbidity and mortality data, erratic supply of essential diabetes products, and advisory boards and guidelines.[2] The health sector is largely underfunded due to competition for meagre resources.[3, 4] This has led to a situation where funding for non-communicable diseases (NCD), including diabetes, is woefully inadequate.[4, 5] Although

there have been some attempts to improve the unmet needs and bridge the gaps, the desired objectives of most interventions are still unachieved.

The absence of diabetes advisory boards or guidelines for managing diabetes exists at all levels of the healthcare system in Ghana. There was an urgent need to develop national guidelines for all aspects of diabetes care. This would help bridge the gaps in diabetes management, standardize diabetes management protocols, and make best practices available to specialists and non-specialist practitioners who manage patients with diabetes at all levels of care across Ghana.

It is expected that, comprehensive diabetes care will be improved with the development and implementation of a national diabetes guideline, ultimately translating into a reduction in morbidity and mortality associated with diabetes and its complications.

Guideline Development Processes

The Ministry of Health and the Non-Communicable Disease (NCD) Unit of Ghana Health Service, in collaboration with the Diabetes Endocrine & Metabolic Society of Ghana (DEMSoG), were the main drivers of these guidelines. There were initial consultative meetings among all stakeholders and potential sponsors. The scope of the anticipated guidelines was defined: to develop a guidance document for all levels of care in Ghana. The main thematic areas conceptualized were as follows: Pathophysiology, Screening and Diagnosis of Diabetes; Non-Pharmacological Management of Diabetes; Pharmacological Management of Diabetes; Management of Complications; Management of comorbidities; Diabetes in Children & Adolescents (including those with Type 2); and Diabetes in Special Situations. The processes are summarized in Table 1.1.

Table 1.1: Processes of the Guideline Development

Initial Planning Meetings (MoH, NCD & DEMSoG)
Pre-Guideline meeting with Governance Committee
Pre-Guideline meeting with Identified Editors
Pre-Guideline meeting with Technical Working Group (TWG)/Writers

Initial Planning Meetings (MoH, NCD & DEMSoG)
Pre-Guideline workshop with all stakeholders
TWG meetings
Editorial meetings
Technical meetings to consider draft (Governing Board/Editors/TWG)
Large stakeholders meeting
Finalization of draft guidelines
Printing final document
Launch and Dissemination

Recommendations according to Level of Care

Ghana's Essential Medicine List (EML) has seven levels of healthcare based on the type of health facility (Table 1.2).

Table 1.2: Ghana Health Service Levels of Healthcare

Level	Type of Facility
Level A	Community-based health planning and services (CHPS); the lowest level)
Level M	Midwifery
Level B1	Health Centre without a doctor
Level B2	Health Centre with doctor
Level C	District Hospital
Level D	Regional/Teaching Hospital
Level SD	Specialist Drugs (Specialist Facility/Service)
Level PD	Programme Drugs

Despite these categories and for ease of application, these guidelines will cover 3 strata of service provision/Levels of care: ***facilities without doctors, facilities with doctors (non-specialists) and facilities with specialists*** (Physicians, Family Physicians, Diabetologists and Endocrinologists) to

cover all levels of care (primary, secondary and tertiary). This is summarised below (Table 1.3).

Table 1.3: Descriptions of Levels of Care

Level of care	Description	Facility
0	**All facilities**	CHPS, Midwifery, Health Centre, Polyclinic, District Hospital, Regional & Teaching Hospital
1	**Facilities without doctors**	CHPS, Midwifery, Health Centre
2	**Facilities with doctors *(non-specialists)***	Health Centre, Polyclinic and District Hospital
3	**Facilities with specialists** (Physicians and Family Physicians, Diabetologists and Endocrinologists)	District Hospital, Regional & Teaching Hospital

Information gathering and recommendations

In developing the guidelines, we conducted searches and examined as well as scored several guidelines from Africa, Europe, the Americas and Asia based on the Appraisal of Guidelines for Research and Evaluation ("AGREE") scoring system/method.[6] Published literature, including randomized controlled trials, systematic reviews, and meta-analyses, were also extensively reviewed.

The "AGREE" instrument for the quality assessment of clinical practice guidelines consists of 23 items grouped into six domains: 1) Scope and purpose, 2) Stakeholders involvement, 3) rigour of development, 4) Clarity and Presentation, 5) Applicability and 6) Editorial independence.[6] We selected guidelines with higher scores in some important areas, including lack of bias, the rigour of development, clarity and comprehensiveness of the recommendations and applicability, especially in the Ghanaian setting. Various sub-committee members made recommendations based on

examined information and their supporting evidence. The recommendations are graded from A to C based on the quality of the supporting evidence.

Strength of Recommendations:

Level A: Generally consistent findings of multiple randomized controlled trials (RCTs)
Level B: Generally consistent findings of single RCTs or large non-randomized studies
Level C: Consensus of the experts and/or small studies, retrospective studies, registries

Conflict of Interest Declaration

The stakeholders, including the technical working group/writers, governance committee, reviewers, and editors, declare that they have no personal interests or benefits in the development of these diabetes guidelines.

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Chapter 2

EPIDEMIOLOGY, CLASSIFICATION AND PATHOPHYSIOLOGY OF DIABETES MELLITUS

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
DKA	Diabetic Ketoacidosis
DPP-4	Dipeptidyl Peptidase-4
GAD	Glutamic Acid Decarboxylase
HLA	Human Leukocyte Antigen
HLA-DR	Human Leukocyte Antigen- DR
HLA-DQ	Human Leukocyte Antigen- DQ
HNF	Hepatocyte Nuclear Factor
IAA	Insulin Autoantibody
IA-2Ab	Insulinoma Associated Antigen 2
ICA	Islet Cell Antibodies
IDF	International Diabetes Federation
K-ATP	Adenosine Triphosphate-sensitive potassium channel
LADA	Latent Autoimmune Diabetes in Adults
LMIC	Low- and Middle-Income Countries

MODY	Maturity Onset Diabetes of the Young
USD	United States Dollars
WHO	World Health Organisation
ZnT8	Zinc Transporter 8 Antibodies

2.0 INTRODUCTION

Diabetes mellitus is a metabolic disorder characterised by persistently raised blood glucose levels resulting from defects in endogenous insulin secretion, insulin action, or both. These defects lead to altered metabolism of lipids, proteins and carbohydrates.[1] Elevated blood glucose levels for prolonged periods damage both the small and large arteries of the body leading to nerve, kidney and retinal disease (microvascular damage). It also leads to cardiovascular, cerebrovascular, and peripheral vascular (macrovascular) damage.

The Burden of Diabetes Mellitus

The global prevalence of diabetes mellitus has tripled in nearly 20 years, from 4.6 % of the global population in 2000 (151 million cases) to 9.3 % of the global population in 2019 (463 million cases). It is now considered to be of epidemic proportions. It is also projected that the prevalence will rise to 700 million cases by 2045, representing 10.9 % of the global population, with the greatest increments occurring in low-and middle-income countries (LMICs).[2]

In Africa, the prevalence of diabetes mellitus has been projected to increase by 143 % between 2019 and 2045 (19 million cases in 2019 to 47 million cases by 2045). In this region, approximately 60% of adults aged 20 - 79 years with diabetes are undiagnosed, representing the highest proportion of undiagnosed diabetes of all International Diabetes Federation (IDF) Regions.[2] Presently, 3 in 4 persons with diabetes live in low- and middle-income countries (LMICs).[3] Although there is a paucity of data on the exact national prevalence in Ghana, findings of a recent systematic review and meta-analysis estimate the prevalence to be 6.46 %.[4]

Diabetes mellitus is currently among the top 10 causes of mortality worldwide, with an estimated 4.2 million deaths recorded in 2019 from diabetes and its related complications.[2]

Annual global health expenditure on diabetes is estimated at 760 billion United States Dollars (USD). It is projected that global expenditure on diabetes will reach USD 845 billion by 2045, with serious financial implications for low-and middle-income countries such as Ghana.[3]

To address the public health burden of diabetes, urgent national actions are required to improve its prevention and management. If appropriate management of diabetes is achieved, the debilitating complications associated with it can be delayed or prevented altogether.

2.1 CLASSIFICATION AND PATHOPHYSIOLOGY OF DIABETES MELLITUS

2.1.1 Classification

Diabetes mellitus is classified as Type 1, Type 2 and gestational diabetes. Hybrid forms include slowly evolving immune-mediated diabetes of adults and ketosis-prone Type 2 diabetes.

There are other uncommon types of diabetes belonging to a large heterogeneous group.[5,6] The various types are summarised below:

1. Type 1 diabetes mellitus
2. Type 2 diabetes mellitus
3. Gestational diabetes
4. Hybrid forms (immune-mediated diabetes of adults and ketosis-prone Type 2 diabetes)
5. Genetic defects of β-cell function, e.g., Monogenic diabetes
6. Genetic defects in insulin action
7. Diseases of the exocrine pancreas
8. Endocrinopathies
9. Drug or chemical-induced
10. Infection-related diabetes
11. Uncommon forms of immune-mediated diabetes

12. Genetic syndromes, sometimes associated with diabetes

Classification of diabetes is of paramount importance in determining therapy. Furthermore, misdiagnosis is common, especially at presentation (e.g., adults with Type 1 diabetes misdiagnosed as having Type 2 diabetes and children with genetic defects of β-cell function or insulin action misdiagnosed as Type 1 diabetes). In general, despite the initial challenges in classification, the diagnosis becomes more obvious over time.

2.1.2 Pathophysiology and Clinical Presentation

Type 1 diabetes

Pathophysiology

Type 1 diabetes was previously referred to as "juvenile-onset diabetes" and "insulin-dependent diabetes". It constitutes less than 5-10% of diabetes cases worldwide and is the commonest type among children.[6] Type 1 diabetes is usually characterised by pancreatic β-cell destruction, leading to absolute insulin deficiency. There are subtypes which include:

- Immune-mediated (1A)– approximately 90% of cases
- Idiopathic (1B)- less than 10 % of cases

Immune-mediated Type 1 diabetes

Concerning the immune-mediated subtype, approximately one-third of the disease susceptibility is due to genes and two-thirds to environmental factors.[5,6] The concordance for identical twins is 25–50%, and about 40% of the genetic risk is contributed by genes related to the HLA loci. Also, nearly 95% of patients with Type 1 diabetes possess either HLA-DR3 or HLA-DR.[6] Other specific markers include HLA-DQ genes and the 5' polymorphic region of the insulin gene.[5,6] Triggers of autoimmunity are thought to be due to infection by viruses (such as rubella, coxsackie B4, cytomegalovirus, adenovirus and mumps virus) and consumption of cow's milk. This leads to β-cell destruction at a variable rate and eventual insulinopaenia and diabetes, as described in Figure 2.1.[5,6,7]

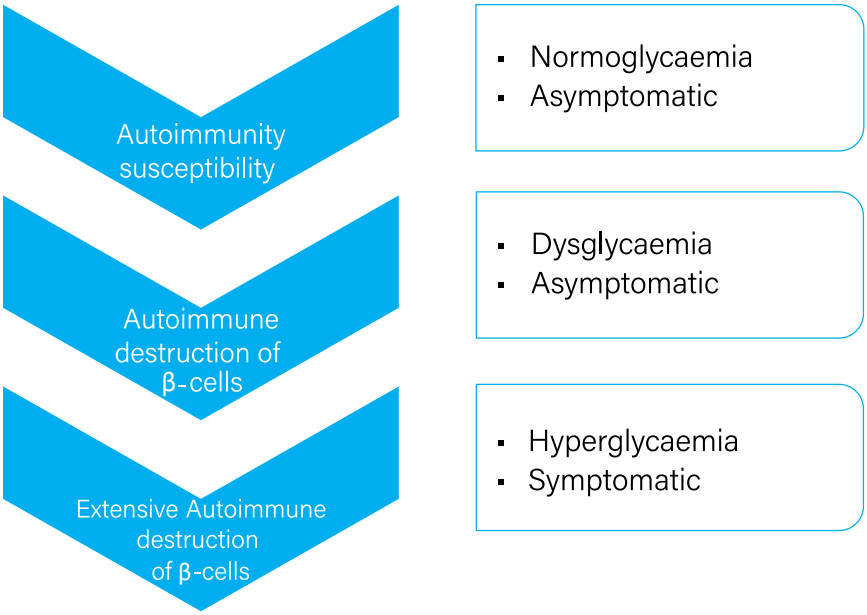

Figure 2.1: Pathophysiology of Type 1 Diabetes Mellitus

At the time of diagnosis, most patients (85-90%) with Type 1 diabetes mellitus have variable combinations of circulating antibodies to islet cells (ICA), insulin (IAA), glutamic acid decarboxylase (GAD65), tyrosine phosphatases (IA-2 and IA2-) and zinc transporter 8 (ZnT8).[6] Assaying for these antibodies may be useful to confirm an autoimmune cause of Type 1 diabetes or immune-mediated diabetes of adults. Patients treated with insulin also tend to develop low levels of anti-insulin antibodies.[5,6]

Immune-mediated Type 1 diabetes may be associated with other autoimmune disorders. Commonly associated autoimmune conditions include coeliac disease and Hashimoto thyroiditis. Less common autoimmune associations include Graves' disease, Addison's disease, vitiligo, myasthenia gravis and pernicious anaemia.[5,6] Recent data suggest three autoantibodies in asymptomatic individuals are associated with an estimated 100% 5-year risk of developing Type 1 diabetes.[8] Individuals with two autoantibodies have a 70% and 84% probability of developing Type 1 diabetes at 10 and 15 years, respectively.[9]

Those with only one autoantibody have a 21% likelihood of developing Type 1 diabetes in 3 years.[10]

The diagnostic sensitivity of IAA and IA-2 decreases with increasing age. While IAAs have their highest diagnostic sensitivity (50–60%) below the age of 10 years, autoantibodies to GAD65 remain at 70–80% regardless of age.[11] Diagnostic sensitivities and specificities of the autoantibodies are shown in Table 2.1 below.[11]

Table 2.1: Diagnostic sensitivity and specificity of autoimmune markers in patients with newly diagnosed Type 1 diabetes mellitus.

	Sensitivity (median)	Specificity (median)
Anti-Glutamic acid decarboxylase (GAD65) antibody	70–90% (80%)	90%
Insulin auto-antibody (IAA)	30–70% (32%)	99-100%
Islet antigen 2 Enzyme (Tyrosine phosphatase) (IA-2) antibodies	50–70% (58%)	99-100%
Islet cell antibody (ICA),	40-100% (81%)	64–100% (96%)

Idiopathic Type 1 diabetes mellitus

Less than 10% of patients have no evidence of pancreatic B cell autoimmunity to explain their insulinopaenia and ketoacidosis. Idiopathic Type 1 diabetes is strongly inherited and occurs in persons of African and Asian ancestry. No HLA associations can be identified.

Clinical Features of Type 1 Diabetes

Patients with Type 1 diabetes often present with acute symptoms of diabetes and markedly elevated blood glucose levels. About one-third are diagnosed with life-threatening diabetic ketoacidosis (DKA).[12] As the rate of β-cell destruction is more rapid among infants and children, children

and adolescents may present with DKA as the first manifestation of the disease.[6] Others have mild to moderate fasting hyperglycaemia that can rapidly change to severe hyperglycaemia, DKA or both in the presence of infection or other stress.

Characteristic symptoms include polyuria (excessive urination), polydipsia, and weight loss. Others include lack of energy/fatigue, bedwetting (enuresis) and failure to thrive in children

In adults, the onset of Type 1 diabetes may be more variable as these patients may not present with the classic symptoms seen in children. Adults may retain sufficient β-cell function to prevent DKA for many years. After diagnosis, some patients may experience temporary remission from the need for insulin.[13] This *"diabetic honeymoon"* variably lasts between two weeks to two years and dramatically reduces insulin requirements, often with a period of insulin non-dependency.[5,6,7] It is thought to be due to the removal of glucotoxicity experienced by the B-cells when insulin is administered after diagnosis. The first sign of re-occurrence is rising in fasting glucose levels. Eventually, such individuals become dependent on insulin for survival and are at risk for DKA.[14] At this latter stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide.[5,6,7] It is important to screen individuals with a long-standing history of Type 1 diabetes (greater than five years) for complications, as early detection and management may slow the progression or reverse these complications. Screening entails assessing clinical features suggestive of microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (stroke, heart attacks, and peripheral vascular disease)

Slowly evolving, immune-mediated diabetes of adults

This was previously called Latent Autoimmune Diabetes of Adults (LADA). It presents as Type 2 diabetes with a demonstration of autoimmunity (anti-GAD or anti-IA2 antibodies positive). Characteristically, it phenotypically behaves as Type 2 (with increased cardiovascular risks) but with genotypic Type 1 diabetes mellitus features. It is probably no more than slow-onset Type 1 diabetes, and its onset is usually after 35 years. It generally can be

controlled on oral agents such as metformin, thiazolidinediones and DPP-4 inhibitors for 3-6 months before insulin may be needed.[5,6,15]

Type 2 diabetes mellitus

Type 2 diabetes mellitus constitutes 90-95% of diabetes cases worldwide. It was previously referred to as "noninsulin-dependent diabetes" or "adult-onset diabetes". It is characterised by insulin resistance and variable insulin secretory defects resulting in relative insulin deficiency. Risk factors include increasing age, obesity, lack of physical activity and women with previous gestational diabetes. Other associations include hypertension, dyslipidaemia, polycystic ovarian syndrome and persons with Black African, Hispanic and Asian ethnic backgrounds. There is a stronger genetic predisposition or family history in first-degree relatives than in Type 1 diabetes, although the susceptible genes have not been extensively described.[5]

Pathophysiology

The major pathophysiological defect is variable β-cell dysfunction and loss, which is less understood than Type 1 diabetes. In response to body tissue resistance to a major action of insulin (i.e., glucose uptake from the blood by specific tissues), there is compensatory hyperinsulinaemia to overcome this resistance. With progressive β-cell dysfunction, insulin levels fall, leading to impaired fasting glucose and impaired glucose tolerance (prediabetes). Further decline in insulin levels results in worsening plasma glucose leading to overt diabetes.[5,16] Current evidence suggests that the insulin secretory defects may be related to inflammation and metabolic stress, among other contributors, including genetic factors. The core pathophysiologic defects in Type 2 diabetes appear to be insulin resistance in muscle (reduced glucose uptake) and liver (increased glucose output), and β-cell failure.[16] Additionally, the fat cell (accelerated lipolysis), gastrointestinal tract (incretin deficiency and resistance), α-cell (hyperglucagonaemia), kidney (increased glucose reabsorption), and brain (neurotransmitter dysfunction) all play important roles in the development of glucose intolerance in patients with Type 2 diabetes.[16] These pathophysiological defects have become targets for intervention. These eight pathophysiological mechanisms comprise the "*ominous octet*" (shown in Figure 2.2).

Figure 2.2 Pathophysiological mechanisms of Type 2 Diabetes

Clinical features of Type 2 diabetes

Type 2 diabetes frequently goes undiagnosed for many years because hyperglycaemia develops gradually and, at earlier stages, is often not severe enough for the patient to notice the classic diabetes symptoms. Undiagnosed patients are at increased risk of developing both macrovascular and microvascular complications of diabetes.[5,6] Typical symptoms include polyuria, polydipsia, nocturia, polyphagia and weight loss. Other symptoms include a history of recurrent furuncles (boils) and vaginal discharge.

Occasionally, patients with Type 2 diabetes may present with DKA[17], particularly among persons of African ancestry.[18] Although DKA may seldom occur spontaneously in Type 2 diabetes, this usually arises in association with stressful conditions such as infection or with certain medications (e.g., corticosteroids, atypical antipsychotics, and sodium-glucose co-transporter-2 inhibitors).[19] Due to the long period of latency before overt clinical features, it is important to elicit clinical features of both macrovascular complications (such as chest pain, intermittent claudication, hemiparesis) or microvascular complications (such as blurred vision, numbness or burning sensation in the hands and feet, oliguria, frothy urine, facial puffiness, pedal oedema, among others.). This is necessary because early detection is essential to prevent disability and death.[6] Other associations relating to metabolic syndrome must be looked for at diagnosis. These features include central obesity, corneal arcus, tendon xanthomas, xanthelasma, hypertension, and acanthosis nigricans in the appropriate setting.[5,6]

2.2 OTHER TYPES OF DIABETES

2.2.1 Genetic defects of β-cell function

Monogenic Diabetes

Monogenic diabetes due to monogenic defects causing β-cell dysfunction constitutes <5% of patients with diabetes. They include Maturity–onset Diabetes of the Young (MODY), neonatal diabetes and mitochondrial diabetes.

i) Maturity-onset Diabetes of the Young (MODY)

The condition results from impaired insulin secretion with usually no associated insulin resistance. It is rare, constituting <2% of diabetes. Eleven subtypes are known: MODY 1-11.[5,19.] It is characterised by a strong family history (autosomal dominant) with early onset hyperglycaemia and diabetes in young individuals, usually before the age of 25 years. The diagnosis of the common subtypes is made by genetic testing using Hepatocyte Nuclear Factor 1 (HNF1) alpha ***(MODY 3),*** glucokinase ***(MODY 2)*** and Hepatocyte Nuclear Factor 4 (HNF4) alpha ***(MODY 1)*** analyses, which are expensive and not widely available.[20]

ii) Neonatal Diabetes

This is a rare type of diabetes diagnosed in the first six months of life which may be transient or permanent with over 20 known genetic causes. Early recognition and urgent genetic testing are important for predicting the clinical course and treatment. Other causes of neonatal hyperglycaemia must be excluded. Children with Adenosine Triphosphate-sensitive potassium (K-ATP) channel defects (40% of cases) can be managed with sulfonylureas.[5] The other subtypes are treated with insulin.

iii) Mitochondrial Diabetes

This condition is autosomal dominant and maternally transmitted. Classification of mitochondrial diseases is dependent on the mutation and organ involved. It presents with mild fasting hyperglycaemia (5.5–8.5 mmol/L), especially in young and non-obese individuals.[5] Management is symptomatic. Oral antidiabetic agents with or without insulin therapy are used to treat diabetes. Hearing aids or cochlear implants are recommended for hearing loss.

2.2.2 Genetic Defects in Insulin Action

Mutations of the insulin receptor may result in changes ranging from hyperinsulinemia and modest hyperglycaemia to severe diabetes. Examples include Type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome and Lipoatrophic diabetes.[5]

2.2.3 Genetic syndromes

These syndromes may be associated with diabetes**.** These include Stiff person syndrome, Down syndrome, Klinefelter syndrome, Turner syndrome, Wolfram syndrome, Friedreich ataxia, Huntington chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria and Prader-Willi syndrome.[5]

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Chapter 3

SCREENING AND DIAGNOSIS OF DIABETES MELLITUS

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
BUE, Cr	Blood Urea Electrolytes and Creatinine
DCCT	Diabetes Control and Complications Trial
EASD	European Association for the Study of Diabetes
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
GAD	Glutamic Acid Decarboxylase
GDM	Gestational Diabetes Mellitus
HbA1c	Glycated Haemoglobin
IAA	Insulin Autoantibody
IA2 AB	Insulinoma Associated Antigen 2 Antibody
ICA	Islet Cell Antibodies
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
NGSP	National Glycohemoglobin Standardization Programme

NGT	Normal Glucose Tolerance
OGTT	Oral Glucose Tolerance Test
PG	Plasma Glucose
RBG	Random Blood Glucose
T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organization
ZnT8	Zinc Transporter 8 Antibodies

3.0 INTRODUCTION

This chapter discusses available tests for screening and diagnosing diabetes mellitus with particular reference to the World Health Organization (WHO) definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia.[1,2,3]

3.1 DIAGNOSIS

An accurate diagnosis of diabetes is based on blood glucose values. Urine glucose values do not accurately reflect blood glucose levels and are therefore not recommended for the diagnosis of diabetes. There are slight differences in glucose levels between venous plasma, whole venous blood and capillary (finger prick) samples. Do not use capillary glucose values for diagnosis. Tests available for diagnosing diabetes mellitus based on a venous plasma sample and laboratory methods include:

- Fasting Plasma Glucose (FPG)
- 2-Hour Plasma Glucose (2-h PG) during a 75-G Oral Glucose Tolerance Test (OGTT)
- Glycated Haemoglobin (HbA1c) and
- Random plasma glucose (RPG)

3.1.1 Diagnostic tests

In the absence of symptomatic hyperglycaemia, if a single laboratory-based glucose test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, HbA1c, 2-h PG in a 75 g OGTT) must be done on another day.[4]

a. Fasting Plasma Glucose (FPG)
   - This test is performed after an 8-12 hour overnight fast. It is a simple, reliable and affordable test to perform. An FPG of ≥ 7 mmol/L is diagnostic of diabetes mellitus (Table 3.1)

b. Oral Glucose Tolerance Test (OGTT)
   - This test diagnoses diabetes in more people than the FPG and the HbA1c. After an overnight fast, a glucose sample is first taken, followed by the administration of 75-g of anhydrous glucose solution, with subsequent venous blood samples taken at 60, 90, and 120 minutes. A 2-h plasma glucose level of ≥ 11.1 mmol/l is diagnostic of diabetes mellitus (Table 3.1). Indications for OGTT include persons showing one abnormal plasma glucose value, asymptomatic persons with sustained or transient glycosuria, symptomatic individuals with no glycosuria or hyperglycaemia, persons with a family history but no symptoms, in persons with neuropathy and retinopathy of unknown origin. An OGTT should not be performed on persons already confirmed to have diabetes and in severely ill patients.

c. Glycated Haemoglobin (HbA1c)
   - Glycated Haemoglobin (HbA1c) is commonly used as a marker of chronic glycaemia and provides information about the average blood glucose concentration over a retrospective period of 2–3 months
   - An HbA1c of ≥ 6.5% is diagnostic of diabetes mellitus (Table 3.1).[5,6]
   - However, to use as a diagnostic criterion, HbA1c must be measured using a validated assay standardized by the National Glycohemoglobin Standardization Program and the Diabetes Control and Complications Trial (DCCT).[7,8]
   - Several advantages to using HbA1c for diabetes diagnosis have been documented [7,9,10]
     - o No effect of diet, exercise, or insulin on test results; blood can be drawn at any time of the day
     - o It correlates well with the development of microvascular complications and, to a lesser extent, macrovascular complications
     - o The HbA1c test has greater pre-analytical stability with less day-to-day variability during stress and illness.

- The test is, however, limited by greater cost, availability, and method of standardisation.[11,12] Further, HbA1c may be misleading in individuals with various haemoglobinopathies, different ethnic and genetic backgrounds, pregnancy, iron deficiency, haemolytic anaemias, and severe hepatic and renal diseases.[13,14]

Table 3.1 (Diagnostic criteria for Diabetes Mellitus)

Criteria
FPG ≥ 7.0 mmol/L. Fasting is defined as no calorie intake for at least 8-12 hours OR 2-h PG ≥11.1 mmol/L during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in 250-300 ml water (flavoured with lime to prevent vomiting). OR HbA1c ≥ 6.5% (48 mmol/mol). The test should be performed in the laboratory using a method that is NGSP certified and standardized to the DCCT assay OR Random plasma glucose ≥ 11.1mmol/L (200 mg/dL). Random is defined as any time of the day without regard to the interval since the last meal

Adapted from the American Diabetes Association's Standard of Medical Care in Diabetes and the World Health Organization/International Diabetes Federation Guidelines[5,6,7]

Prediabetes

Prediabetes encompasses Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG), which are conditions of raised blood glucose levels

above the normal range and below the recommended diabetes diagnostic threshold (Table 3.2).[5,7] Individuals in this category are at a high risk of developing diabetes and its complications. Increasingly, the terms 'non-diabetic hyperglycaemia' and 'intermediate hyperglycaemia' are used as alternatives to prediabetes.[6,15] Currently, the World Health Organization (WHO) and the International Diabetes Federation (IDF) recommend a two-hour oral glucose tolerance test (OGTT) for the detection of IGT and IFG. There is, however, accumulating evidence for the use of a one-hour OGTT (plasma glucose ≥ 8.6 mmol/L) in the diagnosis of prediabetes in individuals with normal glucose tolerance (NGT) as it better predicts progression to T2DM, microvascular and macrovascular complications and mortality in individuals at high risk.[16]

Table 3.2 Criteria for Prediabetes or Increased Risk of Diabetes

Test	Criteria	Prediabetes Category
FPG (mmol/l)	6.1-6.9	IFG
2-h PG in a 75 g OGTT (mmol/L)	7.8-11.0	IGT
HbA1c	5.7-6.4%	Prediabetes

- *Recommended tests for the diagnosis and screening for diabetes mellitus include fasting glucose, random glucose, glycated haemoglobin and oral glucose tolerance tests*
- *Tests must be repeated in the absence of symptoms (for diagnosis)*
- *Urine glucose testing is not recommended for screening, diagnosis and monitoring.*

3.2 SCREENING FOR DIABETES

- Current preferred screening tests are limited to plasma glucose-based tests (FPG, RPG, OGTT) and glycated haemoglobin (HbA1c)
- If fasting venous plasma glucose determination is unavailable or not feasible, capillary blood glucose can be used for screening, as the difference between the two tests is usually insignificant[7,17]

- Recommended screening test in the clinical setting is fasting plasma glucose because of simplicity, cost and patient acceptability[18]
- If the fasting test is normal, the screening test should be repeated every three years. If the fasting blood glucose level is normal but there is a strong clinical indication of diabetes, do an OGTT.[7,17]

3.2.1. Who to screen for diabetes and prediabetes

Screening nonpregnant adults

The following categories of people (adults) should be screened for prediabetes or diabetes mellitus *(Adadapted from World Health Organisation's criteria for diagnosing diabetes mellitus and intermediate hyperglycaemia)*.[7]

1. All asymptomatic individuals ≥ 35 years
2. Individuals who have one or more of the following risk factors:
   - Overweight/obesity
   - First-degree relative with diabetes
   - History of cardiovascular disease
   - Hypertension (Bp ≥140/90mmHg) or on treatment for hypertension
   - Physical inactivity
   - Women with polycystic ovarian syndrome
   - HDL cholesterol level < 0.9 mmol/L and or triglyceride level > 2.82 mmol/L, and
   - Other clinical conditions associated with insulin resistance (e.g. acanthosis nigricans)
3. Patients with prediabetes (HbA1c ≥ 5.7%, IGT or IFG should be tested yearly)
4. Women diagnosed with gestational diabetes should have lifelong testing every three years
5. Because of the high-risk nature of our population, it is recommended that if results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status

Screening for asymptomatic children and adolescents

We recommend that testing should be considered in youth who are overweight or obese and who have one or more additional risk factors based on the strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation
- 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, dyslipidaemia, polycystic ovarian syndrome or large for gestational age birth weight)

3.2.2 Screening and Diagnosis of Gestational Diabetes (GDM)

- GDM is diagnosed for the first time during pregnancy and may occur anytime (most likely after 24 weeks).[7] An OGTT is recommended for the screening of GDM between the 24th and 28th week of pregnancy, but for high-risk women, the screening should be conducted earlier in pregnancy, preferably at booking (first antenatal clinic visit). High-risk women include pregnant women with marked obesity, personal history of GDM, glycosuria or a strong family history of diabetes. Typically, an OGTT is performed by measuring the plasma glucose concentration while fasting and one or two hours after ingesting 75 grams of glucose (one-step strategy). The criteria for diagnosing GDM are shown below.[2,7]
- Fasting: 5.1-6.9 mmol/L
- 1 hour post-prandial: >10.0 mmol/L
- 2 hours post-prandial: 8.5-11.0 mmol/L

3.3.2 Screening according to the Level of Care

The following indications for screening tests are recommended according to the level of care (Table 3.3)

Table 3.3: Indications for screening according to the level of care

Health facility without doctor	Health facility with doctor	Health facility with specialist
Acute symptomatic diabetes	Acute symptomatic diabetes	Acute symptomatic diabetes
• Polyuria (excessive urination) • Polydipsia (excessive drinking of water) • Weight loss • Lack of energy/ fatigue • Enuresis (bedwetting)	• Polyuria (excessive urination) • Polydipsia (excessive drinking of water) • Weight loss • Lack of energy/ fatigue • Enuresis (bedwetting)	• Polyuria (excessive urination) • Polydipsia (excessive drinking of water) • Weight loss • Lack of energy/fatigue • Enuresis (bedwetting)
Other effects of diabetes	Other effects of diabetes	Other effects of diabetes
• Blurred vision • Numbness/burning sensation in fingers and feet • Frequent boils • The obese patient above 35 years • Any patient > 35 years (annual screening)	• Blurred vision • Numbness/ burning sensation in fingers and feet • Frequent boils • Obese patients above 35 years • Any patient > 35 years (annual screening)	• Blurred vision • Numbness/ burning sensation in fingers and feet • Frequent boils • The obese patient above 35 years • Any patient > 35 years (annual screening)

Health facility without doctor	Health facility with doctor	Health facility with specialist
Pregnant women	Pregnant women	Pregnant women
• All pregnant women after 24 weeks of gestation At booking for mothers with: • Previous history of delivery of a big baby (birth weight > 4 kg) • Previous Gestational diabetes	• All pregnant women after 24 weeks of gestation At booking for mothers with: • Previous history of delivery of a big baby (birth weight > 4 kg) • Previous Gestational diabetes	• All pregnant women after 24 weeks of gestation At booking for mothers with: • Previous history of delivery of a big baby (birth weight > 4 kg) • Previous Gestational diabetes
Emergencies	Emergencies	Emergencies
• Any comatose patient or unconscious patient • Any patient admitted to the Emergency Unit (ER), if available	• Any comatose patient or unconscious patient • Any patient admitted to the Emergency Unit (ER), if available	• Any comatose patient or unconscious patient • Any patient admitted to the Emergency Unit (ER), if available

Health facility without doctor	Health facility with doctor	Health facility with specialist
Other situations	Other situations	Other situations
	• Chronic steroid use • Any patient with a history of prediabetes • History of antipsychotic drug use • Polycystic ovarian syndrome • Sedentary/ inactive lifestyle • First-degree relative with diabetes	• Chronic steroid use • Any patient with a history of prediabetes • History of antipsychotic drug use • Polycystic ovarian syndrome • Sedentary/ inactive lifestyle • First-degree relative with diabetes • History of hypogonadism • Endocrine disorders such as acromegaly, phaeochromocytoma, thyrotoxicosis, Cushing's syndrome, glucagonoma

The following diagnostic and screening tests are recommended according to the level of care (Table 3.4).

Table 3.4: Recommended diagnostic and screening tests according to the level of care

Health facility without doctor	Health facility with a doctor	Health facility with specialist
Blood glucose tests	Blood glucose tests	Blood glucose tests
• Fasting blood glucose (FBG)	• Fasting blood glucose (FBG)	• Fasting blood glucose (FBG)
• Random blood glucose (RBG)	• Oral glucose tolerance test	• Oral glucose tolerance test

Health facility without doctor	Health facility with a doctor	Health facility with specialist
•	• Glycated haemoglobin (HbA1c)	• Glycated haemoglobin (HbA1c)
Other ancillary tests	Other ancillary tests	Other ancillary tests
• Urine dipstick - if available	• Urine examination (routine or dipstick)	• Urine examination (routine or dipstick)
	• Renal function tests	• Renal function tests
	• Lipid profile	• Lipid profile
	• Arterial blood gases (If available)	• Arterial blood gases
		• C-Peptide, Pro-insulin
		• Islet Cell Antibodies (ICA) • Insulin Autoantibody (IAA) • Glutamic acid decarboxylase 65 antibodies (anti-GAD 65) • Insulinoma-associated antigen 2 (IA-2Ab) • Zinc transporter antibodies

FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; blood urea electrolytes and creatinine; OGTT, oral glucose tolerance test; Islet Cell Antibodies (ICA), Insulinoma associated antigen 2 (IA-2Ab), Glutamic acid decarboxylase 65 antibodies (anti- GAD 65)

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Chapter 4

NON-PHARMACOLOGICAL MANAGEMENT OF DIABETES

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CVD	Cardiovascular Disease
DHA	Docosahexaenoic acid
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
DSME	Diabetes Self-Management Education
EPA	Eicosapentaenoic Acid
FPG	Fasting Plasma Glucose
GFR	Glomerular Filtration Rate
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
MNT	Medical Nutrition Therapy
PA	Physical Activity
PPG	Post Prandial Glucose

RD	Registered Dietician
SMBG	Self-Monitoring of Blood Glucose
TIR	Time In Range

4.0 INTRODUCTION

Patients diagnosed with diabetes mellitus will require both pharmacological and non-pharmacological management. Both treatment modalities are essential in the managemnet of the patient.

Non-pharmacological management includes medical nutrition therapy (MNT), increased physical activity, self-monitoring of blood glucose and patient education.

General nutritional messages on foods permitted and not permitted are often not useful. A Registered Dietician (RD) should provide individualized MNT based on metabolic goals, socio-economic status, ethnic group, and cultural needs after a thorough assessment.

In young people, older adults, pregnant and lactating women, calories and nutrients must be individualized to meet the unique needs of these groups.

There should be regular MNT sessions between the RD and the patient. At the first session, the patient should be assessed and provided with an individualized meal plan and education on behaviour modification. Dietary approaches to managing diabetes include low glycaemic index, low glycemic load, low carbohydrate, low fat and Mediterranean diets.[1]

MNT is useful for weight loss. A 5-10 % weight loss significantly improves metabolic parameters[2], and a greater effect is achieved with ≥ 15 % weight

- *Non-pharmacological management of diabetes is a crucial part of the management of diabetes and must be ongoing*
- *All patients must have the basic information about diabetes and must have basic survival skills needed to live with diabetes.*
- *All patients must see a registered dietician regularly for MNT*
- *If it is considered safe, all patients must increase their physical activity*

loss.[2] Benefits of MNT can still be seen in the improved glycaemic control even when no weight is lost.[3]

4.1 MEDICAL NUTRITION THERAPY

Dietary counselling from a registered dietitian (RD) or a health professional trained to deliver MNT is crucial in diabetes management regardless of the type of diabetes.[4] Medical Nutritional Therapy (MNT) has been shown to decrease HbA1c by 0.5 – 2 % in patients with Type 2 diabetes.[2]

Goals of Nutrition Therapy for Adults with Diabetes

- To develop a holistic and practical healthy eating pattern involving a variety of foods in the right proportions whilst ensuring that eating is pleasurable (Figure 4.1)
- To factor cultural and personal choices, accessibility to healthy foods, barriers to change and behavioural changes to meet the individual needs

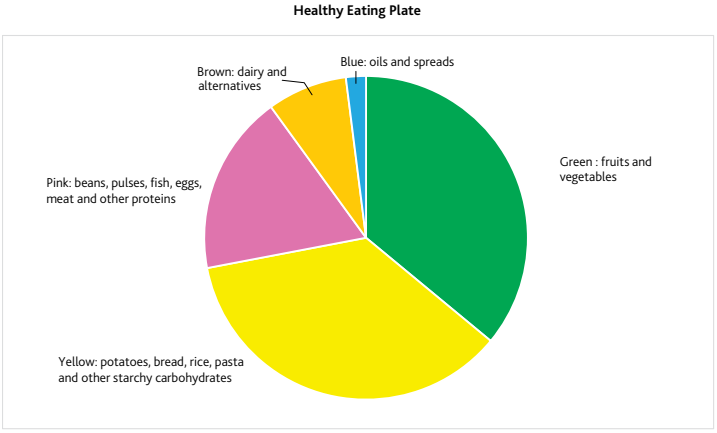

Figure 4.1: Heathy Eating/Meal Plate and Guide

Note:
Green: Eat 5 portions of a variety of fruits and vegetables every day
Yellow: Choose wholegrain or high fibre options with less added fat, salt and sugar
Blue: choose unsaturated oils and use in small amounts
Brown: Choose lower fat and lower sugar options
Pink: Eat more beans and pulses, 2 portions of fish per week, one of which is oily. Eat less red and processed meat

These goals are to achieve and maintain targets set for body weight, glucose level, blood pressure, and lipids and to slow down the progression of diabetes or drive diabetes into remission.[4]

The following are to be taken into consideration (Table 4.1):

- The foundation of the meal plan should constitute a balanced diet and must be sustainable
- Total calorie consumption should be reduced by at least 500Kcal / day with the help of a registered dietician
- Sugar and sugary drinks must be restricted
- Reduce fat and oil intake
- Ideally, all patients living with diabetes should be taught how to count carbohydrates. For patients with low literacy and numeracy skills, handy measures or food models should be utilized to teach appropriate portions of foods required in the meal plan.
- Non-nutritive sweeteners should be consumed within the recommended daily intake to ensure safety
- For individuals who wish to drink alcohol, they should limit the daily intake to a moderate amount (1 unit for women and 2 units for men per day. Examples of one unit are: one mini beer, one glass of wine and 1 shot/tot of gin, rum, vodka and whiskey).

Table 4.1: Recommendations and Considerations for MNT and Nutrient Intake

Calorie Restriction	• For overweight/obese patients, reduction of total energy intake (including carbohydrates, fat, protein and alcohol) is vital to promote weight loss • A reduction of 350 – 500 kcal from maintenance requirements for patients with a BMI of 30 – 34 kg/m2 and 500 – 1000 kcal for patients with a BMI ≥40 kg/m2 in theory, should result in a 10% weight loss over 6 months • Very low-calorie diets (< 800 kcal a day) are very effective in patients with Type 2 diabetes over 8-12 weeks under medical supervision • To achieve modest weight loss, an intensive lifestyle intervention (MNT, physical activity, and behaviour modification with ongoing support is recommended)
Macronutrient Distribution	• There is no ideal percentage of calories from carbohydrates, fat or protein for the general population • Intake should be individualized based on an assessment of the patient, taking into consideration the patient's lifestyle and metabolic goals

Carbohydrates	• Monitoring/regulating carbohydrate intake remains a key strategy for glycaemic control • Carbohydrate intake (both quality and quantity) should be individualized and guided by the patient's glycaemic control • Carbohydrates from whole grains, legumes, low-fat milk, vegetables and fruit should be used instead of refined carbohydrates and carbohydrates with added sugar, fats and sodium • Sugars (including fructose powder and high fructose corn syrup) should ideally be < 5 % of total daily energy intake to improve overall health. This equates to the sugar found in commercial products, e.g., sauces, without adding additional sugar to the diet • A patient's glycaemic control should determine the quality and quantity of carbohydrates consumed. Refined carbohydrates with added sugar, sodium and fats should be replaced with whole grains, vegetables, fruits, milk and legumes • Often, vitamins, minerals, herbs and spices are marketed as having clinical benefits for people with diabetes. There is, however, no evidence to support the use of such products and thus, should not be included in the MNT

Fats	• The type of fat consumed (saturated fat, monounsaturated fat and polyunsaturated fat) may be more important than total fat intake to prevent CVD • Trans fatty acids should be avoided, such as deep-fried and commercially baked foods • Saturated fats increase LDL cholesterol, the main driver of hypercholesterolemia • Replacing saturated fat with either monounsaturated fats or polyunsaturated fats decreases the risk of CVD • Replacing refined carbohydrates with monounsaturated fats or polyunsaturated fats tends to decrease the risk of CVD • Saturated fat and refined carbohydrates have a similar risk for CVD. However, replacing saturated fat with whole grains tends to lower the risk • A minimum of two servings of fatty fish per week is recommended to ensure an adequate intake of long-chain omega 3 fatty acids (EPA and DHA), which reduces risk factors for CVD • Pregnant women should avoid fish high in methyl mercury, such as shark, swordfish, tuna or king mackerel • Individuals intending to follow a nutrition plan high in saturated fats and proteins or a low-calorie diet must be informed of the unknown long-term safety • In preventing cardiovascular disease (CVD) and metabolic goal determination, the type of fat consumed is of greater essence than the total fat consumed. Polyunsaturated and Monounsaturated fats are ideal than saturated fats. Nuts should be eaten in appropriate portions as it is easy to binge on nuts, particularly nuts high in saturated fat. To prevent CVDs, long-chain omega-3 fatty acids, such as fatty fish, nuts and seeds, are recommended. Processed meats and fatty red meats should be limited

Protein	• For individuals with Type 2 diabetes with normal renal function, there is no evidence to suggest that the usual recommended protein intake should be modified • Reducing protein intake to < 0.8g/kg ideal body weight is not recommended for adults with micro and macro albuminuria. It does not alter glycaemia, cardiovascular risk factors or the rate of glomerular filtration (GFR) decline
Alcohol	• If the patient decides to consume alcohol, it should be in moderation (1 unit daily for women and 2 for men. • Alcohol may increase the risk of hypoglycaemia when used in combination with insulin secretagogues (such as sulphonylureas) and insulins. Patients need to be educated on how to consume alcohol safely
Salt	• For general health, sodium intake should be < 2300 mg a day (approximately half a teaspoon) • Further reductions in sodium intake may need to be individualized

Carbohydrate Intake in Diabetes Management

To achieve good glycaemic control, carbohydrate intake should be monitored using exchanges, carbohydrate counting or experience-based estimation. This approach helps patients on insulin to calculate insulin needed per carbohydrate intake.[2,5,6]

Nutritional Quality and Dietary Pattern

A high-quality dietary pattern should be recommended for individuals with diabetes. A meal plan which provides diverse nutrients helps reduce the risk of diabetes-associated complications.[2,5,7] This is illustrated in Table 4.2.

Table 4.2: Characteristics of a High-Quality Dietary Pattern

Food	Nutrient and health benefits / Consequences
Fruit and vegetable intake must be high (minimum of 5 portions daily)	Foods rich in fibre aid satiety. Vitamins, minerals, and phytonutrients help to combat oxidative stress
Whole grain starchy foods in recommended portions are preferred. Examples include oats, unrefined maize, brown rice	The fibre increases satiety and improves glycaemic control. It also contains vitamins B and E
All types of fish are encouraged, especially the omega-3 fatty acid types such as salmon and sardines	Provides the body with omega-3 fatty acids, protein, selenium, magnesium and vitamin D, and its saturated fat content is low
Consumption of legumes such as beans should be encouraged	Provides the body with protein and fibre and enhances a healthy lipid profile
Encourage intake of dairy products (low-fat, sugar-free products), e.g. low-fat milk and low-fat plain yoghurt	Contains calcium, vitamin D and magnesium and is a good protein source
Encourage the use of vegetable fats: avocado pear, nuts and seeds, and unrefined plant oils such as sunflower, canola and olive. Restrict intake of tropical oils such as coconut and palm oil	Saturated fats should constitute < 10% (< 15g/d) of one's total calories. Decrease the risk of CVD by substituting saturated fatty acids with unsaturated fatty acids in a meal. Tropical oils increase fatty acids due to the LDL content
Consumption of fast foods, deep-fried foods, and baked products containing high trans fatty acids should be restricted.	Increase in inflammation, trans fatty acids, total and LDL cholesterol, while HDL cholesterol is decreased
Consumption of processed and fatty meat should be restricted	Levels of nitrates, salt, haem-iron and saturated fat are high
Sugars commonly found in sugar-sweetened beverages, fruit juices, table sugar, honey, sweets, desserts, and baked goods should not be encouraged	As a poor source of nutrition, the following are its effects: obesity, inflammation, poor glycemic control and lipid profiles
Moderate consumption of alcohol such as beer, spirit and wine if desired	Glycaemic control, hypertension and triglyceride are worsened if consumed in large amounts

MNT in Pregnancy

MNT in pregnancy requires adequate calories for mother and child without causing postprandial hyperglycaemia, excessive ketonuria or ketosis.

All patients should be referred to a dietician or health professional trained to deliver MNT for detailed diet therapy advice. The meal plan should be spread out among the different food groups in this manner[5, 8]:

Carbohydrate: 40% (low-glycaemic index, complex, high fibre)
Fat: 40% (at least 50% unsaturated)
Protein: 20%
Daily caloric requirement: The calorie intake for women with GDM is not different from other pregnant women without GDM. The recommended Dietary Reference Intake for pregnant women is a minimum of 175g for carbohydrates, a minimum of 71g of protein and 28g of fibre.[9]

Average weight gain allowed during pregnancy:

- 1st trimester - 2.5kg
- 2nd trimester – 5kg
- 3rd trimester – 5kg

Diet therapy should be tried for no longer than 2 weeks before adding insulin if FPG > 5.3mmol/l.

Each day's menu should comprise three meals and, in addition, two or three snacks. The portion of meals and their timings should consistently enhance good glycaemic control at all times, thereby preventing hypoglycaemia.
A moderate-intensity exercise for at least 30 minutes daily during pregnancy is recommended.

4.2 PHYSICAL ACTIVITY

Benefits of regular exercise include improved blood glucose control, weight loss, improved well-being and reduced cardiovascular risk factors.

For high-risk CVD patients and patients who have previously been sedentary, low-intensity exercise like walking should be started at short periods and then gradually increase in intensity and duration.

Physical activity (PA) should include aerobic or endurance exercise (e.g., walking or running) and anaerobic or resistance training (e.g., lifting weights) and flexibility exercises.[10, 11]

Patients should be encouraged to include increased physical activity, such as climbing stairs and walking, into their daily schedules to reduce sedentary time.

4.2.1 General Principles and Recommendations for Physical Activity in Type 2 DM

Before starting an exercise programme, there should be a detailed physical evaluation of renal, cardiovascular, neurological, eye and foot status.[10,11] These chronic complications may exempt one from certain forms of exercise.[10,11]

- Recommended physical activity (PA) programmes should factor in the patient's age, state of physical fitness, socio-economic status, level of glycaemic control and lifestyle
- Moderate, regular physical activity (five days/week) for at least 20-30minutes per session, i.e., 150 minutes of moderate PA per week
- Strenuous exercise should be avoided in the following situations: ambient glycaemia >14mmol/l, a patient who has ketonuria or whose blood glucose level is less than 4.5mmol/l
- To avoid exercise-induced hypoglycaemia, dosages of insulin secretagogues or insulin may need to be reduced, and peri-exercise carbohydrate intake increased, especially for professional athletes and when activity is likely to last an hour or more
- Before and after strenuous physical activity, glycaemia should be monitored (using glucose strips and meters), as delayed hypoglycaemia may occur
- Always wear the correct size of footwear; avoid footwear that is pointy at the toes.

4.3 PATIENT EDUCATION

Diabetes education is the cornerstone of diabetes management for all types of diabetes at all stages. It should therefore be an integral part of diabetes care and management. It should be client or person-centred and aimed

at assisting the patient/client/caregivers/family to accept and integrate diabetes management tasks efficiently and successfully into their lifestyles.[4]

Diabetes Self-Management Education should be a regular ongoing process starting from diagnosis and reinforced periodically when needed or when a knowledge gap is identified or suspected. It involves the active participation of the patient/client. Therefore, it is imperative to consider the following about the person living with diabetes and evidenced-based practices/ principles during diabetes education:

- Feelings, beliefs, culture, values, religion and coping styles.
- Age, education or literacy levels and learning styles.
- Achievable goals for the education session.
- Language(s) that can be spoken, read, understood and written by the person(s) receiving the diabetes education.
- Person's ability to carry out self-care behaviours, other medical conditions, socio-economic status and home support.

The health care providers must be trained to provide appropriate structured education, and content should be consistent among providers. Diabetes education can also be divided into the following:

- Survival skills- the initial information needed for the person to be safe at home.
- Basic knowledge- this is what enables a better or greater understanding of diabetes and its management.
- Ongoing education- this is the continuing acquisition of new knowledge, including technology and management practices that would be useful and applicable to the individual's self-care.

Diabetes Self-Management Education

Survival Skills

It can be applicable at all levels of care in the diabetes management guidelines. These are essential and are taught at the time of diagnosis. Minimum information (written) to ensure safety at home, person's or family's specific concerns/questions should also be addressed. The patient

should be aware of the type of diabetes or status of diagnosis and be able to[4]:

- Identify medications/have a list of medications and their effects, including insulin.
- Demonstrate appropriate administration of insulin and care of insulin if commenced on insulin.
- Demonstrate safe disposal of needles and other sharps.
- Know the signs and symptoms, causes, prevention and appropriate management of hypoglycaemia depending on the prescribed medications.
- Demonstrate good technique if commencing self-blood glucose monitoring.
- Have an emergency contact number for the health care provider/ facility if help is needed.

Basic Knowledge / Ongoing Education

This is a lifetime process. Both group and or individual programmes will be required. Patients must be taught what the disease is, its complications and management, including non-pharmacological management as outlined previously. Patients must also be taught about the importance of self-monitoring of blood glucose and the need for targets, and targets must be set with patients.[4]

Goals of Patient Education

Gradually, the patient should be able to adhere to the following voluntarily[4,12]:

- Cope in a healthy way-this is needed for learning to occur
- Understand and adhere to healthy eating
- Be active as much as possible
- Understand the role of medications and factors that affect their efficacy. Examples: skipping/missing doses due to cost/unavailability, fasting for religious reasons or inconsistent meal patterns, unexpected/ unexplained reactions etc.
- Monitor blood glucose levels, whether at home or in the facility Frequency and targets should be individualized; and may depend on the type of diabetes, type of treatment, age, literacy, and availability of

testing kits. The knowledge gained, data gathered, and its interpretation can positively modify behaviour

- Reduce risk(s) -all of the above improve general diabetes control, which may delay, prevent or minimize more complex complications
- Solve problems: this significantly promotes motivation, self-setting achievable goals and independence

Referral to a Diabetes Nurse Specialist / Diabetes Educator/ trained Diabetes Resource Nurse may be necessary for effective patient education and support.

4.4 SELF-MONITORING OF BLOOD GLUCOSE

Hyperglycaemia is a driver of diabetes complications, and tight glycaemic control has been associated with a significant reduction of microvascular complications and, to a lesser extent, macrovascular complications.

Blood glucose monitoring is important, particularly early in the disease process. The benefits of tight glycaemic control persist long after the initiation of glucose-lowering therapy.

Intensive glycaemic control earlier in the disease has a "legacy effect" - whereby the earlier period of intensive control results in better outcomes years later, even after glycaemic control may have deteriorated.

Monitoring Glycaemic Control

Glycaemic control may be assessed by:

- Glycated haemoglobin (HbA1c). It assesses average blood glucose over the previous 2-3 months, most of the results being due to the glucose levels in the past month (about 50%).
- Self-monitoring of blood glucose (SMBG)
- Continuous Glucose Monitoring (CGM) or intermittently scanned CGM

The frequency of HbA1c determination depends on whether the patient is at target and when adjustments are made to treatment or under special circumstances such as pregnancy and other acute illnesses.

Point-of-care HbA1c can be used for monitoring where available but should never be used for the diagnosis of diabetes.

HbA1c also does not measure hypoglycaemia or its frequency or glycaemic variability and thus does not replace SMBG but should be used in conjunction with the SMBG.

There are some limitations of HbA1c: certain conditions give falsely raised or low HbA1c levels.[13] Under the circumstances stated below, SMBG should be relied upon.

- Falsely low HbA1c can be seen in the following instances:
  - Haemolysis
  - Certain hemoglobinopathies
  - Recent blood transfusion
  - Acute blood loss
  - Hypertriglyceridemia
  - Chronic liver disease
  - Splenomegaly
  - End Stage Kidney Disease
  - Drugs – Vitamin C & E
- Falsely raised HbA1c values can be seen in the following instances
  - Iron, folate, and vitamin B12 deficiency
  - Asplenia
  - Alcoholism
  - Uremia
  - Anaemia caused by infections and tumours
  - Hyperbilirubinemia
  - Drugs, e.g. aspirin

Monitoring Glycaemic Control Using SMBG

- SMBG done by patients may help with self-management and medication adjustment, particularly in individuals taking insulin
- Optimal use of SMBG requires regular review and interpretation by the patient and healthcare provider. The frequency also depends on the insulin or other anti-hyperglycaemic regimen being used
- Fasting plasma glucose (FPG) and 2hr postprandial glucose (2hr PPG) targets should generally be 4 – 7mmol/L and 4 – 10mmol/L respectively,

but a tighter or less tight target may be appropriate depending on the patient circumstances

- An FPG of 4 – 6mmol/L and 2hr PPG of 4 – 8mmol/L can be a target for young, newly diagnosed patients without any severe comorbidities or complications and with a long life expectancy and low risk of hypoglycaemia
- Similarly, for patients who are frail, elderly, with multiple comorbidities, hypoglycaemia unawareness and recurrent hypoglycaemia, a 2hr PPG of 7– 12mmol/L can be targeted to prevent morbidity and mortality
- SMBG must be structured and coupled with patient education so that appropriate behaviours can be adopted when agreed targets are not being met and also to empower patients to take remedial action when hypoglycaemia occurs
- If HbA1c is above target whilst FPG is satisfactory, a 2hr PPG should be performed after the day's largest meal. However, if HbA1c is at target, then it is unnecessary to do this
- Do not routinely offer SMBG for adults with Type 2 diabetes unless they are on insulin OR there is evidence of hypoglycaemic episodes, or they are on oral medication that may increase their risk of hypoglycaemia while operating machinery or driving OR they are pregnant or planning on becoming pregnant

Continuous Glucose Monitoring (CGM)

- CGM provides the most comprehensive data on glycaemic control. These meters may give real-time glucose results or must be scanned intermittently to obtain results. It permits the calculation of useful indices such as Time in Range (TIR). TIR is the time you spend in the target blood glucose range, which is between 3.9-10mmol/L for most people.
- These are very useful, especially for patients with Type 1 diabetes on multiple daily insulin injections or Type 2 diabetes patients who are also on more than one daily insulin injections
- These types of blood glucose monitoring can detect hypoglycaemia and glucose variability, and some can alert patients to impending hypoglycaemia so that necessary corrective action can be taken
- Patients who require this technology should be referred to a diabetologist or endocrinologist who has experience in the use of such devices/technology

Time In Range Targets

Type 1 & Type 2 diabetes
Time in range target of >70%; and must spend <4% below range

Gestational Diabetes
Time in range target of 85%; and must spend < 4% of the time below range

Frail patients
Time in range target of 50%, must spend < 1% of the time below range

Summary of General Recommendations

- Individualized Glycemic targets should be set considering the duration of their diabetes, general health, life expectancy and risk of hypoglycaemia
  - HbA1c target of <7.0% in MOST patients is adequate
  - HbA1c should be <6.5% in younger healthy patients without increased risk of hypoglycaemia
  - HbA1c of 7.1-8.5% for patients who are elderly, the frail, those with limited life expectancy, multiple comorbidities, severe cardiovascular disease, advanced chronic kidney disease, hypoglycaemia unawareness and severe recurrent hypoglycaemia, is acceptable
- In patients with stable glycaemic control at the HbA1c target, monitor A1c every 6(six) months, and for those who are not at target and for whom treatment intensification is being planned, repeat HbA1c every 3 months until it is at agreed-upon targets
- Ideally, patients who use insulin 2 – 4 times per day should perform SMBG at least 3 times per day
- Self-monitoring of blood glucose (SMBG) records should be reviewed, interpreted and used by both patient and healthcare provider.
- To titrate their doses, patients on basal insulin should check their SMBG at least once a day (usually the FPG). More frequent testing may be needed to monitor their postprandial glucose (PPG).
- More frequent monitoring may be needed in certain situations or conditions such as periods of poor glycaemic control, recurrent hypoglycaemia, pregnancy, severe or acute illness, fasting during Ramadan

4.5 RECOMMENDATION ACCORDING TO THE LEVEL OF CARE

Facility without doctors

MNT - Refer to a hospital with a dietician
Physical activity - Encourage patients to be more physically active
Educate on Survival skills like:

- Symptoms of hypoglycaemia and how to correct it
- Foot care
- Safe disposal of needles & sharps

Facility with non-specialist doctors

MNT - If there is a registered dietician, refer for MNT. If there is not, advice on a reduced carbohydrate diet with an increase in vegetables guided by the healthy plate model
Physical activity - Rule out loss of protective sensation and encourage structured exercises
Educate as above, Plus

- Basic information on diabetes
- Insulin use

Facility with specialist doctors

MNT – As above

Physical activity

- Rule out loss of protective sensation, encourage structured exercise like daily walking
- Rule out DR before encouraging resistance training

Education – As above

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Chapter 5

PHARMACOLOGICAL THERAPY IN DIABETES

LIST OF ABBREVIATIONS

2HPPG	2-hour Postprandial Glucose
ALT	Alanine Transferase
CKD	Chronic Kidney Disease
CV	Cardiovascular
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPP-4	Dipeptidyl-Peptidase-4
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
HBA1c	Glycated Haemoglobin
NASH	Non-Alcoholic Steatohepatitis
PPAR-γ	Peroxisome Proliferator-Activated Receptor--γ
SGLT-2	Sodium-Glucose Co-Transporter-2
SU	Sulphonylureas
UTI	Urinary Tract Infection
T2DM	Type 2 Diabetes

5.0 INTRODUCTION

In selecting medications for lowering blood glucose, consider the side effect profile and the following patient factors – age, comorbidities, current medications, cost, side effect profile, patient preferences, literacy, and convenience for the patient. The options for pharmacological therapy are orals and injectables. The classes of medications include biguanides, sulphonylurea, thiazolidinediones, incretin mimetics, sodium-glucose cotransporter–2 (SGLT-2) inhibitors and insulin. Pharmacological therapy should go hand in hand with non-pharmacological measures. Medications registered by the Food and Drug Authority must be prescribed as much as possible.

5.1 ORAL GLUCOSE-LOWERING MEDICATIONS

5.1.1 Metformin

Metformin, a biguanide, is usually the first-line recommended medication for patients with Type 2 diabetes. Between 0.6% to 1.2% reduction in HbA1c can be achieved with the use of Metformin.[1] Metformin should be prescribed with caution in patients with renal impairment. The dose of Metformin should be adjusted in accordance with the recommendations in Table 5.1

Table 5.1: Renal dose adjustments of metformin

Estimated GFR	Action to be taken
Less than 30 ml/min/1.73 m^2	Use is contraindicated
Falls below 30 ml/min/1.73 m^2 during therapy	Discontinue therapy
30-45 ml/min/1.73 m^2	Initiating therapy is not recommended
Falls below 45 ml/min/1.73 m^2 during therapy	Reduce to half the maximum dose (1000 mg)
≥ 45 ml/min/1.73 m^2	No dose adjustments recommended

GFR-glomerular filtration rate

Precautions: Iodinated contrast imaging

- Discontinue metformin in patients with eGFR between 30 and 60 ml/min/1.73 m2 before an iodinated procedure is performed.
- Re-evaluate eGFR 48 hours after the imaging procedure and restart metformin if there is no deterioration in renal function

Monitoring parameters:

- Determine renal function before treatment and at least annually. Consider doing this at least twice a year in patients with additional risk factors for renal impairment and suspected deterioration
- Prolonged use of metformin can lead to low serum vitamin B12; hence, it is advised to check serum levels annually

5.1.2 Sulphonylurea (SU)

SUs are well-known oral glucose-lowering medications which are readily available and relatively less expensive. Second-generation SUs such as gliclazide, glibenclamide, glipizide and third-generation SU, glimepiride, are currently prescribed. SUs are associated with an HBA1c reduction of 0.7% -1.6%.[2] Refer to Table 5.2 for dosing information.

Precautions:

Patients with renal and hepatic impairment are prone to hypoglycaemia. In such patients, prescribe low doses and titrate cautiously. Generally, SUs are not recommended in severe renal and liver impairment.

5.1.3 Thiazolidinediones

Currently, pioglitazone is the only one readily available thiazolidinedione in Ghana. Troglitazone has been withdrawn from the market due to severe adverse effects. Thiazolidinediones are not usually associated with hypoglycaemia when used as monotherapy. They reduce HbA1c by 0.9% to 1.7%[3]. Refer to table 5.2 for dosing information.

Precautions:

- May cause or exacerbate heart failure and conditions with fluid overload

- May affect liver enzymes. Monitor liver function before treatment and periodically thereafter. Stop treatment if alanine transaminase (ALT) rises to greater than 3 times the upper limit of normal
- May increase the risk of bone fracture
- May increase the risk of macula oedema. An ophthalmologist review is required if patients experience visual symptoms during therapy.

5.1.4 Dipeptidyl-Peptidase IV(DPP-4) Inhibitors

The use of DPP-4 inhibitors results in the reduction of postprandial and fasting plasma glucose. DPP-4 inhibitors reduce HbA1c by 0.5% to 1.4%.[4] They are used as monotherapy or in combination with other glucose-lowering medications. The risk of hypoglycaemia is minimal and generally weight-neutral.[5] DPP-4-1V inhibitors are linked with a lower risk of developing CV events. Refer to table 5.2 for dosing information.

Precautions:

- Use saxagliptin with caution in patients at risk of heart failure (chronic stable heart failure, chronic kidney disease)
- Generally, dose adjustments are required in renal impairment. No renal dose adjustments are, however, needed for linagliptin.

5.1.5 Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors

The mechanism of action of SGLT-2 inhibitors is independent of the action of insulin but is dependent on the glucose level. They reduce HbA1c by 0.6% - 1.0% when used as monotherapy.[6] SGLT-2 inhibitors are associated with a lower risk of hypoglycaemia. However, the risk is higher when combined with insulin and insulin secretagogues.[7] SGLT-2 inhibitors have been shown to reduce cardiovascular (CV) death and hospitalization for heart failure.[8] Refer to Table 5.2 for dosing information.

Non-glycaemic benefits:

- Weight loss
- Decreases serum uric acid levels
- Lowers systolic blood pressure by about 2–10 mmHg
- Reduces CV death and hospitalization for heart failure.
- Renoprotection

Monitoring Parameters:

- Check the renal function before initiating therapy with SGLT-2 inhibitors or any medications that may reduce renal function, then thereafter annually.
- Monitor for ketoacidosis and temporarily discontinue and evaluate conditions which predispose to ketoacidosis.

Precautions:

- Consider temporary interruption in complicated urinary tract infections
- History of hypotension
- Concomitant use of diuretics (increased risk of volume depletion)
- Use in elderly patients over 75 years
- Glucose-lowering effects are limited when eGFR is less than 30ml/min/1.73m2
- Volume-depleted states: correct condition before initiating therapy
- Risk of euglycaemic ketoacidosis

5.2 INJECTABLE GLUCOSE-LOWERING MEDICATIONS

5.2.1 Glucagon-like peptide-1 receptor agonist

Glucagon-like peptide-1 receptor agonists (GLP-1RA) act in the presence of elevated blood glucose. It decreases postprandial glucose levels, suppresses appetite and food intake resulting in weight loss, reduces the risk of atherosclerotic cardiovascular events, and reduces albuminuria. GLP-1 receptor agonists typically lower A1c by 1-2% [9] Refer to Table 5.2 for dosing information.

Precautions:

- Risk of gastrointestinal adverse effects of nausea, vomiting, diarrhoea, and fluid depletion upon initiation
- Dose adjustments when eGFR is less than 30ml/min/1.73m2 for exenatide and lixisenatide.

5.2.2 Amylin mimetic

Pramlintide

- Pramlintide is a soluble synthetic analogue of human amylin. Amylin is a pancreatic hormone secreted alongside insulin by the pancreatic beta cells in response to nutrient stimuli.
- Amylin secretion in response to nutrients is absent in Type 1 diabetes and impaired in patients with Type 2 diabetes
- Amylin suppresses postprandial glucagon secretion, suppresses appetite, and slows gastric emptying time through effects on the brain
- It is used in Type 1 and Type 2 diabetes patients on meal-time/ bolus/ pre-prandial insulin therapy
- Pramlintide decreases A1c level by up to 0.6%.[10] Postprandial glucose excursions are significantly blunted by pramlintide with minimal effects on fasting glucose levels
- Reduce the dose of rapid-acting meal-time insulin (30-50 %) upon initiation of pramlintide treatment to decrease the risk of hypoglycaemia
- Non-glycaemic benefits include weight loss (approximately 1-3 kg) and reduction in gastric emptying. Refer to Table 5.2 for dosing information

Precautions:

Since pramlintide is administered alongside insulin, the risk of hypoglycaemia is increased.

Careful patient selection is essential: Avoid in those with

- Recurrent severe hypoglycaemia
- Hypoglycaemic unawareness
- Gastroparesis (Other oral medications should be taken one hour before or two hours after pramlintide.

Table 5.2: Medication types, mechanism of action and prescribing information

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Biguanide - Metformin	Decreases: -Hepatic glucose production -Intestinal glucose absorption, Increases insulin sensitivity	Starting dose – Immediate release: 500mg once or twice daily, adjusted weekly modified release: 500mg once daily Maximum dose 2g/day To be taken with food	Contraindications: Metabolic acidosis Liver disease Acute heart failure. eGFR < 30ml/min	Gastrointestinal symptoms Lactic acidosis Hepatitis Skin Reaction Vitamin B12 deficiency
Sulphonylurea Glimepiride	Stimulate insulin secretion from pancreatic beta cells May reduce hepatic glucose production Increase insulin sensitivity	 Starting dose: 1-2mg before breakfast; adjust every 1-2 weeks; maximum dose of 8mg/ day	Contraindications: Hypersensitivity: sulphur allergy DKA Severe renal and hepatic impairment	Hypoglycaemia Weight gain Skin rash

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Gliclazide	Stimulate insulin secretion from pancreatic beta cells	Starting dose: 40-80mg twice a day; maximum dose of 320mg Modified release: starting dose – 60mg once a day titrate to a maximum of 120 mg/day		
Glipizide	Stimulate insulin secretion from pancreatic beta cells	Starting dose- 5mg once a day Maximum dose 20mg for extended-release; 40mg for immediate release		

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Thiazolidinediones Pioglitazone	Increases insulin sensitivity in adipose, muscle, and hepatic tissue by acting as an agonist of peroxisome proliferator-activated receptor--γ (PPAR-γ) nuclear receptors.	Starting dose:15-30mg/ day titrate to a maximum dose of 45mg/day In elderly patients, initiate the lowest possible dose and increase gradually	Indications: Non-alcoholic steatohepatitis Severe insulin resistance Contraindication: Age > 75 years old Congestive heart failure Osteoporosis or risk of osteoporotic fractures bladder cancer Haematuria that has not been investigated. CKD > stage 4 elevated liver enzymes (>2 times the normal upper limit), which have not been investigated.	Weight gain Fluid retention and oedema Increase bone fractures Precipitate or worsen heart failure Numbness

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Dipeptidyl-Peptidase-IV(DPP-4) Inhibitors	Inhibit DPP-4 enzyme activity in plasma to prevent the inactivation of glucagon-like peptide (GLP)-1. increased GLP-1stimulates insulin secretion and inhibits glucagon secretion	eGFR<50ml/ minute/1.73 m2 – reduce to half dose. No dose adjustment is needed for Linagliptin	Diabetic Ketoacidosis Pancreatitis Heart failure or high risk of heart failure (saxagliptin). Liver disease	Upper respiratory tract infection Nasopharyngitis Headaches Urinary tract infection History of pancreatitis
Linagliptin		5mg once a day		
Saxagliptin		2.5 mg - 5mg once daily		
Sitagliptin		100mg once daily		
Vildagliptin		50mg once or twice daily		
Alogliptin		25mg once a day		

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors	Inhibits SGLT-2 in the proximal convoluted tubules of the kidney to prevent glucose reabsorption with increased urinary glucose excretion and reduced plasma glucose.		Indication: Type 2 DM Overweight and obese Established cardiovascular disease Multiple risk factors Contraindications: eGFR<45 ml/min//1.73 m2 Diabetic Ketoacidosis Concomitant use of dapagliflozin and pioglitazone in a bladder cancer patient. Concomitant use of canagliflozin with drugs that increase the risk of fracture History of recurrent genital infection History of recurrent UTI	Increased risk of urinary tract infection Increased Urination Thirst Genital mycotic infections Pruritus generalized Dehydration Euglycaemic Diabetic Ketoacidosis

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Dapagliflozin		5 mg or 10 mg per day		
Empagliflozin		10 mg or 25 mg per day		
Canagliflozin (Not approved in Ghana)		100 mg or 300 mg per day		
Ertugliflozin		Starting dose 5 mg per day Maximum dose 15mg per day		

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Glucagon-like peptide-1 receptor agonist (GLP-1 RA)	Increase insulin secretion Inhibit glucagon secretion Delay in gastric emptying Induce satiety		Type 2 Diabetes Mellitus with or without: Established ASCVD Heart failure Chronic kidney disease Obesity Multiple cardiovascular risk factors Contraindications: eGFR <30ml/min- Exenatide not recommended eGFR <15ml/min – Exenatide and Lixisenatide are not recommended No dose adjustments are recommended for Liraglutide, Semaglutide or Dulaglutide	Nausea Vomiting Diarrhoea Gallbladder disease Injection site reactions

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Liraglutide		SC 0.6mg od for one week; increments of 0.6mg after one week. Maximum dose is 1.8mg		
Dulaglutide		SC 0.75mg once weekly; increase at 4 weeks interval; Maximum dose of 4.5mg once weekly		
Semaglutide		SC 0.25mg once weekly; maximum of 2mg		
Exenatide		SC 5ug bd; maximum dose 10ug bd		
Long-acting exenatide		SC 2mg once weekly		
Lixisenatide		SC 10ug od; Maximum dose 20ug		

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Oral semaglutide		Starting dose: 3 mg once daily; increased to 7 mg once daily after 30 days; may be increased to 14 mg. It must be taken 30 minutes before the day's first meal, with plain water, to facilitate absorption.		

Medication	Mechanism of action	Dosing	Indication/ Contraindications	Side effects
Amylin mimetic Pramlintide	Attenuates postprandial glucagon secretion Enhances satiety and reduces food intake Used in diabetes patients on insulin therapy.	Type 2DM SC pramlintide 60 ug immediately before each major meal. Increase dose to 120 ug after 3 days if no clinically significant nausea occurs. Type 1 DM Starting dose: SC pramlintide 15ug immediately before each major meal. Increase dose by 15 ug every 3 days if no clinically significant nausea occurs. Maximum dose is 60ug Maintenance dose: 30-60ug No dose adjustment in renal impairment	Indication: Type 2 DM Type 1 DM Contraindication: Hypoglycaemic unawareness confirmed gastroparesis.	Nausea Hypoglycaemia

5.2.3 Insulin

- Insulin is a peptide hormone produced by beta cells of the pancreatic islets. It is the main hormone that regulates the metabolism of:
  - Carbohydrates - through hepatic gluconeogenesis and glycogenolysis
  - Fats -inhibition of lipolysis
  - Protein – inhibition of protein breakdown
- It promotes glucose uptake and utilization by skeletal muscles and adipose tissue
- Insulin is the only therapeutic option for Type 1 diabetes and can also be used in the management of Type 2 diabetes alongside other therapies or as monotherapy
- Both human and analogue insulins are approved for use in Ghana. See Table 5.3 for details
- Insulin formulations come in different concentrations; the only approved concentration in Ghana is 100 units/ ml
- Insulin may be delivered using syringes, pens and pumps (see Table 5. 4 for details)

Indications for insulin therapy:

- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
  - Patients not achieving glycaemic targets after 3 months on optimized doses of 2 or 3 oral glucose-lowering agents
  - Evidence of weight loss in the presence of hyperglycaemia with no other identifiable cause
  - Patients with HbA1c >10% at the time of new diagnosis
  - Persistent plasma glucose elevations over 3 days in stable individuals on optimized doses of 2 or 3 oral glucose-lowering agents with no acute medical conditions and not on corticosteroids
    - Fasting plasma glucose >14mmol/l
    - Random plasma glucose >16.7mmol/l
  - Hyperglycaemia in patients with acute medical or surgical conditions or pregnancy
- Diabetic ketoacidosis or hyperosmolar hyperglycaemic state
- Gestational diabetes (GDM)

Side effects of insulin therapy:

- Hypoglycaemia
- Weight gain
- Lipodystrophy at injection sites
- Local or systemic allergic reaction – rare with modern insulin

Table 5.3 Types of insulin

Type of Insulin	Onset of Action	Duration of Action	Examples	Other Properties	Advantages	Disadvantages/ Drawback
Rapid-acting/ Ultra short-acting Insulin analogues	5 – 15 minutes	3-4 hours	Insulin lispro, aspart, glulisine	Immediately before or with a meal. Usually used with longer-acting insulin	Faster onset of action but shorter duration of action	Relatively more expensive
Short-acting	30 minutes	5-8 hours	Regular insulin/ soluble insulin	30 minutes before a meal	Less expensive than ultra-short-acting analogues Commonly used insulin in emergencies	Timing of injection with meals may be a challenge for patients Increased risk of hypoglycaemia
Intermediate-acting insulin (Human or analogue insulin)	1 - 2 hours	14 - 24 hours	NPH insulin	Once or twice a day, 30 minutes before breakfast and dinner	Less expensive than long- and ultra-long-acting insulin analogues	increased risk of hypoglycaemia

Type of Insulin	Onset of Action	Duration of Action	Examples	Other Properties	Advantages	Disadvantages/ Drawback
Long-acting (basal) insulin	2 hours	20- ≥24 hours	Detemir, Insulin glargine (U-100)	Once daily dosing	Less nocturnal hypoglycaemia compared to NPH	Cost
Ultra-long-acting insulin	30-90 minutes	Up to 42 hours	Glargine U-300, Insulin degludec	Once daily dosing	Least risk of hypoglycaemia	Cost
Premixed insulin – human insulin	30minutes	10-20hours	Premixed 30/70 50/50	Taken 30 minutes before a meal Twice daily regimen Initial dosing is a ratio of two-thirds total daily requirement given before breakfast and one-third before dinner	Less expensive than insulin analogue	Higher hypoglycaemia compared to basal insulin

Type of Insulin	Onset of Action	Duration of Action	Examples	Other Properties	Advantages	Disadvantages/ Drawback
Premixed -insulin analogue	5-15 minutes		Biphasic insulin aspart Biphasic insulin lispro	Immediately before or with a meal	Less hypoglycaemia than premixed human insulin	cost

Table 5.4 Insulin Delivery devices

Insulin delivery device	Description	Advantages	Disadvantages
Vials and syringes	There are 0.3, 0.5 and 1-millilitre syringes available. The 0.3ml is preferred if the insulin dose does not exceed 30 units per injection 1 ml syringe is seldom required for up to 100units of insulin	Less expensive compared to insulin pens and pumps	Inaccurate dosing of insulin due to human errors Painful injection compared to insulin pens

Insulin delivery device	Description	Advantages	Disadvantages
Pens	Insulin pens have fixed or replaceable needles The disposable pen contains a prefilled insulin cartridge to be discarded once the cartridge is used up Reusable insulin pen: contains an insulin cartridge that can be replaced once empty Modern insulin pens are more accurate and equipped with safety features such as audible clicks with each dose to improve accuracy and decrease chances of human dosing errors	More accurate compared to vials and syringes Less painful injections User friendly	Expensive compared to vials and syringes

Insulin delivery device	Description	Advantages	Disadvantages
Pumps	For continuous subcutaneous insulin infusion(CSII) Insulin pumps deliver rapid-acting insulin throughout the day	More effective in achieving glycaemic goals compared to multiple daily injections using insulin Reduced hypoglycaemic episodes Reduced glycaemic variability (episode of hypo- and hyperglycaemia) Improved patient satisfaction Improved quality of life	Expensive compared to multiple daily injections Increased subcutaneous infection Inconvenience of being attached to a device Higher risk of diabetic ketoacidosis in case of an infusion set failure, dislodgement or occlusion Requires patient education and motivation to avoid complications.

5.3 THERAPEUTIC OPTIONS IN TYPE 2 DIABETES

Early diagnosis and more aggressive treatment of blood glucose levels are associated with improved clinical outcomes.

Discuss the benefits and risks of drug treatment and the options available with the patient.

Base the choice of drug treatment(s) on the following (Figure 5:1):

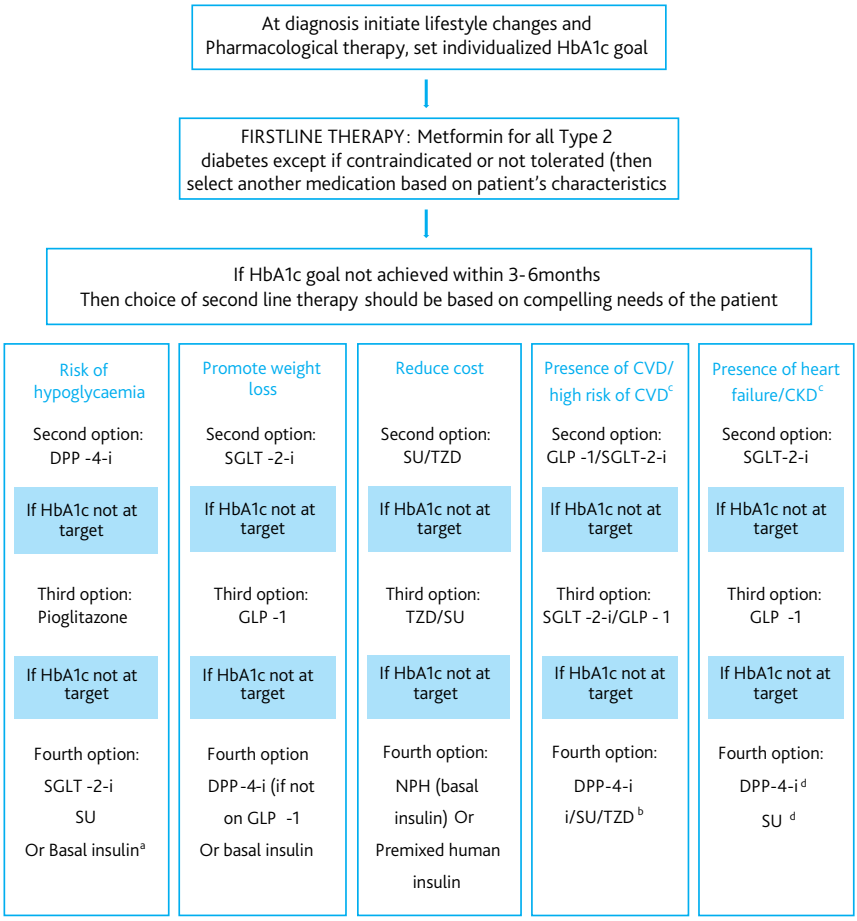
- The effectiveness of the drug treatment(s) in terms of metabolic response
- Safety
- The person's clinical circumstances, comorbidities, risks from polypharmacy, risk of hypoglycaemia, obesity, and the individual preferences and needs
- The licensed indications or combinations available
- Cost

Glycaemic Targets

The following glycaemic targets are recommended: FPG 4.5-7.0mmol/L, 2HPPG <10mmol/L, and HbA1c <7 %. These must however be individualized according to patient characteristics such as age, co-morbidities, duration of diabetes, and life expectancy.

How to Initiate Insulin in Type 2 Diabetes

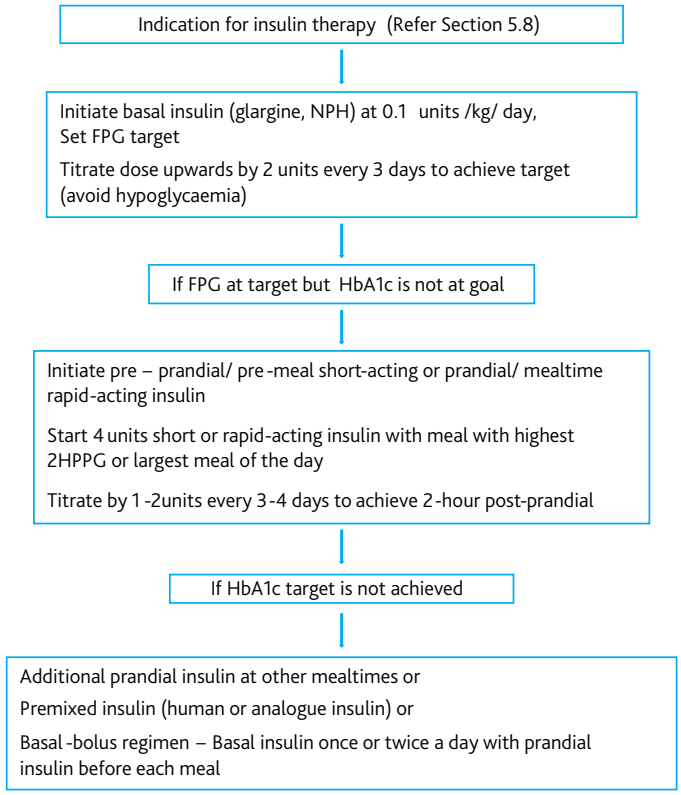
The indications for insulin therapy have been discussed in Section 5.8. Figure 5.2 describes how to initiate and intensify insulin therapy in Type 2 diabetes.



DPP-4-i: dipeptidyl peptidase-4 inhibitors; GLP-1: glucagon-like peptide-1 analogue; SGLT-2-i: sodium glucose cotransporter-2 inhibitor; SU: sulphonylurea; TZD: thiazolidinedione

[a] With low risk of hypoglycaemia, [b] If GLP-1 and SGLT-2-i not available or contraindicated
[c] For facilities with doctors
[d] DPP-4-i (Linagliptin) and SU (Gliclazide) with proven safety in HF or CKD

Figure 5.1: Algorithm for T2DM treatment



2HPPG: 2-hour Postprandial Glucose; FPG: Fasting Plasma Glucose

Figure 5.2 Insulin initiation and intensification for Type 2DM

5.4 LEVELS OF CARE FOR PHARMACOLOGICAL THERAPY

Facilities without a doctor:

Can prescribe or provide a refill of metformin, sulphonylurea, and thiazolidinedione after review by a doctor

Facilities with non-specialist doctors

Can prescribe all glucose-lowering medications (if expertise allow)

Facilities with a specialist

Can prescribe all glucose-lowering medications

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Chapter 6

ACUTE COMPLICATIONS OF DIABETES MELLITUS

LIST OF ABBREVIATIONS

CVA	Cerebrovascular Accident
DKA	Diabetic ketoacidosis
EDKA	Euglycaemic ketoacidosis
GCS	Glasgow Coma Score
HDU	High Dependency Unit
HHS	Hyperglycaemic Hyperosmolar State
HONK	Hyperglycemic Hyperosmolar Non-ketotic Coma
IM	Intramuscular
IV	Intravenous
K	Potassium
KCl	Potassium Chloride
NS	Normal saline
SBP	Systolic Blood Pressure
SC	Subcutaneous
SGLT-2	Sodium Glucose Co-transportor-2
SU	Sulphonylurea

6.0 INTRODUCTION

Complications occurring in diabetes may be either acute or chronic. The underlying pathophysiology of acute complications is a recent elevation in blood glucose levels over several hours or days, while that for chronic complications is longstanding hyperglycaemia and other risk factors. Chronic complications may be microvascular or macrovascular (Table 6.1).

Table 6.1: Complications of Diabetes Mellitus

Acute complications	Chronic complications
Diabetic ketoacidosis (DKA)	Microvascular • Neuropathy • Nephropathy • Retinopathy
Hyperglycaemic Hyperosmolar State (HHS)	Macrovascular • Ischaemic stroke • Peripheral vascular disease • Coronary heart disease
Hypoglycaemia (Treatment-induced)	
Lactic acidosis	

6.1 DIABETIC KETOACIDOSIS (DKA) & HYPERGLYCAEMIC HYPEROSMOLAR STATE (HHS) IN ADULTS

The main acute hyperglycaemic emergencies in diabetes are diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS), the latter formerly referred to as hyperosmolar non-ketotic state (HONK). Both conditions are potentially life-threatening and must be identified and managed promptly.

Type 1 diabetes patients are more at risk of developing DKA compared to Type 2 patients. It is often the first manifestation of newly diagnosed diabetes, and in such patients, the majority will be Type 1, and about 15% will be Type 2.[1]

On the other hand, HHS occurs in Type 2 diabetes individuals who commonly have multiple co-morbidities. It is associated with a higher mortality rate than DKA[2]. HHS typically occurs in adults, but with the increasing prevalence of Type 2 diabetes in children, adolescents and young adults, its prevalence has increased in younger individuals.[2-4]

The clinical presentation of DKA and HHS are similar in many ways but must be differentiated. Both are associated with hyperglycaemia, metabolic derangements, and fluid deficits, but these are more severe in HHS. The clinical presentation of DKA evolves rapidly over a few hours, whereas HHS may occur over days to weeks.

6.2 DIABETIC KETOACIDOSIS

Pathophysiology of DKA

DKA results when there is absolute or relative insulin deficiency. Absolute insulin deficiency occurs in Type 1 diabetes, whilst relative insulin deficiency occurs mainly in individuals with Type 2 diabetes whose endogenous insulin production is insufficient for glucose, fat and protein metabolism.

Absolute or relative insulin deficiency results in poor glucose uptake by tissues (resulting in hyperglycaemia) and the associated increase in counter-regulatory hormones, i.e. glucagon, cortisol, growth hormone, and epinephrine.[5] This situation leads to lipolysis with the accumulation of ketone bodies (beta-hydroxybutyric acid, acetone, and acetoacetate). The accumulation of ketone bodies may induce nausea and vomiting, whilst the acetone results in the characteristic fruity breath of patients with DKA.

Hyperglycaemia leads to glucosuria and osmotic diuresis in DKA, which may result in hypovolaemia, hypotension and acute kidney injury.[6] Metabolic acidosis and electrolyte disturbances, particularly hypokalaemia, often accompany fluid loss.

It is important to note that, particularly in DKA, significant total body loss of potassium may not always be accompanied by low serum potassium.

Causes/ predisposing factors

- Infections
- Severe acute conditions (e.g. myocardial infarction, stroke, trauma etc.)
- Missed insulin doses or non-compliance with medications
- Undiagnosed diabetes/First presentation
- Other causes are insulin pumps or catheter blockage, medications (corticosteroids, diuretics etc.)

Symptoms	Signs
• Polyuria • Polydipsia • Nocturia • Dehydration • Lethargy • Nausea • Vomiting • Abdominal pain (may present as 'acute abdomen') • Anorexia • Weight loss • Altered consciousness disorientation, confusion • Symptoms of the precipitating illness, e.g. fever in infection, chest pain in acute coronary syndrome	• Ill-looking • Dehydration • Tachycardia • Hypotension • Tachypnea with deep breaths ('acidotic breathing' or 'Kussmaul breathing') • Fever (infection) • Confusion, disorientation, or coma

Diagnosis

Diagnosis is based on a triad of hyperglycaemia, ketonaemia/ketonuria and acidosis.

- Blood glucose ≥11.1 mmol/l or known diabetes regardless of blood glucose level (euglycaemic DKA)
- Ketonuria ≥2+ or ketonaemia ≥3mmol/l
- Bicarbonate (HCO3)<15.0mmol/l and /or venous pH <7.3, anion gap >10

In the absence of blood gases, demonstrating hyperglycaemia and ketonuria/ ketonaemia may be sufficient to diagnose DKA.

Euglycaemic ketoacidosis DKA (EDKA)

EDKA may occur with blood glucose levels of less than 11.1mmols/L in Type 1 and Type 2 Diabetes. A high index of suspicion is needed to diagnose it.

Factors associated with euglycaemic ketoacidosis (EDKA)

- Use of SGLT-2 inhibitors
- Pregnancy
- Low caloric intake/starvation/fasting
- Cocaine intoxication
- Prolonged vomiting or diarrhoea
- Insulin pump use
- Prior treatment with intravenous fluids and or insulin

Investigations according to Level of Care

Facility without a Doctor (Level 1)

Assess blood glucose level using a glucose meter
Urine dipstick for ketones, if available

Facility with a Doctor

- Blood glucose
- Urine Ketones (≥2+)
- Serum electrolytes and creatinine
- Full blood count
- Bicarbonate levels (if available)
- HbA1c (optional)
- Anion Gap = ($[Na^+ + K^+] - [Cl^- + HCO^{3-}]$) >10-12mEq/L in mild cases; >12mEq/L in moderate to severe disease
- Renal function studies- This may be impaired by severe dehydration, causing prerenal failure
- Investigating precipitating events
    - Blood film for malaria parasites or rapid tests
    - Cultures- blood, urine
    - ECG, cardiac enzymes
    - Serum amylase

- Antigen test or PCR for epidemic/pandemic viruses
- Chest X-rays, MRI, CT scan

Facility with a Specialist Doctor

As for Facility with a Doctor plus:

- Serum capillary beta-hydroxybutyric acid levels (where available)
- Arterial/venous blood gases (where available)

Management according to the Level of Care

The steps involved in the management of DKA are summarized in Figure 6.1 below

Facility without Doctors (Level 1)

DKA must not be managed at this level of care; however, if symptoms and signs are suggestive and blood glucose is 13mmol/l and above, set up 500-1000 ml of normal saline and refer to the next level of care. Patients must be encouraged to drink water in transit if they can tolerate it.

Facility with non-specialist doctors and specialist doctors (Levels 2 & 3)

Principles of management

1. Correction of fluid deficit
2. Correction of electrolyte abnormalities
3. Reduction of hyperglycaemia
4. Reversal of acidosis and ketosis
5. Identifying and managing the underlying causes/ precipitants

Correction of fluid and electrolyte abnormalities

Correction of fluid and electrolyte abnormalities is an important aspect of management in the first hour of treatment. Even mild dehydration may signify severe fluid deficit; correcting fluid often improves acidosis.

Initiate rapid IV fluid replacement to correct hypovolaemia, hyperosmolality and acidosis.

The initial fluid of choice for DKA is isotonic saline/ 0.9% saline (normal saline), aiming at giving about a total of 4 litres within 4 hours. Attempt to correct fluid deficit within 24 hours

- 1litre in the first 30 mins
- 1litre in the next 1 hour
- 1litre in the next 2 hours
- 1litre in the next 4 hours

If serum sodium is above the upper limit, consider 0.45% saline as the fluid of choice.

Ensure patients are examined frequently for hydration, monitor urine volume, and examine lung bases for pulmonary oedema.

When blood glucose reaches 13 mmol/L, switch to dextrose saline. It allows insulin to be given to correct acidosis whilst preventing hypoglycaemia.

Aim to replace about 50% of fluid losses in the first 12 hours and the remainder in the next 12 hours (fluid loss is estimated to be 10% of body weight).

In centres with specialists, in addition to the above, central venous pressure measurements via continuous telemetry should be done when available.

Electrolyte Correction

Assess the electrolyte status of the patient and correct. Remember that insulin may precipitate dangerous hypokalaemia. Initial hyperkalaemia may be due to insulin deficiency, causing an extracellular shift of potassium. The average potassium deficit is typically 300-600mEq. Potassium replacement should be done using IV potassium chloride (KCl) in IV fluids based on the potassium charts below.

Even when serum potassium levels are normal, there may be considerable intracellular potassium deficit (whole-body potassium).

Electrolyte correction:

- K+ >5.5 mmol/L- do not give potassium (this may be rechecked after adequate hydration)
- K+ 3.3-5.5mmol/L start 20- 30 mmol/L/hr of potassium chloride (KCl) in 1000mls of saline
- K+<3.3 mmol/L (DO NOT INITIATE INSULIN), give 20-40 mmol/L /hr until K+ >3.3 mmol/L

If potassium levels cannot be checked immediately, monitor urine output. If urine output is adequate, i.e. at least >30ml/hour, give 20-40 mmol of KCI in each litre of fluid and start insulin.

Insulin Therapy in DKA

A few considerations to note before insulin therapy [7, 8]:

- Insulin is needed if there is acidosis, hence the need to give a dextrose solution when blood glucose levels drop to 13 mmol/l
- Avoid large drops of blood glucose (>5.5 mmol/L/hour is not desirable)
- Avoid hypoglycaemia, as activation of counter-regulatory hormones may result in ketosis
- IV regular insulin should be used as it is readily available, cheaper and as effective as IV rapid-acting insulin analogues in managing DKA. [9]

Recommendations

1. Administer IV insulin infusion at 0.1 units/kg/hour via perfuser in severe DKA who have potassium of >3.3 mmol/L or are passing adequate urine (at least >30-50ml/hour) and have started potassium replacement. The rate should be reduced to 0.05u- 0.075u/kg/hour when blood glucose drops to 11.1mmol/h and normal saline is changed to dextrose infusion.

   Under Specialist level care only, long-acting insulin may be added during the initial management if the patient is already on a long-acting basal analogue with good monitoring.

2. IM insulin (modified Alberti's regime) can be used in mild-moderate DKA, and when IV insulin infusions cannot be administered [10, 11] Insulin can be given at a dose of 0.3u/kg, then 0.1units/kg every hour until

the serum glucose is less than 13.0 mmol/L. Normal saline is then switched to dextrose saline, and insulin is decreased to 0.05-0.75 units/kg hourly until the resolution of ketoacidosis. Although sliding scale is not encouraged, it may be used when serum glucose is less than 13-15 mmol/L.

IV (infusion) or IM Insulin must be continued until the patient is out of acidosis, is conscious and is eating normally; then SC insulin may be initiated. IV insulin and SC insulin should overlap for about 30 mins- 1 hour to avoid rebound ketosis when using human insulin; however, this overlap may not be needed if the analogue insulins are used.

- In patients on insulin before DKA, their previous dose can be restarted
- Insulin naive patients can be given 0.5-0.8units/kg/day divided as:
    - 50% basal insulin and 50% prandial in divided doses (basal-bolus) when the patient can tolerate food. This method is preferred.
    - Biphasic/premix insulin could be used by giving 60-70 % (2/3) in the morning and 30-40 % (1/3) in the evening.

Correction of Acidosis

Insulin will inhibit lipolysis and help correct acidosis; the use of bicarbonate is generally not recommended except in the ICU setting, where patients can be monitored.[12]

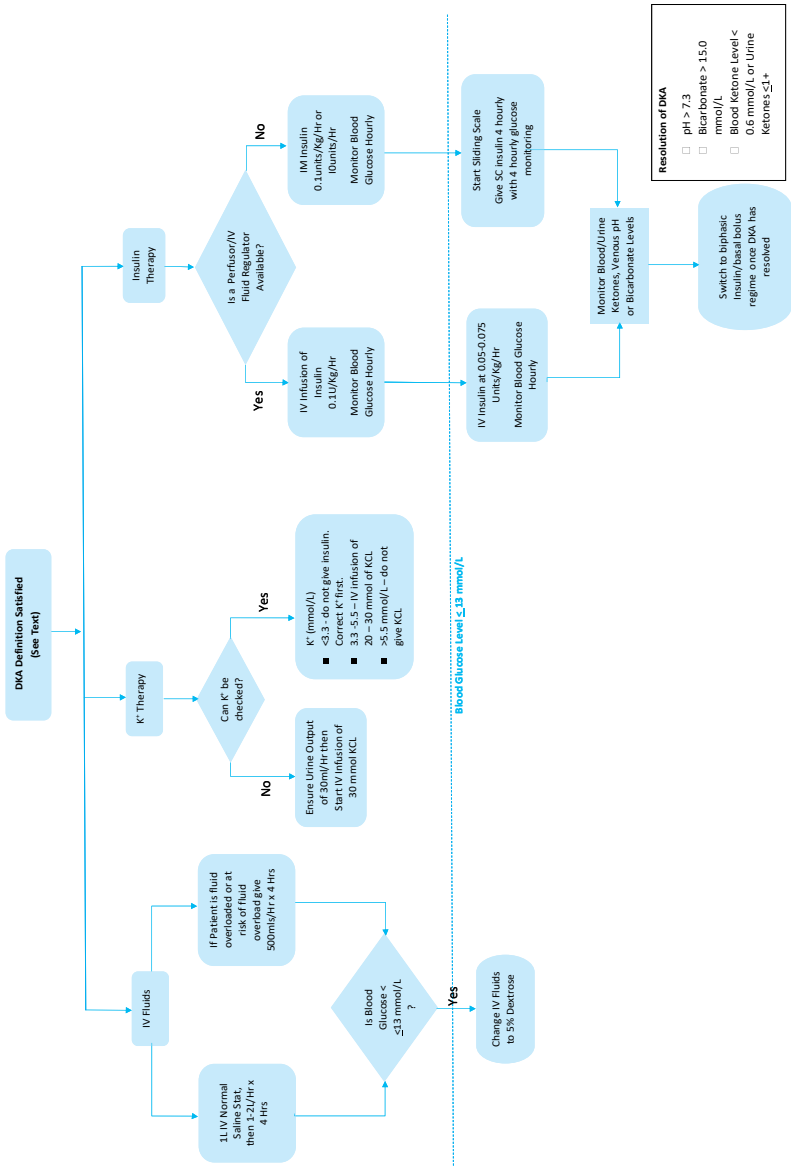

Figure 6.1: Algorithm for the Management of Diabetes Ketoacidosis in Adults

Treat precipitating causes

Treat any precipitating factor such as myocardial infarction, CVA and infection as appropriate.

Monitoring

- Serum glucose should be measured every hour
- Serum electrolyte sodium (Na^+) and potassium (K^+) should be measured every 6 hours to inform treatment and must be documented in a flow sheet
- Bedside ketone meters can be used to monitor acidosis; when not available, venous pH or urine ketones can be used

Any one of these may indicate severe DKA and may require admission into HDU[13]

- Venous/ arterial pH <7.0
- Hypokalaemia<3.5mmol/l
- GCS<12
- Oxygen saturation <92%
- Systolic blood pressure (SBP) <90mmHg
- Pulse >100bpm or <60bpm
- Anion gap >16 [anion gap=$(Na^+ + K^+)-(Cl^- + HCO^{3-})$]
- Blood ketones >6mmol/L
- Bicarbonate level <5mmol/l

Complications of DKA include

• Acute kidney injury • Myocardial infarction • CVA • Deep vein thrombosis • Erosive gastritis • Septicaemia • Mucormycosis • Rhabdomyolysis	• Cerebral oedema is more common in young children (often occurs during management when there are rapid changes in blood glucose levels) • Non-anion gap hyperchloraemic metabolic acidosis due to urinary loss of ketoanions needed for bicarbonate regeneration and reabsorption of chloride in proximal renal tubule in the presence of administering chloride-containing fluids

Resolution of DKA is defined as:

- pH > 7.3
- bicarbonate > 15.0mmol/L
- Blood ketone level < 0.6mmol/l (or urine ketones ≤1+ if blood ketone testing not available)

Urine ketones are not a good measure of resolution because ketonuria >1+ may occur in the absence of ketonemia when beta-hydroxybutyric acid is converted to water-soluble acetoacetate for excretion and may take up to 36 hours to be negative.

Recovery phase

- Encourage early mobilization and good nutrition.
- Continue IV fluids if intake is not adequate.
- Most patients should be discharged home on SC insulin; however, newly diagnosed T2DM patients and those on orals should be considered for oral hypoglycaemics after a period of stability (weeks or months).
- Provide diabetes education to all patients to reduce the risk of recurrence and prevent complications.
- Arrange follow-up by the diabetes team.

Prevention of DKA

Every patient diagnosed with DKA must be educated on diabetes mellitus in general, particularly on diabetic ketoacidosis, i.e., risk factors, signs and symptoms and prevention before discharge from the hospital.

Never stop insulin in Type 1 diabetes patients. If such a patient is so ill and cannot eat because of anorexia, vomiting or ill health, they may have to be detained and given IV fluids, glucose, and insulin.

Patient Education

- Patients must realize that symptoms of hyperglycemia, weight loss, abdominal pain, and sweet fruity breath may warrant seeing a health care practitioner
- Sick day rules- during ill health:

- Sugar- check your blood sugar more often than usual
- Insulin must be continued even during ill health. Insulin dose may increase during ill health
- Carbohydrates must be taken in, especially if sugar is getting low
- Blood or urine ketones must be checked frequently, flushed out with lots of fluids

The following groups of people should be managed by specialists or in centres with expertise in managing DKA:

- Elderly
- Pregnant women
- Persons younger than 25 years, and
- Heart or kidney failure.

6.3 HYPERGLYCAEMIC HYPEROSMOLAR STATE (HHS)

Introduction

The pathophysiology, precipitating factors, and management principles of HHS have many similarities with DKA. This section highlights the peculiar differences between HHS and DKA.

Pathophysiological differences

There is variable relative insulin deficiency which is further heightened by stressful situations. It is not entirely known why HHS produces less ketones. Even though there is inadequate insulin for glucose utilization, it is probably enough to prevent lipolysis. Lower free fatty acid levels and higher portal vein insulin levels are also found.

Clinical characteristics

- HHS tend to evolve over several days to weeks
- HHS is associated with a higher degree of dehydration
- Less ketosis (usually 1+) and acidosis
- High blood glucose, often 30mmol/L or more
- High plasma osmolality, usually 320 mosmol/kg or more

- In HHS, there may be acute focal and global neurological changes such as drowsiness, lethargy, delirium, focal or generalized seizures, visual changes or disturbance, hemiparesis, and sensory deficits
- Mortality rate in HHS ranges from 10-50%, depending on the underlying cause

Principles of management

Refer to the principles already discussed under DKA. Less insulin is usually required compared to DKA.

Fluids

- In HHS, IV fluid (N/S) should be given at a rate of 15-20ml/kg/hr or more in the first hour but not exceed 50ml/kg in the first 4 hours[14]. Give 1 litre over 1 hour, then 0.5 to 1L/hr. Very rapid fluid correction may also compromise cardiovascular status among elderly frail patients

Insulin

- Do not start insulin immediately when there are no significant ketones
- Start insulin if the rate of fall of blood glucose <5mmol/L/hr after 2 hours
- Start insulin at a rate of 0.05iu/kg/hr
- Start 5% dextrose if blood glucose falls below 13mmol/L

Sodium

- There may be hypo/hypernatraemia. Pseudohyponatraemia results from hyperglycaemia as sodium draws water into the vascular space. Sodium can be corrected for hyperglycaemia using; Corrected Na = Na + ([Glucose-5]/3.5) mmol/L

Severity of HHS

The following may indicate severe HHS and may indicate admission into a high dependency unit (HDU)[15]:

• Osmolality >350mosmol/kg • Serum sodium >160mmol/L • Venous/arterial pH<7.1 • Hypokalaemia (<3.5mmol/L) or hyperkalaemia (>6mmol/L) on admission • Glasgow coma scale <12 or abnormal AVPU (Alert, Voice, Pain, Unresponsive) scale • Oxygen saturation <92% on room air (assuming normal basal respiratory function)	• Systolic blood pressure <90mmHg • Pulse >100bpm or <60bpm • Urine output <0.5ml/kg/hr • Serum creatinine >200umol/L • Hypothermia • Macrovascular events such as myocardial infarction or stroke

In HHS, myocardial infarction, stroke and peripheral arterial thrombosis are thrombotic complications that may occur; therefore, patients with HHS may require prophylactic heparin.

Resolution of HHS

- Blood glucose <11mmol/l with normal osmolality
- When the calculation of osmolality is not possible, use the clinical picture, i.e. the patient is well hydrated, conscious and eating well

Venous and arterial thrombosis

Because of the high osmolality associated with HHS, consideration must be given on a case-by-case basis for anticoagulation, especially among those with co-morbidities.

Cerebral oedema

HHS patients are generally more dehydrated, older and very hyperosmolar, there is therefore an increased risk of complications such as cerebral oedema with rapid correction.

6.4 HYPOGLYCAEMIA

Introduction

Hypoglycaemia has been defined as a blood glucose level that is low enough to expose the individual to harm. It is considered a treatment-related event associated with the use of anti-hyperglycaemic medications and not as a complication of diabetes.

A specific value does not define it because glucose thresholds that set off symptoms are variable between individuals with diabetes. However, in patients with diabetes on glucose-lowering medications, blood glucose < 3.9 mmol/l is considered hypoglycaemia. It is a barrier to good glycaemic control in patients with diabetes and must be avoided as much as possible. It is more common in patients with Type 1 diabetes and Type 2 diabetes on insulin and insulin secretagogues (medications that promote increased endogenous insulin release) such as sulfonylureas and meglitinides.

While we aim to get patients to maintain optimum glucose levels at home, this must be done safely by reducing the risk of hypoglycaemia. This is usually achieved through patient education and patient empowerment through:

- Encouraging regular self-monitoring of blood glucose
- Individualizing glucose targets for each patient
- Providing patients with flexible and rational insulin regimes

Risk factors for hypoglycaemia

- Long duration of diabetes
- Older age
- History of severe hypoglycaemia (especially if recent)
- Tight glycaemic control, i.e. lower glycemic targets
- Exercise
- Alcohol consumption
- Chronic kidney disease
- Chronic liver disease
- Autonomic neuropathy

Causes of hypoglycaemia

Hypoglycaemia is often caused by relative or absolute insulin excess and includes but is not limited to the following:

- The use of insulin or insulin-secreting drugs, especially when it is the wrong type of insulin, the dose is too much, or it is ill-timed
- Reduced glucose intake (fasting, missed meals or reduction in portions)
- Reduction in glucose production, e.g., alcohol and liver disease
- Increased glucose utilization (during and after exercise)
- Increased response to insulin – middle of the night, weight loss
- Reduced insulin clearance, e.g. renal failure

Signs and symptoms of hypoglycaemia

The specific point at which symptoms start may differ between individuals and even in the same individual differ from time to time. The value at which symptoms start may be higher in individuals with poorly controlled diabetes, known as relative hypoglycaemia.

Symptoms of hypoglycaemia are broadly divided into autonomic/adrenergic and neuroglycopaenic symptoms.

***Autonomic symptoms**: tremors, palpitations, anxiety, sweating, hunger, paresthesia.*

***Neuroglycopaenic symptoms:** weakness/ fatigue, dizziness/ visual changes, inappropriate behaviour, focal neurological deficits, drowsiness, delirium, confusion, seizures and coma.*

6.4.1 Management of Hypoglycaemia

Hypoglycaemia is a dangerous emergency for every patient with diabetes. It is prudent to identify risk factors that predispose to hypoglycaemia and individualize preventive and treatment strategies.

Generally, all patients must be asked at every visit of:

- Symptoms of hypoglycaemia
- Records of low blood sugar
- Episodes of hypoglycaemia requiring assistance from others

Level 1- Facilities without Doctors

Asymptomatic

When the patient records < 3.9mmol/l blood glucose, ingest fast-acting 15g glucose or carbohydrates, recheck blood glucose in 15 minutes, and repeat if 15g of glucose is still low.

15 g of glucose is equivalent to:

- 150-175 ml of glucose-containing drink
- 1 tablespoon granulated/ 2 cubes of sugar
- 1 tablespoon or 15 ml of honey
- 1 hard candy/toffee
- 3-4 glucose tablets

Symptomatic

If conscious and able to swallow, give 15g of fast-acting carbohydrates as described under asymptomatic management.[16]

Repeat the test after 15 minutes, and if still < 3.9mmol/l, repeat 15g of glucose and follow up with a snack/ meal

Severe

Severe hypoglycaemia is an emergency requiring another person's help to correct it.

IV access available

- IV 50 ml of 50% dextrose (line must be flushed with saline after this)
- 10 % (250 ml) IV dextrose is preferred because it is a less irritant to the veins compared to 50% dextrose
- Often, the effect of dextrose is transient and must be followed up by a continuous infusion of dextrose (5% or 10%) or ingestion of food if tolerable.

IV access unavailable

- IM glucagon 1mg; may be given, but there may be associated nausea and vomiting.
- Glucagon may not be useful in patients with chronic liver disease
- After resuscitation, refer to a higher level of care

Level 2 and level 3-Facilities with non-specialist doctors and specialist doctors

As for Level 1, and investigate the cause and correct it. The type, timing and dose of medication, renal and hepatic function, liver function and other possible hypoglycaemia causes must be checked.

If the patient is on an alpha-glucosidase inhibitor, only pure glucose will be effective as the drug inhibits the absorption of disaccharides.

6.4.2 Prevention of Hypoglycaemia

- All patients must be educated and empowered to identify and reverse hypoglycaemia at the first visit and frequently thereafter
- Patients must be encouraged to own and use a glucose monitoring device frequently, particularly when they have symptoms of hypoglycaemia
- With physician guidance, insulin use must be individualized, rational and, where possible flexible
- Individualized glycaemic goals and giving higher targets in patients at high risk for hypoglycaemia
- Use insulin secretagogues with caution in individuals who are at risk of hypoglycaemia, such as the elderly
- Friends and family should be educated to recognize the symptoms of hypoglycaemia and how to manage it

Management under specific circumstances

Impaired awareness of hypoglycaemia/hypoglycaemic unawareness

Some patients may not get autonomic symptoms during an episode of hypoglycaemia. This is known as hypoglycaemic unawareness and is potentially life-threatening and must be avoided at all costs. Hypoglycaemic

unawareness can be corrected often by keeping blood glucose targets high between 8-10mmol/l for 2 -3 weeks.[17]

Risk factors for hypoglycemic unawareness include:

- Recurrent hypoglycaemia
- Old age
- Autonomic neuropathy

Sulphonylurea (SU) induced hypoglycaemia

Sulphonylurea-associated hypoglycaemia may be prolonged and require detaining the patient for up to 48 hours to administer dextrose infusion and regular monitoring.

6.4.3 Complications

- Falls and Fractures
- Arrhythmias
- Seizures
- Strokes
- Cognitive deficits
- Unexplained death

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Chapter 7

CHRONIC COMPLICATIONS OF DIABETES MELLITUS

LIST OF ABBREVIATIONS

ACEI	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AGEs	Advanced Glycated End Products
VEGF	Vascular Endothelial Growth Factor
ARB	Angiotensin Receptor Blocker
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
Cmax	Maximum or Peak Concentration
CPAP	Continuous Positive Airway Pressure
CVD	Cardiovascular Disease
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DN	Diabetic Nephropathy
DPP-4	Dipeptidyl Peptidase-4
DR	Diabetic Retinopathy

ED	Erectile Dysfunction
eGFR	Estimated Glomerular Filtration Rate
ESKD	End Stage Kidney Disease
FBC	Full Blood Count
FBG	Fasting Blood Glucose
GLP-1 RA	Glucagon-like Peptide 1 Receptor Agonist
HBA1c	Glycated Haemoglobin
MI	Myocardial Infarction
MNSI	Michigan Neuropathy Screening Index
MRAs	Mineralocorticoid Receptor Antagonists
NDMRC	National Diabetes Management and Research Centre
PDE5i	Phosphodiesterase 5 Inhibitors
PGE1	Phosphodiesterase prostaglandin 1
PKC	Protein Kinase C
PSN	Peripheral Sensory Neuropathy
RBG	Random Blood Glucose
RASi	Renin-Angiotensin System Inhibitors
SGLT2	Sodium Glucose Cotransporter 2
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
TZD	Thiazolidinediones
VTDR	Vision Threatening Diabetic Retinopathy
WHO	World Health Organisation

7.0 INTRODUCTION

The chronic complications of diabetes mellitus broadly include microvascular (neuropathy, nephropathy, and retinopathy) and macrovascular complications (cerebrovascular disease, peripheral vascular disease and coronary heart disease)

7.1 DIABETIC NEUROPATHY

7.1.1 Introduction

Diabetic neuropathy is a common microvascular complication of diabetes. There are different forms of diabetic neuropathy: peripheral sensory neuropathy, autonomic neuropathy, polyradiculopathy, diabetic mononeuropathy and mononeuropathy multiplex.

Peripheral sensory neuropathy (PSN) is defined as the presence of symptoms or signs of peripheral nerve dysfunction in individuals with diabetes after the exclusion of other causes. PSN is the most common form of neuropathy, with up to 60% prevalence.[1] The prevalence of PSN in patients attending the National Diabetes Management and Research Centre (NDMRC) of the Korle-Bu Teaching Hospital is over 51.5% using the Michigan Neuropathy Screening Index (MNSI) examination score.[2]

Diabetic peripheral neuropathy can have devastating consequences. In individuals with diabetic neuropathy, nearly 50% will develop a foot ulcer during their lifetime.[3, 4] Diabetes is the leading cause of non-traumatic lower limb amputation.[3,4] Painful neuropathy and decreased sensation can lead to poor outcomes, such as depression, poor quality of life, restrictions in activities of daily living and falls.[5]

7.1.2 Pathophysiology

The main pathological processes are oxidative stress, advanced glycated end products (AGEs) formation and protein kinase C (PKC) activation, which cause damage and occlusion of vasa vasora, leading to nerve ischaemia. Accumulation of fructose and sorbitol through the polyol pathway, in addition to PKC activation, disrupts the structure and function of nerves. The accumulation of AGEs which results from hyperglycaemia reduces nitric oxide synthesis, induces endothelial dysfunction, and accelerates atherosclerosis.

Risk factors

- Advanced age
- Long duration of diabetes

- Poor glycaemic control
- Cigarette smoking
- Alcohol
- Hypertension
- Dyslipidaemia

7.1.3 Clinical assessment

Type 2 diabetes patients should be screened for neuropathy at diagnosis and yearly after that. In Type 1 diabetes, screening should begin 5 years after diagnosis and at least annually thereafter.[1] You must take a detailed history and examine the patient fully. Common symptoms and signs are described in Table 7.1 below.

Table 7.1: Signs and symptoms of diabetic neuropathy

Symptoms	Signs
• Numbness • Pin-prick sensation • Burning sensation • Tingling • Paraesthesia (typically glove-stocking pattern) • Shooting/" electric shock-like symptoms" • Walking on thick socks or cotton wool, which is typically worse at night • Patients with autonomic neuropathy may present with gastroparesis (constipation, diarrhoea), erectile dysfunction and atonic bladder	• Clawing of toes/ prominent metatarsal heads • Muscle wasting and weakness • Hallux valgus • Charcot deformity (swollen, erythematous, warm, deformed foot) • Calluses • Dryness and cracking of skin with hair loss • Impaired pin-prick sensation • Impaired vibration sense • Postural hypotension • Resting tachycardia

7.1.4 Investigations

- HbA1c
- Renal function tests

- Urine albumin estimation (if available)
- Liver function tests
- Lipid profile
- Thyroid function test
- Serum B12 and folic acid assay
- Full blood count

7.1.5 Management

Management goals are:
- Good glycaemic control
- Symptomatic relief
- Slow or halt progressive nerve damage

Non-pharmacological Management

Levels 0 (All Levels of care)

Patient Education

- Daily foot inspection looking for cuts, breaks in the skin, blisters, calluses, spots, and ingrown nails and examination of the soles with a mirror
- Wash feet daily, dry in between toes, moisturize dry skin
- Trim nails and file edges, trim calluses, avoid the use of blades and other sharp instruments
- Avoid walking bare-footed and use shoes with soft in-soles and hard under-soles, checking shoe lining before use
- Protect feet from hot and cold surfaces (extremes of temperature)
- Raise feet and wiggle toes to improve circulation when sitting
- Educate patient to comply with good glycaemic and metabolic control measures

Pharmacological Management of Painful Diabetic Neuropathy (Level 2 & 3)

- Treat initially with either amitriptyline, duloxetine, gabapentin or pregabalin[6, 7]
- If the initial treatment is ineffective, any of the other 3 can be used and again switched if the second line is not effective[7]

- Tramadol should be considered only if acute rescue therapy is needed[7]
- Capsaicin cream may be considered in individuals with localized neuropathic pain or those intolerant of oral medications[7]

7.1.6 Referral

Individuals with inadequate relief may be referred to a chronic pain management clinic.

Referral to a neurologist should be considered in individuals with atypical features such as asymmetry of symptoms and signs, motor symptoms greater than sensory neuropathy and rapid progression.

7.2 ERECTILE DYSFUNCTION

7.2.1 Introduction

Erectile dysfunction (ED) is the consistent and recurrent inability to attain or maintain penile erection sufficient for sexual satisfaction, including satisfactory sexual performance. The prevalence may be as high as 50 to 75% in adult men with Type 2 diabetes[8] and 31% in men with newly diagnosed diabetes.[9] In men with diabetes, ED occurs more than a decade earlier, is more severe and less responsive to oral therapy.[10] Erectile dysfunction impairs the quality of life of affected individuals[11]. Despite this, only 58% of patients with erectile dysfunction consult a physician, and even fewer maintain treatment.[12]

7.2.2 Pathophysiology

Erectile function requires intact neuronal and cardiovascular function; and ED results from both micro and macrovascular complications of diabetes. There are multifactorial mechanisms responsible for ED in diabetes. These include elevated advanced glycated end products (AGEs), increased levels of oxygen free radicals, and impaired nitric oxide synthesis, among others.[13] Endothelial dysfunction is a significant factor, explaining the consistent relationship between ED, risk of cardiovascular disease and mortality.[9, 10, 14] ED is a proven precursor to symptomatic coronary artery disease (CAD) in men, with an average lead time of 38.8 months.[15] Men with ED have been shown to have a 65-85% increased risk of subsequent CAD.[16]

Risk factors for ED include the following[17]:

- Long duration of diabetes
- Increasing age
- Poor glycaemic control
- Hypertension
- Obesity
- Dyslipidaemia
- Cigarette smoking
- Hypogonadism
- Presence of neuropathy-peripheral and autonomic
- Obstructive sleep apnoea
- Psychological factors, including depression
- Cavernosal smooth muscle disorder
- Drug-related side effects
- Interpersonal conflict

7.2.3 Clinical features

The cornerstone for diagnosis is a detailed history. ED is a delicate topic, and clinicians must be sensitive to a patient's cultural, ethnic and personal background in the evaluation process. The privacy of patients must be maintained during consultation. Partners may be invited to clarify issues. It is important to identify potentially reversible causes such as drugs and depression. Validated questionnaires, which are sensitive and specific for determining the presence of ED, are available and may also be used to assess response to therapy. The 5-item version of the International Index of Erectile Function (IIEF-5) can be used for the evaluation.[18]

7.2.4 Investigations (Levels 2 &3)

Patients with ED should be referred for specialist care

- Serum testosterone and prolactin should be measured on a case-by-case basis. Measure these hormones in patients with reduced libido, depression, and diminished secondary sexual characteristics. Morning assays are preferred.
- HbA1c
- Lipid profile
- Urinalysis to exclude genitourinary disorders

- ECG
- Routine chemistry, unless recently done, including thyroid dysfunction

7.2.5 Management

Non-pharmacological (Levels 2 &3)

- Therapeutic lifestyle intervention, i.e. diet and exercise for weight loss in the overweight or obese
- Stop smoking
- Limit alcohol use
- Withdraw any medication that may cause or exacerbate ED if possible
- Sexual counselling
- Address psychosocial issues such as depression and anxiety

Pharmacological (Levels 2 &3)

- Phosphodiesterase 5 (PDE5) Inhibitors (sildenafil, vardenafil, tadalafil and avanafil) are the first line. There is insufficient evidence to support the superiority of one over the other.[19] Do not use it in combination with nitrates. Caution must be taken when used in combination with alpha-blockers.
- Androgen replacement for those with hypogonadism.
- Treatment of hypogonadism before starting PDE5 inhibitors has been found to reduce non-responders to PDE5 inhibitors.[20, 21]

7.2.6 Referral

Patients with inadequate response to PDE5 inhibitors require referral to a urologist. Treatment options include vacuum constriction devices, intracorporal phosphodiesterase prostaglandin 1 (PGE1) injections, oral phentolamine, oral yohimbe.

Patients with hypogonadism must be referred to an endocrinologist for management

7.3 DIABETIC EYE DISEASE

7.3.1 Introduction

Diabetic eye diseases are a group of eye-related disorders affecting people with diabetes, including diabetic retinopathy (DR), cataracts and neovascular glaucoma. Diabetes also acts as a risk factor for several ocular conditions, such as a branch or central retinal vein occlusion, cranial neuropathies, branch or central retinal artery occlusion and non-arteritic ischaemic optic neuropathy.[22] Diabetic retinopathy will be the focus of this section on eye complications of diabetes as it is the eye complication with the most significant morbidity.

Prevalence

Worldwide the prevalence of DR is estimated at 34.6% of people living with diabetes. About 93 million people worldwide have some form of DR, with 10.2% having vision-threatening diabetic retinopathy (VTDR).[23] The Ghana Blindness and Visual Impairment Survey reported that the third highest cause of visual impairment in Ghana was retinal disease (12.9%), of which the majority are diabetic retinopathy related.[24]

7.3.2 Pathophysiology

Diabetic retinopathy is a chronically progressive, potentially sight-threatening manifestation of end-organ damage in the retina of the eyes of people living with Type 1 and Type 2 diabetes. It has traditionally been thought to be a predominantly microvascular complication; however, there is mounting evidence that retinal neurodegeneration plays a key role in the manifestation of this complication.[25] The microvascular changes, caused by relative hyperglycaemia, lead to retinal ischaemia, which then results in the formation of microaneurysms, followed by leakage of haemorrhage or fluid, causing retinal oedema and then arteriovenous shunts and neovascularisation. The new blood vessels that occur are fragile and easily bleed, causing a vitreous haemorrhage. With time the new blood vessels fibrose and then contract, potentially causing a retinal detachment.[26]

Risk factors

The main risk factors for diabetic retinopathy are:

- Duration of relative hyperglycaemia, particularly the severity and the length of time of diabetes in the individual. Among individuals diagnosed with diabetes before age 30, the incidence of diabetic retinopathy after 10 years is 50%, increasing to almost 90% after 30 years of living with diabetes
- Glycaemic control: HbA1c remains the most significant predictor of the progression of DR
- Systemic conditions like hypertension, hypercholesterolaemia and renal disease can influence the onset and progression of diabetic retinopathy
- Smoking is another risk factor affecting the onset and progression of DR.
- Pregnancy can also be associated with the rapid progression of diabetic retinopathy

7.3.3 Common Clinical Features

The difficulty with the management of diabetic retinopathy is that several patients with the vision-threatening disease may not notice any change in their eyesight till it is late. The two main mechanisms of visual loss are macular oedema and proliferative diabetic retinopathy (Table 7.2), leading to vitreous haemorrhage, retinal detachment, or both.

Clinical examination by means of dilated fundoscopy using a direct ophthalmoscope, a slit lamp with lenses, an indirect fundoscopy, lenses or a fundus camera is the mainstay of diagnosing diabetic retinopathy. As DR progresses, retinal vasculature is closed, which causes impaired perfusion and retinal ischaemia. If not appropriately managed, DR progresses almost stepwise along the severity levels. The clinical findings in DR are listed in the Table below, as are the associated disease severity levels. [27]

Table 7.2 Classification of diabetic retinopathy and disease severity

Disease Grade	Findings on fundoscopy
No Diabetic Retinopathy	No abnormalities
Mild Non-Proliferative DR	Retinal microaneurysms only
Moderate Non-Proliferative DR	More than just microaneurysm but less than severe Non-proliferative Diabetic Retinopathy With or without any of the following: 1. Retinal Haemorrhages 2. Exudates 3. Cotton wool spots 4. Venous beading
Severe Non-Proliferative DR	Any of the following: 1. More than 20 intraretinal haemorrhages in each of 4 quadrants 2. Definite venous beading in 2 or more quadrants 3. Prominent intraretinal microvascular abnormalities in 1 or more quadrants AND no sins of proliferative diabetic retinopathy
Proliferative Diabetic Retinopathy	One of the following: 1. Neovascularisation 2. Vitreous/preretinal haemorrhage
Advanced Diabetic Eye Disease	One of the following: 1. Formation of fibrovascular tissue proliferation 2. Tractional retinal detachment 3. Dragging of retina and distortion 4. Rhegmatogenous retinal detachment

7.3.4 Non-pharmacological management: Screening

Many aspects of non-pharmacological management of diabetes and DR have been discussed elsewhere in these guidelines. The main strand

missing is regarding the retinal screening of all diabetes patients. There is good evidence to show that healthcare systems that employ screening of all diabetes patients have fewer long-term complications of diabetic retinopathy than those who do not.

Screening According to Level of Care

Facility without Doctors

Refer all patients with diabetes for an eye examination at a level 2 facility

Facilities with non-specialist Doctors (without Ophthalmologists)

- All patients with diabetes should be screened at least once a year by the District Ophthalmic Nurse using whichever examination technique, they are comfortable with, such as an ophthalmoscope.[28] There is an eye healthcare worker present in every district in Ghana
- Alternatively, a screening system that allows all diabetes patients to have yearly retinal examinations either by a trained healthcare professional or using a fundus camera by a trained screener and the image analysed later by a trained grader at a Level 3 facility

Facilities with Ophthalmologists

Screening methods for DR at this level include traditional slit-lamp examination and ophthalmoscopy. Screening with digital fundus photography/camera is increasingly becoming available.

7.3.5 Investigations

Investigating eye diseases is generally done at Level 3 or a facility with an ophthalmologist.

Clinical examination is sensitive in picking up diabetic retinopathy, and as such most investigations help to define the morbidity and severity of DR better.

- The main retinal investigations are fundus fluorescein angiogram, which helps assess the vascular supply's patency and check the vascular tree's function
- Ocular Coherence Tomography: helps assess the retina's structure and decide if there is retinal oedema and how much there is

These two modalities are mainly found in teaching hospital settings.

- The other investigation is ultrasonography of the eye using an ultrasound scan in B mode. It helps to assess eyes with vitreous haemorrhage or cataracts that preclude dilated fundus examination. These can be found in all regional hospitals and some district hospitals.

7.3.6 Pharmacological management

Facilities with an Ophthalmologist

The treatment goals in managing the complications arising from DR are mainly to prevent and reduce macular oedema and to cause regression of any neovascularisation. Medications available for managing DR are shown in Table 7.3.

- Steroids: Pharmacologically, this is done with the aid of steroids (particularly Triamcinolone) given either periocular or intravitreally. Though the cost of Triamcinolone is low, it has potential side effects of cataracts and ocular hypertension, limiting its use.
- Anti-Vascular Endothelial Growth Factors (Anti-VEGF) have recently become the mainstay in the management of macular oedema secondary to DR. They are given intravitreally, usually 4 to 8 weekly depending on the brand and administration protocol used. The anti-VEGF agents are well tolerated with minimal side effect profiles; unfortunately, their cost makes them inaccessible to many persons with diabetic retinopathy. These injections can safely be given in any hospital or facility where cataract surgery occurs. However, they are predominantly administered in teaching and a few regional hospitals.
- An ophthalmologist best manages the pharmacological management of DR, so it is prudent to refer all persons with diabetes who get DR to an eye specialist.

Table 7.3 Medications available for managing Diabetic Retinopathy

Drug	Route	Frequency
*Triamcinolone	Periocular or Intravitreal	Every Three months
*Bevacizumab	Intravitreal	Every 4 weeks for three doses, then PRN or on a treat and extend interval regimen
Ranibizumab	Intravitreal	Every 4 weeks for three doses, then PRN or on a treat and extend interval regimen
Aflibercept	Intravitreal	Every 4 to 6 weeks for three doses, then PRN or on a treat and extend interval regimen
*Ziv-Aflibercept	Intravitreal	Every 4 to 6 weeks for three doses, then PRN or on a treat and extend interval regimen

**Off-label use of a licensed medication*

7.3.7 Surgical Management

Facilities with an Ophthalmologist

Laser therapy

The use of lasers for managing macular oedema has been waning since the emergence of anti-VEGF agents. Laser of 532mw wavelength is used to treat both macular oedema and proliferative diabetic retinopathy.

Laser is used to gently stimulate the retina to absorb oedema. Proliferative diabetic retinopathy and sometimes severe non-proliferative diabetic retinopathy require aggressive pan-retinal laser photocoagulation to coagulate the peripheral retina and reduce the ischaemic drive of the eye, to aid regression of neovascularisation.

This treatment is mainly available in teaching hospitals.[29]

Vitrectomy

Vitreous haemorrhage and retinal detachment secondary to DR require vitrectomy surgery to prevent blindness. The outcomes of surgery vary depending on the duration of the vitreous haemorrhage or the retinal detachment, the complexity of the surgery, and the surgeon's experience[30].

7.3.8 Referral

Diabetes patients must be referred to their local or nearest eye health professional for yearly screening tests. Patients found to have any vision-threatening diabetic retinopathy, such as diabetic macular oedema, proliferative diabetic retinopathy, vitreous haemorrhage, or retinal detachment, should be referred to their closest teaching hospital or facility with ophthalmologist for treatment.[31]

7.4 DIABETIC NEPHROPATHY

7.4.1 Introduction

Definition

Diabetic nephropathy (DN) is defined as glomerular sclerosis and fibrosis caused by the metabolic and haemodynamic changes of diabetes mellitus (DM). It manifests as slowly progressive albuminuria with worsening hypertension and renal insufficiency.[32]

It is a clinical syndrome characterized by the following[33]:

- Persistent albuminuria (>300 mg/day or >200 µg/min) that is confirmed on at least 2 occasions 3-6 months apart after exclusion of other causes (refer to Table 7.4 below)
- Progressive decline in the glomerular filtration rate (GFR)
- Elevated arterial blood pressure

7.4.2 Epidemiology

The prevalence of DN is increasing steeply in tandem with the diabetes epidemic.[34]

Diabetes is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide.[35, 36] In Ghana, a study showed that the prevalence of CKD among participants with both DM and hypertension was 28.5%, while participants with hypertension alone and DM alone had a prevalence rate of 26.3% and 16.1%, respectively.[37] Hence, the effects of diabetes and hypertension on kidney disease cannot be underestimated.

The prevalence of DN is higher in Africans compared to Caucasians. This situation is due to late diagnosis, scarcity of screening and diagnostic resources, poor control of blood glucose and other precipitating factors, and inappropriate treatment.[38]

Good evidence suggests that early treatment delays or prevents the onset of DN or diabetic kidney disease.[32]

Table 7.4: Other causes of proteinuria/albuminuria which must be excluded

- Hypertensive nephrosclerosis
- Acute and chronic glomerulonephritis
- Urinary tract infections
- Preeclampsia
- Haemoglobinuria and rhabdomyolysis (myoglobinuria)
- Nephrolithiasis
- Genitourinary tumours
- Myeloma and related diseases
- Congestive heart failure
- Heavy metal poisoning
- Autoimmune or allergic interstitial inflammation or medication-induced interstitial injury
- Immune disorders like Systemic Lupus Erythematosus (SLE) and Goodpasture's syndrome
- Trauma

While the gold standard for diagnosis of DN is by histology of the kidney, most patients are presumed to have diabetic kidney disease based on their clinical history and laboratory investigations, especially if another kidney disease is not suggested or atypical features are not present.[33, 39, 40]

7.4.3 Risk Factors

Risk factors for DN are categorized into modifiable and non-modifiable risk factors (Table 7.5).

Table 7.5: Risk factors for Diabetic nephropathy

Non-Modifiable risk factors	Modifiable risk factors
1. Increasing Age 2. Race/Ethnicity (Black, Asian and Native American) 3. Gender (more common in women) 4. Genetic factors*	1. Obesity 2. Hypertension* 3. Hyperglycaemia* 4. Smoking 5. Alcohol abuse 6. Hyperlipidaemia 7. Low socio-economic status

**Hyperglycaemia, hypertension, and genetic predisposition are the main risk factors for the development of diabetic nephropathy.* [41]

Pathophysiology

Diabetic nephropathy begins as glomerular hyperfiltration (increased glomerular filtration rate [GFR]) due to persistent hyperglycaemia and polyuria, followed by early renal injury and mild hypertension, which worsens over time but is associated with normal GFR. Microalbuminuria (urinary albumin excretion of 30 to 300 mg albumin/day) then occurs. Microalbuminuria progresses to macroalbuminuria (proteinuria > 300 mg/day) over a variable period (usually 3 to 5 years on average). [32]

Microalbuminuria is not always predictive of diabetic nephropathy. Nevertheless, a majority of the cases of diabetic nephropathy present with proteinuria, which progressively worsens as the disease progresses and is almost uniformly associated with hypertension. [33]

Certain factors favour the diagnosis of diabetic nephropathy, as shown in Table 7.6.

Table 7.6: Factors favouring diabetic nephropathy versus other diagnoses

Favours diabetic nephropathy	Other diagnoses
Persistent albuminuria	Heavy proteinuria (>6g/day)
Absent/few cells or casts in urine (bland urine)	Persistent haematuria (micro or macroscopic) or active urinary sediments
Slow deterioration of eGFR	Rapidly falling eGFR
Low eGFR with overt proteinuria	Low eGFR with little or no proteinuria
Other complications of diabetes, e.g. retinopathy	Absence of other complications of diabetes or not severe
Known duration of diabetes > 10 years	Known duration of diabetes < 10 years
	Family history of non-diabetic kidney disease (e.g. polycystic kidney disease)
	Symptoms and signs suggestive of other systemic diseases

7.4.4 Prognosis of DN

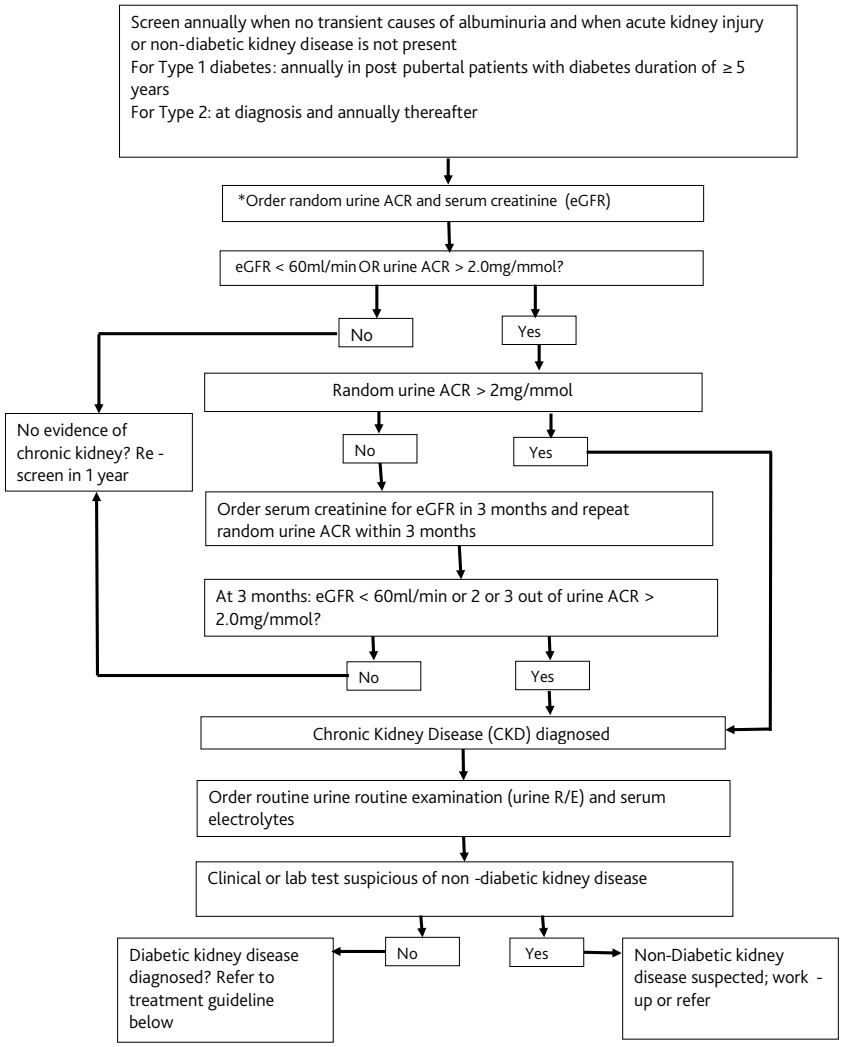
Prognosis is good for patients who are meticulously treated and monitored. Nonetheless, this is difficult to achieve, and most patients gradually lose renal function. Even prehypertension (BP of 120 to 139/80 to 89 mm Hg) or stage 1 hypertension (BP 140 to 159/90 to 99 mm Hg) may accelerate injury. The lowest risk is associated with a systolic pressure below 120 mm Hg.[42] Systemic atherosclerotic diseases such as stroke, myocardial infarction and peripheral arterial disease predict an increase in mortality.[43, 44]

7.4.5 Management of Diabetic Nephropathy

Screening for Diabetic Nephropathy

The 24-hour urine for protein/albumin is the gold standard but cumbersome to implement in routine clinical practice, inconvenient for patients and

often not performed accurately. In practice, the test of choice for screening for albuminuria is the random urine albumin to creatinine ratio (ACR) or urine protein to creatinine ratio (UPCR) (Figure 7.1).



**If ACR is unavailable, do routine urinalysis for proteinuria and discuss with a nephrologist or diabetologist. You may also refer for ACR at a facility that can offer the test at least on an annual basis*

Figure 7.1: Screening for DN

Investigations

The following investigations are recommended according to the level of care (Table 7.7)

Table 7.7: Investigations according to the level of care

Level 1 Facility without a Doctor	Level 2 Facility with non-Specialist Doctor	Level 3 Facility with a Specialist Doctor
FBC	All investigations at Level 1	All investigations at Level 2
Fasting or random blood glucose	Albumin/creatinine ratio (ACR), if available	Serum albumin
Urinalysis	BUE, Cr	Serum parathyroid hormone (PTH)
	HbA1C	Renal Biopsy (If available)
	Serum Lipids	
	Serum Calcium, Phosphate	
	Urine and Plasma Electrophoresis (mainly to exclude Multiple Myeloma and classify the proteinuria)	
	Chest X-ray	
	Renal Ultrasound	

Treatment goals

- To detect DN early in susceptible individuals
- Glycaemic control (HbA1C) ≤ 7.0 %
- Management of Hypertension (BP < 130/80mmHg)

- Prevention of complications and further worsening of the renal function

Non-Pharmacological

Facilities without Doctors (Level 1)

Refer to a facility with a Doctor if proteinuria is > 2+ on at least 2 occasions

Facilities with Doctors and Specialists

- Dietary protein restriction: Patients with diabetes and overt nephropathy should restrict to 0.8 to 1.2 g protein/kg/day
- Dietary sodium restriction < 2 g/day or <5g/day NaCl
- Adequate hydration – at least 25 to 35mls/kg/day (except if ESKD or in pulmonary oedema)
- Reduce intake of potassium-containing foods (coconut water, banana, avocado etc.)
- Exercise- moderate-intensity exercise at least 150mins per week/ to a level compatible with CVS and physical tolerance
- Cessation of smoking
- Dialysis

Level 3 (Nephrologists)

- All activities under Facilities with Doctors and Specialists
- Kidney transplantation with or without simultaneous or subsequent pancreas transplantation is an option for patients with end-stage renal disease.

Pharmacological

- Level 1: DN are only to be managed at Levels 2 & 3
- Levels 2 & 3 (Facilities with Doctors or Specialists)

Glycaemic control:

Metformin[45]:

- Start from 500mg OD and titrate upwards until the maximum tolerable dose
- Avoid or discontinue metformin if eGFR/CrCl < 30ml/min/1.73m2

- For an eGFR between 45–59 ml/min per 1.73 m2, dose reduction may be considered in the presence of conditions that predispose patients to hypoperfusion and hypoxemia

SGLT-2 inhibitors:

SGLT-2 inhibitors reduce the risk of disease progression of diabetic kidney disease and ESKD, regardless of the degree of proteinuria. However, there is a greater absolute benefit from SGLT-2 inhibitors in patients with severely increased albuminuria (albumin-to-creatinine ratio ≥300 mg/g).[46, 47] SGLT-2 inhibitors with established kidney and cardiovascular benefits and dosing information are shown below (Table 7.8).[46-48]

Table 7.8: SGLT-2 Inhibitors with established kidney and cardiovascular benefits and dose adjustments

	Assessment	Intervention	Follow-up
Patient selection	Eligible patients: • eGFR ≥20 ml/ min/1.73 m2 High priority features: • ACR ≥200 mg/g [≥20 mg/mmol] • Heart failure Potential contraindications: • Genital infection risk • Diabetic ketoacidosis • Foot ulcers • Immuno-suppression	SGLT2 inhibitor with proven benefits: • Canagliflozin 100 mg • Dapagliflozin 10 mg • Empagliflozin 10 mg Education: • Sick day protocol** • Perioperative care† • Foot care	• Assess adverse effects • Review knowledge • Anticipate an acute drop in eGFR, which is generally not a reason to stop the SGLT2 inhibitor
Glycaemia	**Hypoglycemia risk? • Insulin or sulphonyurea • History of severe hypoglycaemia • HbA1c at or below goal **if risk is high educate as indicated in the next column	Education: • Hypoglycaemia symptoms • Glycaemia monitoring Consider insulin/ sulphonyurea dose reduction	• Ask about hypoglycaemia • Reduce sulphonyurea or insulin if needed

Volume	Volume depletion risk? • Concurrent diuretic use • Tenuous volume status • History of AKI **if high educate as indictated in the next column	Education: • Volume depletion symptoms Consider diuretic dose reduction	• Re-assess volume • Reduce concomitant diuretic if needed

**Adapted from: Zoungas S and de Boer IH publication on SGLT2 Inhibitors in Diabetic Kidney Disease (2021)* [49]

***Sick day protocol: illness or excessive exercise or alcohol intake: temporarily withhold SGLT2i, advise patients to keep drinking and eating, check blood glucose and blood ketone levels more often.*

†Periprocedural/perioperative care: inform patients about the risk of diabetic ketoacidosis; withhold SGLT2 inhibitors the day of day-stay procedures and limit fasting; withhold SGLT2 inhibitors at least 2 days in advance and the day of procedures/surgery requiring 1 or more days in hospital and/or bowel preparation (which may require increasing other glucose-lowering drugs during that time), measure both blood glucose and blood ketone levels on hospital admission (proceed with procedure/surgery if the patient is clinically well and ketones are <1.0 mmol/l), and restart SGLT2i after procedure/surgery only when eating and drinking normally.

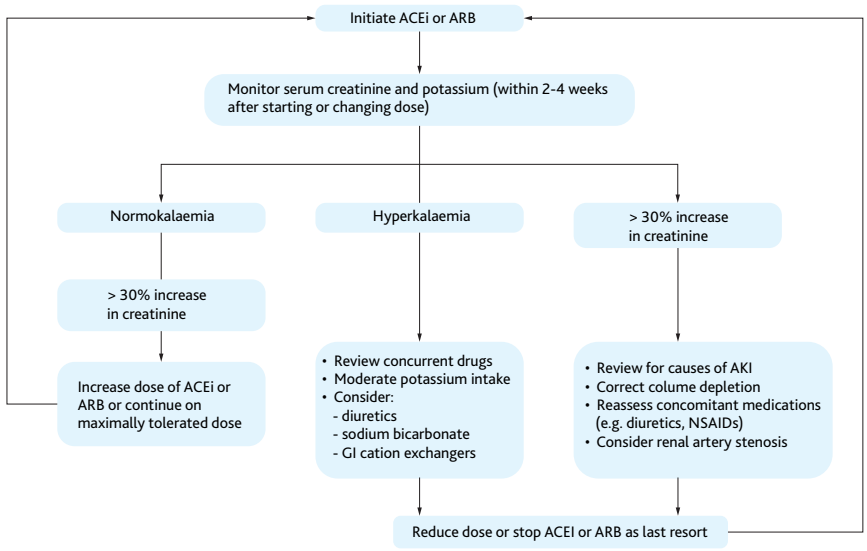
ACR: albumin-creatinine:ratio; AKI: acute kidney injury; eGFR, estimated glomerular filtration rate; HbA1c: glycated haemoglobin.

Other blood glucose-lowering medications:

Include other oral or injectable antiglycaemic agents, including insulin, to achieve the HbA1C target. Glycemic control targets are typically individualized, but an HbA1c goal of <7% is frequently recommended. *Refer to Chapter 5 for further details of the recommended renal dosages of antiglycaemic agents.*

Blood pressure control:

Angiotensin-converting enzyme inhibitors (ACE-I) or Angiotensin receptor blockers (ARBs) are preferred (Figure 7.2), especially in the presence of albuminuria/proteinuria. However, other agents may be deployed to achieve BP targets.



Monitoring of serum creatinine and potassium during ACEi or ARB treatment—dose adjustment and monitoring of side effects. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug

Figure 7.2: Blood pressure control in CKD[45]

Note:

1. *Reduce the dose or discontinue ACEi or ARB therapy in the setting of either symptomatic hypotension or uncontrolled hyperkalaemia despite the medical treatment (estimated glomerular filtration rate [eGFR] <15 ml/ min per 1.73 m2).*

2. *Use only one agent at a time to block the RAS. Combining an ACEi with an ARB or an ACEi or ARB with a direct renin inhibitor is potentially harmful.*

3. *Mineralocorticoid receptor antagonists (MRAs) are effective for managing refractory hypertension but may cause hyperkalemia or a reversible decline in glomerular filtration, particularly among patients with a low eGFR.*

   Non-steroidal MARs such as finerenone are preferred over steroidal MRAs. They can be used with RASi or in combination with RASi and SGLT-2 inhibitors. 50 Potassium measurement should be monitored during treatment with finerenone (Figure 7.3).

   The combined Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease [FIDELIO-DKD] and Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease [FIGARO-DKD] Trial programme analysis 51 resulted in a lower incidence of kidney failure, death from kidney failure and lower albumin excretion. MRAs reduced death from cardiovascular diseases such as stroke, non-fatal MI and heart failure.

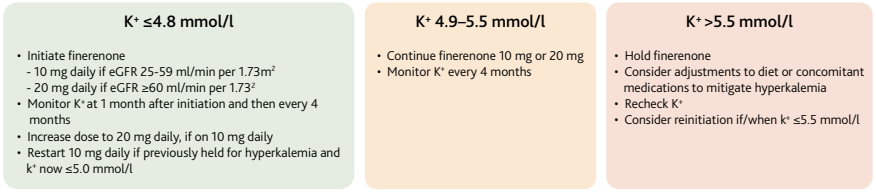


Figure 7.3: Serum potassium monitoring during treatment with finerenone[50]

The steroidal MRAs such as spironolactone and eplerenone have been extensively evaluated in long-term outcomes trials for heart failure. They are indicated for the management of heart failure, resistant hypertension, and hyperaldosteronism. In situations where there is an indication for both steroidal and nonsteroidal MRAs (e.g. heart failure and persistent albuminuria), the most pressing clinical indication should be used to make a choice. Avoid combining the two as this may worsen side effects such as hyperkalemia and acute kidney injury.[50]

Management of Dyslipidemia in CKD

Statin therapy is recommended in the following patients[52]:

- If patient has CKD and diabetes mellitus and age >18 years

- If patient has CKD, does not have diabetes mellitus and age >50 years
- If patient has CKD, does not have diabetes mellitus, is age 18-49 years, has known coronary artery disease, had had a previous stroke, or has a 10-year Framingham Risk score >10% or WHO Cardiovascular Risk score of >20%

7.4.6 Patient Information/ Education

All levels of care

- Encourage patients to adhere to lifestyle modifications *(see Non-Pharmacological Management of Diabetes- Chapter 4)*
- Encourage patients to comply with antihypertensives and anti-diabetic medications as they significantly impact the prognosis
- Educate clients with or without detected nephropathy to bring in a first-pass morning urine specimen yearly for urinalysis

7.4.7 Prevention of Diabetic Nephropathy

All levels of care

Primary prevention:

- Lifestyle changes that can help with this include:
- A healthy diet that is high in fibre and low in glucose, processed carbohydrates, and salt
- Regular exercise
- Reducing alcohol intake
- Avoid tobacco
- Reducing weight
- Avoid potentially nephrotoxic substances such as NSAIDs, aminoglycosides and some herbal preparations.

Secondary prevention

- Check blood glucose levels regularly
- Follow the doctor's treatment plan, such as taking diabetes medications and antihypertensives.

7.4.8 Referral

- It is advisable to refer all clients with the following indications to the physician specialist/diabetologist or a nephrologist (or a paediatrician if a child) for further management:
  1. eGFR < 45ml/min (Stage 3b CKD) with or without abnormal urinary findings
  2. eGFR < 60ml/min (Stage 3a CKD) with albuminuria, proteinuria, pyuria or microscopic haematuria
  3. eGFR <60 ml/min with diabetes or uncontrolled hypertension (patient requiring >3 drugs for BP control)- CKD with CHF and fluid management issues
  4. Urine ACR persistently >2 mg/mmol
  5. Patients should be referred for evaluation for renal replacement treatment (dialysis or kidney transplantation or both) if they have an eGFR below 30 mL/min/1.73
  6. Unable to remain on renal-protective therapies due to adverse effects, such as hyperkalaemia or a >30% increase in serum creatinine within 2 weeks of starting an ACE inhibitor or ARB
  7. Unable to achieve target BP
- Refer all clients needing renal replacement therapy to a nephrologist.

**Adapted from the KDIGO 2020 clinical practice guideline for diabetes Management in Chronic Kidney Disease*[53]

7.5 FOOT CARE

7.5.1 Introduction

Diabetic foot problems comprise skin lesions, foot deformity, ulceration, infection, necrosis, gangrene and eventually amputation. Diabetes is the most common cause of non-traumatic amputations of lower limbs accounting for >70% of lower limb amputations worldwide.[54, 55]

7.5.2 Pathophysiology

Diabetic foot problems arise from neuropathy (motor, sensory and autonomic), immune dysfunction and vasculopathy, with the latter playing a very important role.

The vasculopathy associated with DM is either macroangiopathy or microangiopathy. Macroangiopathy involves atherosclerosis (a plaque) which builds up in the sub-endothelial space and causes narrowing/ stenosis of the lumen and impairing perfusion. Progression of stenosis leads to occlusion of the arterial lumen associated with chronic limb-threatening ischaemia.

Microangiopathy involves medial calcinosis (calcification of the arterial wall's media layer) and other metabolic waste deposition. Both processes cause impairment of the movement of nutrients from the lumen via the wall into the cells. Eventually, this leads to the deprivation of the cells of vital nutrients necessary for viability.

In summary, both macro and microangiopathy cause tissue ischaemia and, finally, gangrene if not treated.

7.5.3 Screening

For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times:

- At diagnosis for Type 2, and at least annually after that for symptomatic and asymptomatic patients.
- Screen initially 5 years after diagnosis in type 1 and annually thereafter
- If any foot problems arise
- Whilst on admission to the hospital, and if there is any change in their status.

Examination of the foot and risk assessment

When examining the feet of a person with diabetes, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following risk factors:

- Ulceration
- Callus
- Infection and/or inflammation
- Deformity
- Gangrene
- Charcot arthropathy
- Limb ischaemia (peripheral pulse palpation, ankle brachial pressure index (ABPI), or duplex ultrasound)
- Ankle reflexes
- Sensation
    - Use a 10 g monofilament as part of a foot sensory examination
    - Vibration using 128Hz tuning fork
    - Pin-prick sensation

When using the ankle-brachial pressure index, interpret results carefully in people with diabetes because calcified arteries may falsely elevate results.

Risk stratification

Assess the patient's current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification: low risk, moderate risk, high risk or active diabetic foot problem. Emphasize the importance of foot care and advise them that they could progress to moderate or high risk. Refer people at moderate or high risk of developing a diabetic foot problem to the foot team, if available (Table 7.9).

Table 7.9: Diabetic foot risk stratification*

Risk level	Characteristics	Frequency of assessment
Low risk	• No risk factors present except callus alone	Annually for people who are at low risk
Moderate risk	• Deformity or • Neuropathy or • Non-chronic limb-threatening ischemia	Frequently (for example, every 3 to 6 months)**
High risk	• Previous ulceration or • Previous amputation or • On renal replacement therapy or • Neuropathy and non-chronic limb-threatening ischemia together or • Neuropathy in combination with callus and/or deformity or • Non-chronic limb-threatening ischemia in combination with callus and/or deformity.	More frequently (for example, every 1 to 2 months) if there is no immediate concern. Very frequently (for example, every 1 to 2 weeks) if there is an immediate concern.
Active diabetic foot problem	• Ulceration or • Spreading infection or • Critical limb ischaemia or • Gangrene or • Suspicion of an acute Charcot arthropathy or an unexplained hot, red, swollen foot with or without pain.	Refer immediately to the foot team if available, DST, or foot surgeon

**Adapted from NICE guidelines on diabetic foot problems: prevention and management 2015 (updated 2023)* [56]

***Consider frequent assessment for persons who check their own feet*

DST-Diabetes Specialist Team

7.5.4 Investigations

Levels 2 & 3

- Fasting blood glucose
- Random blood glucose
- HbA1c
- Lipid profile
- Renal function tests
- X-ray or MRI of the affected limb if osteomyelitis is suspected
- Arterial duplex scan/map
- CT angiogram of the infra-renal aorta and both lower limbs
- On-table angiogram (with the advantage of intervention if need be)

7.5.5 Management

Non-Pharmacological Management

Refer to the section on non-pharmacological management of diabetes (Chapter 4)

1. Lifestyle Modification- regular exercise (preferably supervised), healthy diet (less carbohydrate and healthy cholesterol-free fat, lot of fruits and vegetables)

2. Patient Education- regular out-patient department (OPD) pre-consultation education of patients on lifestyle modification and healthy diet, proper foot care

3. Self-Monitoring of Blood Glucose at home and record in a diary to be reviewed by a specialist at every OPD visit

4. Proper foot care:
   - Daily examination of feet by either patient or a relative with better eyesight, twice daily cleaning of feet and all web spaces dry. Examine the sole of the feet with mirrors
   - Cut nails when it flushes with skin (not to allow nail ends to recede into the flesh)

- Wear medically prescribed orthotic shoes with soft insoles which are not tight
- Do not walk barefoot, even at home.
- Professional podiatrists care for cones, minor abrasions and pressure point treatment with a total contact cast or a removable boot.

Pharmacological Management

Glucose-lowering medications (with or without insulin) are required to achieve good glycaemic control, reduce the risk of vascular-related complications, and promote wound healing.

Antibiotics must only be used where there is clinical evidence of an infection. The choice should be based on culture and sensitivity tests. Empirical broad-spectrum antibiotics could be started while waiting for culture results in case of a foot infection.

Antiplatelet therapy and statins are usually recommended in the presence of atherosclerotic cardiovascular disease.

7.5.6 Diabetic foot ulcer

Management of the diabetic foot is multidisciplinary, involving diabetologists, podiatrists, diabetic foot care nurses, general and vascular surgeons, psychologists, and physiotherapists

Principles of management:

- Discourage weight-bearing on the affected foot with plantar ulcers
- Off-loading: non-weight bearing on pressure points, e.g. total contact casts, special insoles)
- Control of foot infection
- Management of ischaemia
- Wound debridement
- Wound dressings

Principles of Vascular/Surgical Management of the ischemic foot (Levels 2 & 3)

- Patient admission and bed rest
- Grading of tissue loss into two categories (salvageable and non-salvageable limb)
- Adequate analgesia, either oral or parenteral

Salvageable

- Wound debridement using various methods (mechanical with the scalpel blade or versajet, biological with sterile worms or papain or other commercial preparations, osmotic debridement with commercial preparations)
- Moist wound dressing preferred or open dry dressing as appropriate (no wet dressing of wounds)
- Minimal limb elevation to avoid pedal oedema
- Endovascular or open vascular surgery intervention to improve arterial blood flow
- Graft or flap application in case of extensive wounds

Non-salvageable

- Lower limb ablation/amputation for non-salvageable limbs
- Psychological counselling pre and post-amputation
- Physiotherapy and fittings (prosthesis)

7.6 HEART FAILURE

7.6.1 Introduction

Heart failure (HF) is a clinical syndrome characterized by abnormal heart function leading to dyspnoea and oedema.[57] Diabetes mellitus is a common risk factor for heart failure and heart failure hospitalization in patients with diabetes.[58, 59] Left ventricular hypertrophy is a characteristic feature of diabetic heart disease.

7.6.2 Causes of heart failure in patients with diabetes

The causes of heart failure are numerous, but the most common causes in patients with diabetes mellitus are:

- Ischaemic heart disease commonly due to coronary artery disease
- Dilated cardiomyopathy, usually non-ischaemic
- Hypertension

All other causes of heart failure may also occur in patients with diabetes. Some glucose-lowering medications, such as rosiglitazone, and pioglitazone, predispose to heart failure.

Clinical Presentation

Symptoms and signs of heart failure may occur in addition to diabetes or other complications.

7.6.3 Management of Heart Failure

Pharmacological and non-pharmacological management of heart failure is outlined below.[60]

Non-pharmacological

All levels (Level 0)

These are the same for patients with or without diabetes mellitus and include:

- Diet and nutrition. Encourage eating of fruits and vegetables and other potassium-rich diets. Plan for the patient should be in collaboration with the diet therapist
- Decrease salt intake by restricting sodium chloride to <6g daily (or <2g of sodium) per day
- Fluid restriction in severe heart failure to not more than 1500mls/day carried out in accordance with daily weighing
- Smoking cessation
- Avoidance of alcohol
- Supervised exercise training based on the patient's exercise tolerance level

Health facility without a Doctor (Level 1)

- Refer all patients with hyperglycaemic or other diabetes complications with heart failure to facilities with physician specialists (Level 3).
- Acute heart failure
  - Admit patient and prop up in bed
  - Give intranasal oxygen in case of hypoxaemia (low oxygen saturation), SPO2 < 90%
  - Diuretics: Furosemide 40-80mg 8-12 hourly intravenously
  - Do a full blood cell count (FBC) and fasting blood glucose (FBG)
  - Refer the patient to a health facility with a doctor
- Refer all patients with chronic heart failure, atrial fibrillation, and other arrhythmias to a facility with a physician specialist (Level 3)

Health facility with a Doctor/Physician Specialist/Cardiologist (Levels 2 & 3)

Acute heart failure

Investigations for heart failure are the same for patients with or without diabetes and may include baseline investigations in addition to specific ones such as:

- Chest x-ray
- Electrocardiography (ECG)
- B-type natriuretic peptides (BNPs) and N-terminal pro-B-type natriuretic peptides (if available)
- Troponin and CK-MB
- D-dimer
- Echocardiogram
- Ambulatory ECG monitoring (Holter)
- Ambulatory blood pressure monitoring (ABPM)
- Coronary angiography
- Left and right heart haemodynamic evaluation/catheterization if expertise is available.
- Cardiac magnetic resonance (CMR) imaging

Management

- The patient should be propped up in bed
- Give oxygen in case of hypoxaemia (SPO2 <90%) (oxygen should not be given routinely in the absence of hypoxaemia)
- Non-invasive positive pressure ventilation (e.g. CPAP) in patients with respiratory distress (if facility and expertise are available)
- Intubation should be considered if hypoxaemia, hypercapnia and/or acidosis cannot be managed non-invasively and when the patient is fatigued

Pharmacological treatment

- Diuretic therapy
    - Furosemide 40 to 80mg intravenously, which may be repeated
    - For resistant cases, use metolazone oral 5 – 10mg in combination with frusemide
    - Other options for resistant cases include bumetanide 0.5mg -5mg orally twice daily and torsemide 5mg – 20mg orally
- Treat precipitants such as infections, arrhythmia, acute coronary syndrome, and pulmonary embolism
- Patients in cardiogenic shock with no evidence of coronary artery disease, pulmonary embolism or hypovolaemia, short-term intravenous inotropic support with dobutamine 0.5-1mg/kg/min should be given as a continuous infusion
- Manage atrial fibrillation with digoxin (125-250 micrograms daily orally) and/or beta-blocker should be considered. Amiodarone may be considered if expertise is available
- Manage diabetes or its complications according to protocol

Chronic heart failure

In patients with diabetes and chronic heart failure, such as heart failure with reduced ejection fraction (HFrEF) and heart failure with presered ejection fraction (HFpEF), non-pharmacological therapy and lifestyle modifications are essential to prevent acute decompensation and reduce the hospitalization rate. Glycaemic control to target HbA1C is essential. Refer the patient to a physician specialist or cardiologist.

Pharmacological treatment may include:

- Diuretics
  - Furosemide 40-120 mg in divided doses (or titrate to patient's need)
  - Bendroflumethiazide 2.5–10mg daily orally or thiazide-like diuretic (Metolazone 2.5–10mg daily orally)
- Digoxin
  - digoxin is less effective in the presence of hypokalaemia or hypocalcaemia
  - Avoid hypercalcemia or hypomagnesaemia.
- Angiotensin-converting enzyme inhibitors (ACEI)
- Angiotensin receptor blockers (ARB)
- Angiotensin receptor neprilysin inhibitor (ARNI)
- Beta-blockers (e.g. bisoprolol, carvedilol, nebivolol)
- Mineralocorticoid Receptor Antagonists (MRA) e.g. spironolactone and eplerenone
- Combination of Hydralazine and nitrates
- Ivabradine
  - Recommended for patients with symptomatic HFrEF in sinus rhythm with heart rate >70 bpm despite maximum doses of beta-blocker and an ACEI (or ARB) and an MRA (or ARB)
  - Reduces heart failure hospital admissions
- SGLT-2 inhibitors:
  - Recommended for use in patients with Type 2 diabetes mellitus with heart failure to reduce hospitalization
  - Shown to reduce all-cause and cardiovascular death in patients with HFrEF and HFpEF[61]
  - It also controls hyperglycaemia
  - Dapagliflozin 10mg orally in the morning in patients with eGFR ≥ 30mL/min/1.73m2
  - Empagliflozin 10mg orally in the morning in patients with eGFR ≥ 30mL/min/1.73m2. May increase to 25mg/day in patients with uncontrolled diabetes

7.7 MYOCARDIAL INFARCTION/ACUTE CORONARY SYNDROME

7.7.1 Introduction

Myocardial infarction (MI) is part of the acute coronary syndromes (ACS), usually due to disruption of blood supply to the myocardium or increased myocardial oxygen demand leading to injury or necrosis to the cardiomyocytes. It may be acute to subacute.[62]

Diabetes mellitus is a major risk factor for myocardial infarction and is largely described as a cardiovascular disease risk equivalent.[63, 64, 65]

7.7.2 Signs and Symptoms of myocardial infarction

Typical chest pains may be absent among patients with diabetes mellitus. Other symptoms may include:

- Shortness of breath
- Epigastric discomfort
- Excessive belching
- Easy fatigability
- Nausea
- Vomiting
- Loss of consciousness
- Delirium or confusion

Signs of ACS in patients with diabetes can be a combination of the following:

- Normal examination findings
- Cool, clammy extremities
- Diaphoresis
- Hypotension
- Hypertension
- Jugular venous distention
- Pulmonary oedema and other signs of heart failure, such as S3, S4, systolic murmurs, basal crackles

Complications of MI

- Arrhythmic: heart blocks, atrial and ventricular arrhythmias
- Ischaemic: reinfarction, peri-infarct ischemia, and infarct extension
- Mechanical: mitral valve and chordae rupture/tear, ventricular septal defect (VSD), ventricular free wall rupture, tamponade, and aneurysm
- Inflammatory: pericarditis, post-myocardial infarction (MI), Dressler syndrome
- Systemic: cardiogenic shock, heart failure, embolic cerebrovascular accident, MI, and systemic and lower extremity embolism

7.7.3 Management of Acute Coronary Syndrome in Diabetes Patients.

The management principles are the same as in patients without diabetes, except that the management of hyperglycaemia or acute diabetic complications should go in tandem. The preferred glucose-lowering medication in patients with ACS is soluble insulin until the patient is hemodynamically stable.

Initial management

Rapidly assess all patients with diabetes presenting with acute severe chest pain or suspected acute coronary syndrome:

- Assess airways, breathing, circulation,
- Give oxygen if oxygen saturation is less than 95%, either by a nasal prong or mask.

At a health facility without a doctor (Level 1)

- Administer Aspirin 300mg by mouth (to chew) and transfer immediately to the appropriate higher facility.
- Obtain blood pressure.
- Laboratory investigation could be done but should not delay the transfer of the patient.
    - o blood sugar
    - o oxygen saturation

At a health facility with a doctor or physician specialist (Levels 2 & 3)

- All activities under Level 1
- Administer Aspirin 300mg by mouth (to chew)
- Give clopidogrel 300mg start, orally
- Obtain a 12-lead ECG immediately
- Obtain blood pressure in both arms
- Oxygen saturation (and blood gas analysis, if available)

Laboratory Investigation

- Chest X-ray
- Blood glucose level and urine dipstick for proteins, glucose and red blood cells.
- Cardiac biomarkers (Troponin/CK-MB)
- Blood lipid profile
- Blood urea electrolytes and creatinine
- C-reactive protein
- Serum uric acid

In facilities with a trained cardiologist, the following additional procedures can be done:

- Doppler echocardiogram
- Stress test in the case of unstable angina
- Coronary angiography
- Fractional flow reserve
- Intravascular ultrasound

Continuation of Care

- Optimise or initiate treatment for hypertension
- Optimise or initiate treatment for diabetes mellitus per appropriate guidelines
- Optimize cholesterol treatment
- Identify heart failure early and manage it
- Maximise optimal medical therapy before stress testing in patients with unstable angina

- In patients with diabetes presenting with acute myocardial infarction, insulin therapy by perfuser (if available) for controlling hyperglycaemia is preferred and safer in the acute stage and must be according to protocol (refer to Chapter 5). Oral glucose-lowering medications may be considered once patients are stable. It is important to note that hyperglycaemia may be a response to the acute stress of myocardial infarction.
- Refer to a centre with a cardiologist or facility for reperfusion therapy

Management of stable coronary artery disease (CAD) (Levels 2 & 3)

Diabetes is a major risk factor for stable coronary artery disease, and glycaemic control is essential in preventing the worsening of CAD.[66] The objectives of the treatment of stable CADs [67] are:

- To relieve or reduce chest pain and any other symptoms
- To avoid complications of CAD, acute myocardial infarction, heart failure, cardiac arrhythmias, and related death
- To identify and manage modifiable risk factors and
- To improve the quality of life of patients

To achieve the above objectives, the following strategies could be employed:

- Education of patients about the aetiology, clinical manifestations, treatment options and prognosis of ischaemic heart disease (IHD)
- Encouraging active participation of patients in their treatment decisions
- Identifying and treating conditions that contribute to, worsen, or complicate IHD
- Effectively modifying risk factors for IHD by both pharmacological and non-pharmacological methods
- Use of evidence-based pharmacological treatments to improve patients' health status and survival, with attention to avoiding drug interactions and side effects

Non-pharmacological treatment

- Healthy lifestyle modifications:
  - Weight control
  - Lipid management
  - Ensure compliance with BP control

- Smoking cessation and avoidance of exposure to second-hand smoke and the use of tobacco products such as "shisha"
- Reduction of alcohol intake
- Appropriate referral of patients.

- Identify and manage diabetes and other risk factors such as hypertension, hyperlipidaemias
  - Optimise or initiate treatment for diabetes mellitus aiming for an appropriate A1C level
  - Optimise or initiate treatment for hypertension
  - Optimize cholesterol treatment
  - Identify and manage heart failure appropriately (refer to the management of heart failure)
  - Refer patient to physician specialist/cardiologist for further evaluation and adequate treatment

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Chapter 8

MANAGING COMORBIDITIES IN DIABETES

LIST OF ABBREVIATIONS

ACE-I	Angiotensin-Converting Enzyme Inhibitor
ARB	Angiotensin Receptor Blocker
ARNI	Angiotensin Receptor Neprilysin Inhibitor
ASCVD	Atherosclerotic Cardiovascular Disease
CCB	Calcium Channel Blocker
CVD	Cardiovascular Disease
ECG	Electrocardiogram
EGFR	Estimated Glomerular Filtration Rate
ER	Extended-Release
LDL	Low-Density Lipoprotein
MRA	Mineralocorticoid Receptor Antagonist
SR	Slow Release
UACR	Urine Albumin Creatinine Ratio
WHO	World Health Organization

8.0 INTRODUCTION

Often, patients with Type 2 diabetes have comorbid cardiovascular risk factors such as hypertension, dyslipidaemia and obesity. These risk factors must be managed to reduce the possibility of atherosclerotic cardiovascular disease (ASCVD).

8.1 CARDIOVASCULAR RISK ASSESSMENT

Cardiovascular risk refers to the likelihood of a person developing an ASCVD event over a defined period.

The importance of ASCVD prevention remains key and should be delivered at the general population level by promoting healthy lifestyle behaviour. At the individual level, tackling unhealthy lifestyles and reducing causal cardiovascular (CV) risk factors, such as LDL cholesterol, blood pressure levels, and blood glucose control are important.

Despite the availability of a number of assessment tools for estimating the risk of initial ASCVD events in asymptomatic individuals, no single risk tool is best suited for all patient types. These guidelines adopt the *World Health Organization/International Society of Hypertension (WHO/ISH) risk assessment tool*[2] (Table 8.1).

World Health Organization/International Society of Hypertension (WHO/ISH) risk prediction tool

The WHO/ISH risk prediction charts, indicate a 10-year risk of a fatal or non-fatal major cardiovascular event (myocardial infarction or stroke) according to age, sex, blood pressure, smoking status, total blood cholesterol and the presence or absence of diabetes mellitus for 14 WHO epidemiological sub-regions.

The Western Sub-Saharan Laboratory-based Chart of the WHO/ISH risk prediction charts is appropriate for Ghana as it covers countries in the West African sub-region.[2]

HOW TO USE THE WHO/ISH PREDICTION CHART

The following information is needed for risk assessment:

- Age
- Sex
- Smoker or non-smoker
- Presence or absence of diabetes mellitus
- Systolic blood pressure
- Total blood cholesterol

Steps involved in calculating the risk

STEP 1: Select the section of the chart as relevant for people with or without Diabetes.
STEP 2: Select the table for men or women, as appropriate
STEP 3: Select smoker or non-smoker column
STEP 4: Age group
STEP 5: Within the selected box, find the cell where the person's systolic blood pressure and total blood cholesterol intersect
STEP 6: The colour of the cell indicates the 10-year risk of a fatal or non-fatal CVD event. The value within the cell is the risk percentage. Colour coding is based on the grouping
STEP 7: Record the CVD risk percentage in the person's chart
STEP 8: Counsel, treat and refer according to risk level

Risk Score and Category

Category	Score
Low 10-year risk	<10%
Intermediate 10-year risk	10-20%
High 10-year risk	>20%

Important considerations for all patients with or without diabetes

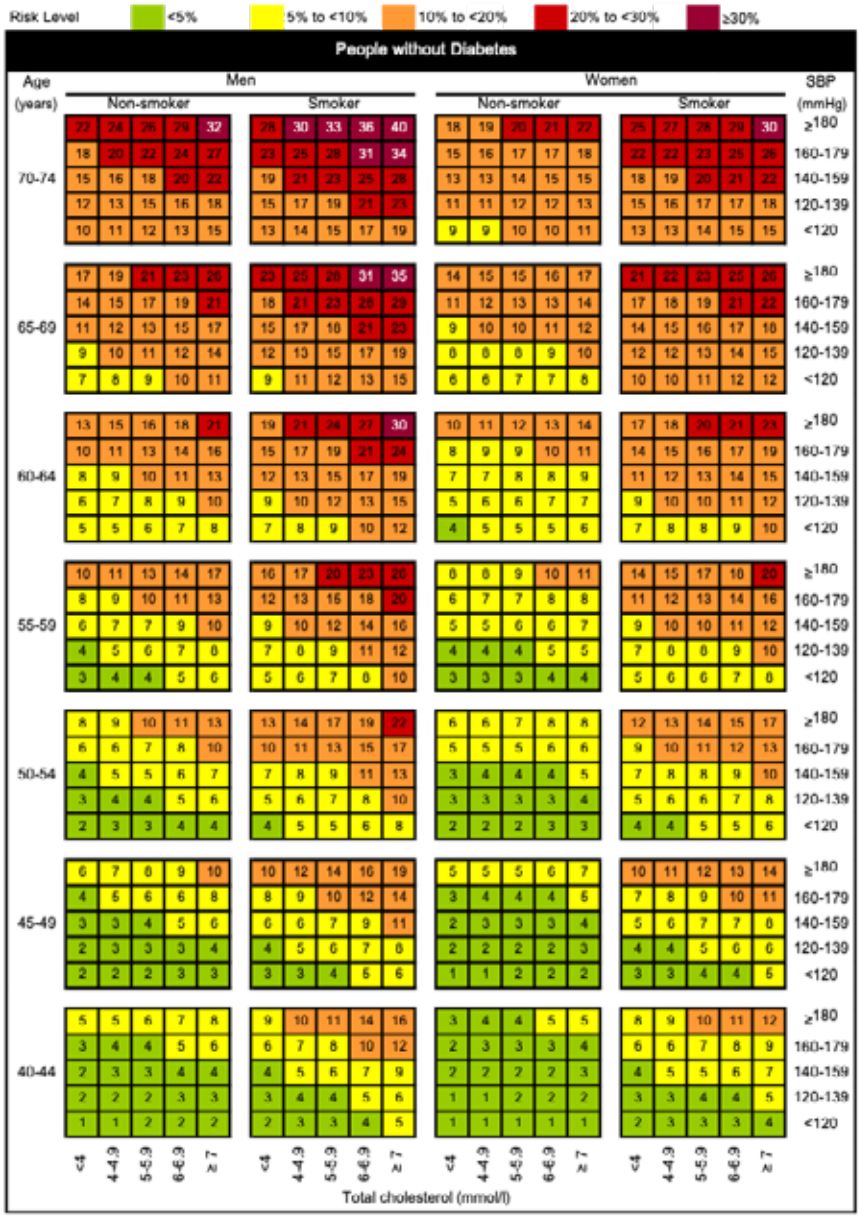
1. Consider statin treatment for the following categories:
   a. All adult patients with diabetes mellitus >40 years
   b. Patients with the following:

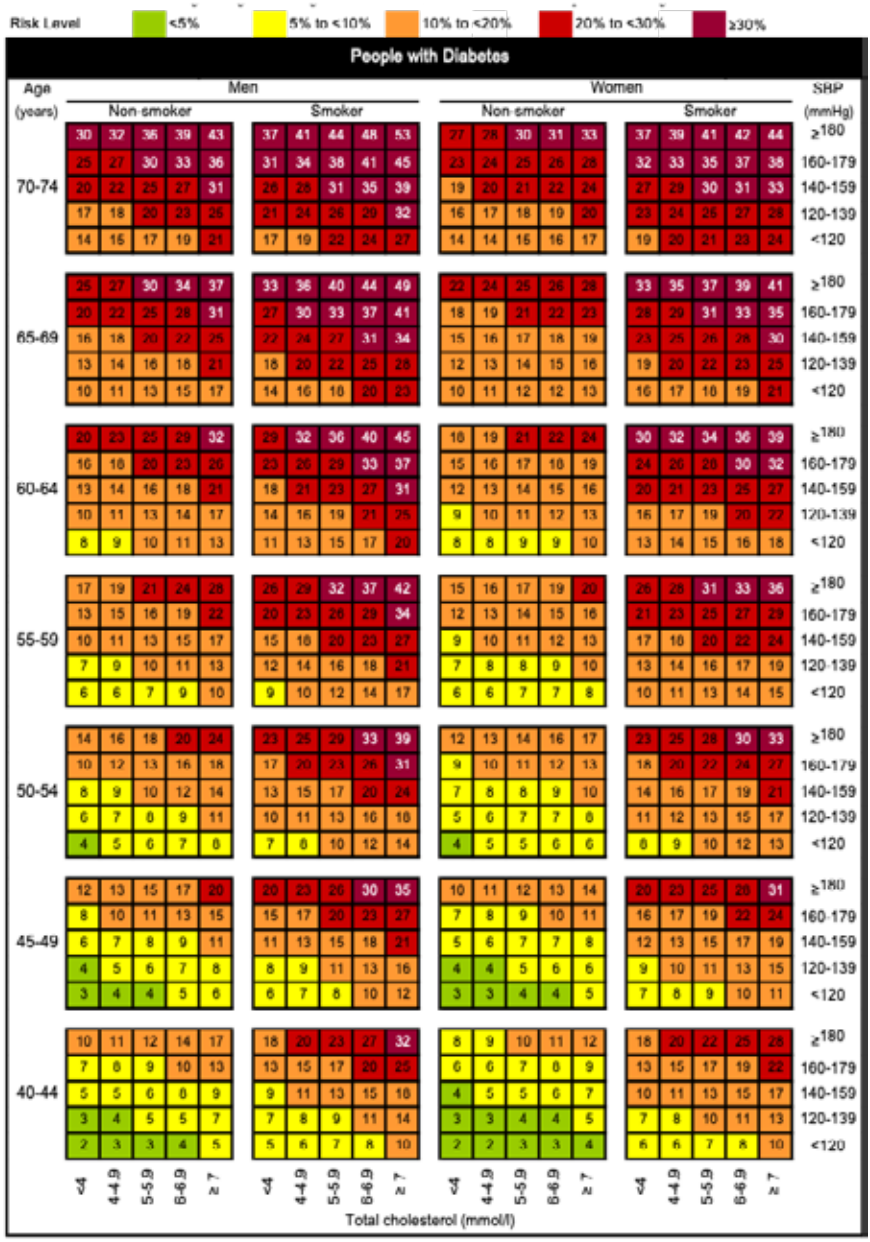
- Established CVD (coronary heart disease, myocardial infarction (recent or past), transient ischaemic attacks, cerebrovascular disease (ischemic) or peripheral vascular disease),

2. These patients do not require the use of risk assessment tools. If stable, should continue the treatment already prescribed and be considered as having risk (>20%)
   - Patients with albuminuria, retinopathy, and left ventricular hypertrophy

Table 8.1: WHO cardiovascular disease risk laboratory-based charts[2]

Western Sub-Saharan Africa




Risk Level
<5%
5% to <10%
10% to <20%
20% to <30%
≥30%
People with Diabetes
Age (years)
Men
Women
SBP (mmHg)
Non-smoker
Smoker
70-74
65-69
60-64
55-59
50-54
45-49
40-44
≥180
160-179
140-159
120-139
<120
<4
4-4.9
5-5.9
6-6.9
≥7
Total cholesterol (mmol/l)

8.2 DYSLIPIDAEMIA IN DIABETES

8.2.1 Introduction

Dyslipidaemia is defined as a metabolic disorder characterized by elevated levels of low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and elevated levels of triglycerides (TG).

Dyslipidaemia is one of the significant risk factors for CVD in people with Type 2 diabetes, abdominal obesity and insulin resistance or impaired glucose tolerance. CVD has remained the leading cause of morbidity and mortality in patients with Type 2 diabetes. LDL-C (especially small dense LDL) is considered most atherogenic and is the primary target for treatment.

Statins are the first line of recommended pharmacological agents for LDL-C reduction. Intensification of statin therapy should be considered before the introduction of combination therapy. Categorise patients into low, intermediate, and high cardiovascular risks by using the WHO/ISH risk assessment tool.

8.2.2 Diagnosis of Dyslipidaemia

Assessment

Measure fasting lipids: total cholesterol, TG, HDL-C and LDL-C.

How often:

If the cardiovascular risk is low, done annually.
If abnormal or on treatment, every 3-6 months.

8.2.3 Management of Dyslipidaemia

Use non-pharmacological interventions as initial treatment for all patients:

- Improve blood glucose control
- Reduce weight if indicated
- Reduce or avoid alcohol intake if triglycerides elevated

- Advice on smoking (tobacco) cessation
- Physical activity (PA) At least 150 minutes a week of moderate aerobic physical activity and not less than 10 minutes at a stretch
- Diet low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish

The potency of statins and indications for starting therapy according to risk categorization are set out in Tables 8.2 and 8.3, respectively.

Table 8.2: Potency of Statins

Intensity	LDL-C lowering effect	Statins (oral)
High intensity	≥50%	Atorvastatin 40–80mg Rosuvastatin 20-40mg
Moderate intensity	30%–49%	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastatin 20-40 mg
Low intensity	<30%	Simvastatin 10mg

Table 8.3: Risk Category and pharmacological intervention

Adult patient risk category	Recommendation/goals
Diabetes mellitus and aged 40 to 75 years (2 categories) (LDL-C ≥1.8 -4.9 mmol/L)	
1. High risk	High-intensity statin (if not possible, moderate-intensity statins)
2. Intermediate risk	Moderate-intensity statins
Age >75 years (with or without diabetes mellitus)	Individualized clinical assessment, risk discussion, and encouraged shared decision-making with the patient
All patients with confirmed ASCVD	High-intensity statin therapy with a target LDL-C < 1.8 mmol/L or reduction >50%
Other Categories	
Familial Hypercholesterolemia	No risk assessment; high-intensity statin therapy
20 to 39 years old with a family history of premature ASCVD	Estimate lifetime risk and manage (using a lifetime risk assessment tool) If LDL >4.1 mmol/l, consider statin therapy
Primary Hypercholesterolaemia (LDL-C ≥4.9 mmol/L)	No risk assessment; moderate to high-intensity statin

Ezetimibe and PCSK-9 inhibitors such as evolocumab, alirocumab and inclisiran can be added to maximum tolerable doses of statins to enhance further reduction of LDL-C to target levels.

Statins are recommended in patients with Type 1 diabetes mellitus who are at high-risk.

Statin therapy is not recommended in pregnant women and pre-menopausal patients with DM who are considering pregnancy.

Targets for Treatment

- High-risk: LDL <1.8 mmol/l, or a reduction of at least 50%
- Intermediate-risk: LDL <2.6 mmol/l, or a reduction of at least 50%
- Low risk: LDL <3.0 mmol/l
- HDL >1.0 mmol/l in men and >1.2 mmol/l in women indicate lower risk
- Triglycerides <1.7 mmol/l indicate lower risk, and higher levels indicate a need to look for other risk factors

Certain risk factors may increase the risk of ASCVD in diabetes patients (Table 8.4). A shared decision must be made to commence statin therapy.

Table 8.4: Diabetes-specific Risk Enhancers

- Long duration (≥10 years for Type 2 diabetes or ≥ 20 years for Type 1 diabetes)
- Albuminuria ≥30 mcg albumin/mg creatinine
- eGFR <60 ml/min/1.73 m2
- Retinopathy
- Neuropathy
- ABI <0.9
- Chronic inflammatory conditions such as psoriasis, rheumatoid arthritis, lupus, HIV/AIDS)

MANAGEMENT OF DYSLIPIDAEMIA ACCORDING TO THE LEVEL OF CARE

Health Facility Without A Doctor (Level 1)

MANAGEMENT

Educate patients on the following:

- CVD risk factor reduction
- Need to maintain normal blood pressure. If blood pressure needs to be treated, refer to the section on blood pressure management below
  - do a lipid panel if available and refer.

Health Facility With A Doctor (Level 2)

MANAGEMENT
Educate patients on the following:

- CVD risk factor reduction, including lifestyle changes
- Need to maintain normal blood pressure. *If blood pressure needs to be treated, refer to the section on blood pressure management*
- Potential ASCVD risk reduction from lipid-lowering therapy
- The potential adverse effects of lipid-lowering therapy

Investigations

- Fasting blood lipid profile
- Thyroid function test (if lipid levels are very high)
- Serum albumin (if lipid levels are very high, to exclude nephrotic syndrome)
- Urine protein (if lipid levels are very high, to exclude nephrotic syndrome and diabetic nephropathy)
- Fasting glucose level
- Baseline Liver function tests and, when clinically indicated

Pharmacological Management

Refer to the guidance on statin therapy above (Table 8.3).

Follow Up

Monitor for side effects. Do baseline liver function tests and only when clinically indicated. Interrupt treatment when transaminases are three times or more above their upper limits.

Repeat lipids in 4 to 12 weeks to check LDL reductions/targets

Refer if the patient remains outside the target values beyond 6 months to a health facility with a specialist.

Health Facility with a Physician Specialist/ Tertiary Hospital (Level 3)

MANAGEMENT

Educate patients on:
As mentioned above, for a facility with a Doctor

Investigations

- Fasting blood lipid profile
- Thyroid function test (if lipid levels are very high)
- Serum protein (if lipid levels are very high, to exclude nephrotic syndrome)
- Urine protein (if lipid levels are very high, to exclude nephrotic syndrome and DM nephropathy)
- Fasting blood sugar
- Liver function test (at the beginning and if clinically indicated)
- Creatinine kinase (only if clinically indicated)

Pharmacological Management

Refer to the guidance on statin therapy above.

In all cases, assess adherence and percentage LDL reduction and lifestyle changes with repeated lipid measurement 4 to 12 weeks after statin initiation or dose adjustment. This may be repeated every 3 to 12 months as needed.
High-risk ASCVD patients
Such as patients with a history of major ASCVD events or Multiple high-risk conditions:

- Add Ezetimibe to the patient's maximally tolerated statin therapy if the LDL-C level remains ≥ 1.8 mmol/l
- If the LDL-C level on a maximally tolerated statin and Ezetimibe remains ≥ 1.8 mmol/l, a PCSK9 Inhibitor can be added.

In patients with severe hypercholesterolaemia (LDL-C level ≥ 4.9 mmol/l), add Ezetimibe if the LDL-C level remains ≥ 2.6 mmol

- Add a PCSK9 inhibitor if the LDL-C level on a statin and Ezetimibe remains > (2.6 mmol/L), and the patient has multiple factors that increase the subsequent risk of ASCVD events,7.

8.3 HYPERTENSION IN DIABETES

8.3.1 Introduction

High blood pressure is defined as a sustained pressure of more than 140/90mmHg in adults 18 years or above. Among children less that 18 years, age-related centiles are preferred in diagnosing hypertension. It is commonly prevalent in patients with diabetes, conferring additional risk for the development of atherosclerotic cardiovascular and kidney disease. Thus, efficiently treating hypertension modifies this macrovascular risk with beneficial effects on microvascular complications.

Hypertension is twice as common in Type 2 diabetes populations compared with age-matched controls. It may predate or occur after the diagnosis of diabetes or present because of co-existing kidney disease. The risk of hypertension tends to increase in Type 1 diabetes patients with long duration after diagnosis or the presence of albuminuria.

Blood pressure should be measured at each clinic visit with an appropriately sized cuff after the patient has rested for at least 5 minutes. Home blood pressure measurements complement the diagnosis by identifying white coat or masked hypertension while providing feedback that ensures patient medication adherence. During treatment, a blood pressure of < 130/80 mmHg should generally be the target for diabetes patients with hypertension.

8.3.2 Clinical Features

Most patients present with no or subtle symptoms and signs, so clinicians must have a high index of suspicion. Symptoms and signs may be related to the effect of hypertension on end-organ (such as the eye, kidney, heart and brain) or a secondary cause.

Symptoms

- Headaches
- Light-headedness
- Palpitations
- Difficulty in breathing

- Easy fatiguability
- Chest pains
- Blurred vision
- Loss of consciousness
- Seizures

Signs

- Displaced apex
- Enlarged and sustained apical impulse
- S3 heart sound indicating heart failure
- Cotton wool spots, flame-shaped haemorrhage indicating retinopathy
- Faint or absent peripheral pulses in peripheral artery disease
- Irregular heartbeat
- Radio-femoral delay suggestive of coarctation of the aorta
- Renal bruit-suggestive of renal artery stenosis

8.3.3 Complications

Hypertension exerts deleterious effects on various end organs, particularly the heart, kidney, brain, eyes and blood vessels.[1] Atherosclerotic cardiovascular disease is the number one cause of mortality in patients with diabetes. These consequences of poorly controlled hypertension outlined below can be mitigated with efficient control.

- Coronary heart disease
- Stroke
- Subarachnoid haemorrhage
- Hypertensive encephalopathy
- Peripheral artery disease
- Hypertensive heart disease
- Heart failure
- Aortic dissection
- Chronic kidney disease
- Retinopathy
- Arrhythmias

Therapy-related complications may also arise in the course of treatment; hence clinicians must be on the lookout for them.

- Angiotensin Converting Enzyme Inhibitors/Angiotensin Receptor Blockers (ACEI/ ARBs)/ may induce hyperkalaemia, angioedema, and chronic cough
- Mineralocorticoid Receptor Antagonists (/MRAs) may cause hyperkalaemia
- β-blockers may mask the symptoms of hypoglycaemia and worsen peripheral artery disease
- Thiazide diuretics may cause hyperglycaemia by inhibiting insulin release
- Calcium Channel Blockers (CCBs) may induce palpitations, headaches and peripheral oedema

8.3.4 MANAGEMENT OF HYPERTENSION ACCORDING TO LEVEL OF CARE

Non-Pharmacological Management for All Levels of Care

- Lifestyle management should form the backbone of therapy for all patients before initiating antihypertensive medications[2]
- Nutritional counselling, including Dietary Approaches to Stop Hypertension (DASH)- style diet is recommended[3]: reduction of salt intake to less than 2g/day[4], avoiding the addition of salt to food at the table, avoiding canned foods preserved with brine, increase intake of fresh fruit, vegetable and low-fat dairy foods, avoiding/reducing alcohol intake
- Counselling or referring for smoking cessation and increasing physical activity to at least 30 minutes daily about 5 times per week have all been shown to impact blood pressure control

Refer to Chapter 4 for more details on lifestyle management.

Health Facility Without A Doctor

Adapted from the National Guidelines for the Management of Cardiovascular Diseases, 2019)[15]

Laboratory Investigation

- Random blood glucose (finger prick)
- Urine dipstick for proteins
- If the above tests are unavailable, or laboratory tests suggest high glucose or proteins present, refer to a facility with a doctor
- Renal function tests

Pharmacological Management

- Monotherapy: thiazide-like diuretic or CCBs

If after 2-4 weeks of treatment, the response is not adequate, add a second drug (dual therapy):

- CCB + Thiazide-like diuretic

Refer to Table 8.5 below for examples and doses of drugs

- If BP remains uncontrolled (refer to treatment objectives for target BP values), refer the patient to the next level of care: a health facility with a doctor.)
- Optimise glycaemic control using metformin, sulphonylureas or thiazolidinediones as monotherapy or in combination.

Refer to guideline recommendation for glycaemic control according to the level of care.

Health Facility With Non-Specialist Doctors

Investigations

It behoves the consulting clinician to request appropriate investigations that will aid in assessing complications or end-organ damage arising from hypertension or its treatment, depending on the clinical presentation of the individual patient. Those identified should be referred to the appropriate specialist, such as a physician specialist, diabetologist, nephrologist, cardiologist, etc.

- Fasting/random blood glucose
- Glycated haemoglobin (HbA1c)
- Full blood count

- Serum lipid profile
- Blood urea, creatinine and electrolytes with estimated glomerular filtration rate (eGFR)
- Urinalysis (dipstick and microscopy)
- Urine albumin/creatinine ratio (UACR), if available
- 12-lead ECG
- Chest X-ray
- Echocardiogram if available
- Serum uric acid
- Renal ultrasound to assess kidney structure
- Ophthalmologic assessment to look for retinopathy
- Computed Tomography of the head to look for stroke and subarachnoid/ intracranial haemorrhage when indicated

Pharmacological Management

- Optimise glycaemic control by reviewing anti-glycaemic agents/ medications

Start monotherapy if BP>140-159/90-99 and titrate up till target BP of <130/80 with either

- ACE-I/ARBs, preferably if albuminuria is present or
- Thiazide-like diuretics or
- Calcium channel blockers (CCB)

Dual therapy if BP >160/100

- ACE-I/ARBs + Thiazide-like diuretics
- ACE-I/ARBs + CCBs
- 3-drug combination ACE-I/ARBs, Thiazide-like diuretics and CCBs if the response is not adequate after 2-4 weeks of treatment

If BP remains uncontrolled (refer to treatment objectives for target BP values), refer the patient to the next level of care: a health facility with a Specialist

Health Facility With Specialist Doctors

Investigations

These include but are not limited to the following;

- All investigations under Levels 1 and 2
- Echocardiogram if signs of hypertensive heart disease or heart failure present
- Investigate for other secondary causes when indicated (such as polycystic kidney disease, phaeochromocytoma, Cushing syndrome, hyperthyroidism, hyperparathyroidism, acromegaly, Conn's syndrome, coarctation of the aorta and renal artery stenosis)

Pharmacologic Management

- Optimise glycaemic control by reviewing anti-glycaemic agents/ medications

If there is no evidence of albuminuria, initiate medications if BP > 140/90[6, 7, 8,19] using either

- ACE-I/ARBs or
- Thiazide-like diuretics or
- Calcium channel blockers

These can be used as monotherapy or in combination. Multiple drug therapy may be required in patients with comorbidities or compelling indications to attain target BP. Options include the use of angiotensin-receptor neprilysin inhibitor (ARNI) /ACE-I/ARBs/CCBs/β-blockers/ mineralocorticoid receptor antagonists (MRAs).

Strive to attain a **BP target of <130/80 or lower** in such patients if they can be tolerated;

- The 10-year cardiovascular risk is >10% or
- The patient has evidence of end-organ damage, such as
  - Moderately increased albuminuria 30-300mg/g or severely increased albuminuria >300mg/g - ACE I/ARBs. Thiazide-like diuretics and non-dihydropyridine calcium channel blockers (diltiazem/verapamil)[19,20] may be used if ACE-I/ARB are not tolerated or unavailable.

- Evidence of hypertensive heart disease- ACE inhibitors/ARBs/B-blockers
- Myocardial infarction/ischaemic heart disease- ACE inhibitors/ARBs/β-blockers/aspirin
- Evidence of heart failure- ACE-I/ARNI/ β-blockers/diuretics inhibitors/ARBs/ARNI/MRA/diuretics[1]
- High risk of stroke- dihydropyridine calcium channel blockers (amlodipine)
- Retinopathy – control BP and refer appropriately to an ophthalmologist

- Treatment targets must be tailored to individual patients taking into account the presence of comorbidities, age, cost and ability to tolerate the target blood pressure.
- If blood pressure fails to come down despite the patient being on maximal tolerable doses of 3 appropriate medications, including a thiazide or thiazide-like diuretic, commence investigations or refer to an endocrinologist to evaluate for secondary causes of hypertension.

Table 8.5: Antihypertensives dosing

	Drug Class	Dosing	Prescribing level	
		Initial	**Maximum**	
1.	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACE-I)			
	Enalapril	2.5mg daily	20mg daily (in one or two divided doses)	Levels 2 and 3
	Ramipril	1.25mg daily	10mg daily	
	Lisinopril	10mg daily	40mg daily	
	Perindopril	4/5 mg daily	8/10 mg daily	
	Captopril	6.25mg 3x daily	50mg 3x daily	

2.	**Angiotensin Receptor Blocker (ARB)**			
	Losartan	25mg daily	100mg daily	Levels 2 and 3
	Valsartan	80mg daily	160-320 mg daily	
	Telmisartan	20mg daily	80mg daily	
	Candesartan	4mg daily	32mg daily	
	Irbesartan	150mg daily	300 mg daily	
3.	**Angiotensin Receptor Neprilysin Inhibitor**			
	Valsartan/sacubitril	26mg/24mg 2x daily	103mg/ 97mg 2x daily	Levels 2 and 3
4.	**Beta Blocker (BB)**			
	Carvedilol	3.125mg 2x daily	25mg 2x daily	Level 2 and 3
	Metoprolol	25mg daily	100mg daily	
	Bisoprolol	1.25mg daily	10mg daily	
	Labetalol	100mg 2x daily	400 mg 2x daily	
	Atenolol	25mg daily	100mg daily	
	Nebivolol	5mg daily	20 mg daily	
5.	**Dihydropyridine Calcium Channel Blocker (CCB)**			
	Amlodipine	5mg	10mg	All levels
	Nifedipine retard	10-20mg 2x daily	30mg 2x daily	
	Felodipine	5 mg daily	10 mg daily	
6.	**Non-Dihydropyridine Calcium Channel Blockers**			
	Diltiazem	180mg daily	360mg daily	Levels 2 and 3
	Verapamil	80mg daily	320mg daily	
7.	**Thiazide-Like Diuretics**			
	Indapamide SR	1.25mg daily	5mg daily	All levels

8.	Mineralocorticoid Receptor Antagonist			
	Spironolactone	25 mg daily	200mg daily	Levels 2 & 3
	Eplerenone	25mg daily	50mg daily	
	Amiloride	5 mg daily or in divided doses	10mg daily or divided doses	
9.	Centrally acting agents			
	Methyldopa	250mg two-three times daily	1000mg daily or in divided doses	Levels 2 & 3
	Clonidine	0.1 mg two times daily	2.4mg/daily	
	Phenoxybenzamine	10 mg two times daily	40mg three times daily	
10.	Vasodilators			
	Hydralazine	25mg two-three times daily	150mg daily	Levels 2 and 3
11.	Alpha 1 receptor blocker			
	Terazosin	1mg daily	20mg daily	Levels 2 and 3
	Prazosin	1mg two-three times daily	20mg daily	

8. 4 OBESITY IN TYPE 2 DIABETES.

8.4.1 Introduction

Weight gain is a strong risk factor for developing Type 2 diabetes, and a 5 – 10% weight loss has been consistently associated with good diabetes and cardiovascular risk control.[22, 23]

Data from the RODAM study demonstrated this strong association between excess weight gain and diabetes. In rural Ghana, the prevalence of

obesity was 1.3 % in men and 8.3 % in women, with the prevalence being considerably higher in urban Ghana (men, 6.9 %; women, 33.9 %). The prevalence of Type 2 diabetes was low at 3.6 % and 5.5 % in rural Ghanaian men and women and increased in urban Ghanaians (men, 10.3 %; women, 9.2%).[4]

Weight loss for overweight/obese patients with diabetes must be considered an integral part of management. There is strong and consistent evidence that obesity management can delay the progression from prediabetes to Type 2 diabetes[25, 26] and is beneficial in the treatment of Type 2 diabetes.[27, 28]

Management of obesity must have a multidisciplinary approach which involves dietary changes, exercise, behavioural therapy, pharmacotherapy, and surgical options.

8.4.2 Common causes of obesity:

- Physical inactivity
- Overeating
- Genetics
- A diet high in simple carbohydrates
- Increased frequency of eating
- Medications such as prolonged steroid usage, antipsychotics, insulins and sulfonylureas
- Psychological factors such as depression
- Diseases such as hypothyroidism, insulin resistance, polycystic ovary syndrome, and Cushing syndrome also contribute to obesity

8.4.3 Classification of overweight and obesity

The WHO classification of obesity is illustrated in Table 8.6

Table 8.6: WHO Classification of Weight by Body Mass Index (BMI) in Adults

Classification	International BMI category (kg/m2)
Underweight	<18
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obese	>30.0
Class I Obesity Class II Obesity Class III Obesity	30.0–34.9 35.0–39.9 ≥40.0
Normal weight	18.5–24.9
Overweight	25.0–29.9

NB: Formula to calculate BMI = weight in kilograms divided by the square of the height in meters (kg/m2)

8.4.4 Evaluation of Obesity:

a. For all Levels of care
   1. Determine Obesity Measurements
      - Body Mass Index (BMI) OR
      - Waist Circumference (with cut-offs < 102cm for men and < 88cm for women)
      - Waist-to-Hip Ratio (only for a Facility with a doctor)

b. Facility with a Doctor/Specialist
   1. Evaluate Comorbid Conditions
      - Hypertension and Dyslipidaemia
      - Respiratory Diseases; Sleep Apnoea, Pickwickian hypoventilation, Asthma, Pulmonary Hypertension (Cardiomegaly, Congestive Heart Failure)
      - Gastrointestinal Diseases; Gall bladder Disease (Cholecystitis. Cholelithiasis), Non-alcoholic Steatohepatitis
      - Joint Diseases; Osteoarthritis, Degenerative Joint Disease, Gouty Arthritis
      - Menstrual irregularities

- Malignancies; Endometrial, Breast, Cervical and Ovarian in women. Colorectal and Prostate in men.
- Psychosocial issues

2 Evaluate patients' readiness and ability to lose weight
Encourage and counsel the patient to lose weight

3 Laboratory Investigations
   a) Fasting Lipid profile
   b) Fasting Plasma Glucose, HbA1c
   c) Liver Function Test
   d) Renal Function Test
   e) Serum Uric Acid
   f) Thyroid Stimulating Hormone (TSH)
   g) Others may include Highly Sensitive C-Reactive Protein (hs-CRP) etc., based on findings on evaluation

NB: Where facilities do not permit most of the above assessments, please refer for specialist care.

8.4.5 Management options for overweight and obesity

Management options for managing obesity include lifestyle measures, pharmacotherapy, and surgery (Table 8.7).

Table 8.7: Management options for Overweight and Obesity in Type 2 Diabetes[29]

Treatment	BMI category (kg/m^2)				
	25-26.9	27-29.9	30-34.9	35-39.9	>40
Lifestyle changes	Indicated when with comorbidity	+	+	+	+
Pharma-cotherapy		Indicated when with comorbidity	+	+	+
Surgery				Indicated when with comorbidity	+

- Management of Obesity MUST be at a centre with a DOCTOR or SPECIALIST
- Management must involve a multidisciplinary approach.
- Facilities without a doctor must advise on lifestyle measures and institute appropriate referrals after an initial assessment and diagnosis of overweight/obesity
- Facilities with a doctor but without a multidisciplinary approach to care MUST consider referral for SPECIALIST/MULTIDISCIPLINARY CARE under the following instances:
    1. Failure to achieve set goals/targets within six (6) months of care
    2. Obese clients at moderate, high or extreme risk, as explained above

Non-pharmacological Management

Adapted from American Diabetes Association and American College of Clinical Endocrinologists guidelines on non-pharmacological management of obesity in type 2 diabetes [29, 30]

- Diet, physical activity, and behavioural therapy designed to achieve, and maintain ≥ 5% weight loss are recommended for patients with Type 2 diabetes who have overweight or obesity and are ready to achieve weight loss. More significant benefits in the control of diabetes and cardiovascular risk factors may be gained from even greater weight loss.

Refer to Chapter 4 for further details about lifestyle changes.

Pharmacological Management:

a) When choosing glucose-lowering medications for patients with Type 2 diabetes and overweight or obesity, consider the medication's effect on weight.
b) Weight-loss medications (Table 8.8) are effective as adjuncts to diet, physical activity, and behavioural counselling for selected patients with Type 2 diabetes and BMI ≥27 kg/m^2. Potential benefits must be weighed against the potential risks of medications.
c) If a patient's response to weight loss medications is < 5% after 3 months or there are significant safety or tolerability issues at any time, the medication should be discontinued, and alternative medications or treatment approaches should be considered.

Table 8.8: Obesity Medications

Medication	Mechanism of action	Drug tolerability
Orlistat	Reversibly inhibits gastric and pancreatic lipases	Steatorrhoea
Lorcaserin	Selective serotonin receptor antagonist (SSRA)	Headaches Dizziness Fatigue
Phentermine/ topiramte ER,	Sympathomimetic/ anticonvulsant	Paraesthesia Dysgeusia Dizziness Dry mouth
Naltrexone SR/ bupropion SR	Opioid receptor antagonist/ dopamine/noradrenalin reuptake inhibitor	Nausea Vomiting Headaches Dizziness Insomnia
SC Liraglutide 3 mg daily *(Start from 0.6 mg, and increase dose by 0.6mg each week)*	GLP-1 receptor agonist	Nausea Vomiting Diarrhoea Dyspepsia Abdominal pain
SC Semaglutide 2.4 mg once weekly *(Start from 0.25 mg, and increase dose every 4 weeks till a maximum dose of 2.4 mg once weekly)*	GLP-1 receptor agonist	Nausea Vomiting Diarrhoea Dyspepsia Abdominal pain

Specialists only

- Employ all other weight loss strategies concurrently
- Most obesity medications are expensive
- Phentermine and Orlistat are the least expensive
- Orlistat is preferred among the medications as first-line
- The usual dosing of Orlistat should be 120mg TID PO, preferably with each meal containing some fat
- Orlistat should be supplemented with fat-soluble vitamins; A, E, D and K in view of the malabsorptive adverse effect of these vitamins
- Re-evaluate efficacy, compliance and adverse effects on a schedule;
    1. Stop weight loss medications if the patient fails to lose 5% of body weight after 12 weeks at the maximal dose
    2. Document BMI and treatment plan at a minimum of every six (6) months

Metabolic Surgery (Bariatric Surgery) - Specialist Centres Only

a) Surgery (restrictive, malabsorptive or a combination) may be considered an option for adults with Type 2 diabetes and BMI above 35 kg/m2 who do not achieve durable weight loss and improvement in comorbidities (including hyperglycaemia) with tested efficacious non-surgical methods.
b) Consider other anti-glycaemic drugs that enhance weight loss and avoid those that promote weight gain.

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Chapter 9

MANAGEMENT OF CHILDREN AND ADOLESCENTS WITH DIABETES MELLITUS

LIST OF ABBREVIATIONS

ANC	Antenatal Care
TG	Thyroglobulin
TPO	Thyroid Peroxidase
BMI	Body Mass Index
BUE & Cr	Blood Urea, Electrolytes & Creatinine
DKA	Diabetes Ketoacidosis
ECG	Electrocardiogram
GLP-1	Glucagon-Like Peptide 1
HbA1c	Glycated Haemoglobin
HHS	Hyperosmolar Hyperglycaemic State
LFT	Liver Function Tests
MODY	Maturity-Onset Diabetes Of The Young
OGTT	Oral Glucose Tolerance Test
ORS	Oral Rehydration Salts
PALS	Paediatric Advanced Life Support

PBG	Plasma Blood Glucose
RBG	Random Blood Glucose
TSH	Thyroid Stimulating Hormone
SMBG	Self-Monitoring of Blood Glucose

9.0 INTRODUCTION

The predominant type of diabetes in children and adolescents is Type 1; however, Type 2 diabetes is becoming increasingly common in this age group due to the increasing prevalence of obesity among this age group (Figure 9.1).[1] The presentation of diabetes in children and adolescents is generally similar to adults; the peculiar differences in the management will be highlighted in this chapter.

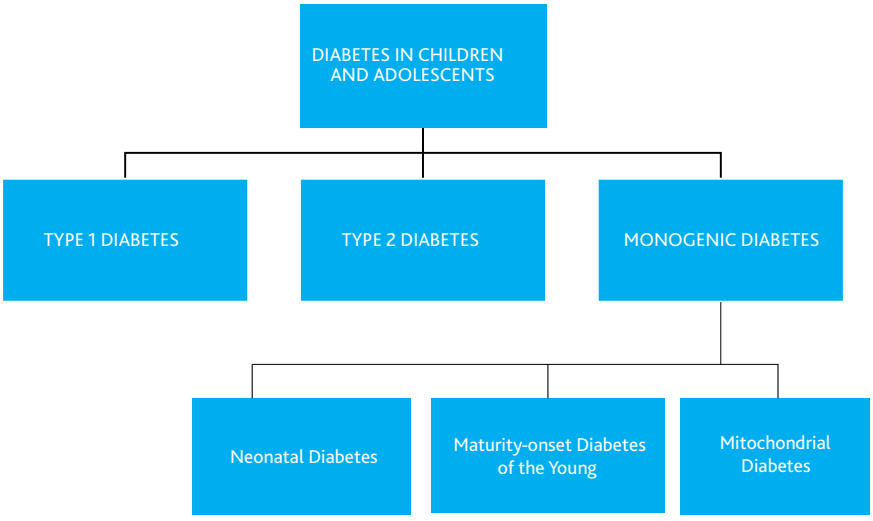

Figure 9.1: Types of diabetes in children and adolescents

9.1 TYPE 1 DIABETES

Type 1 diabetes is the commonest form of diabetes in children and adolescents.

9.1.1 Clinical presentations

- Polyuria, nocturia, polydipsia, polyphagia
- Changing diapers more frequently in babies / nocturnal enuresis (secondary enuresis)
- Weakness/ Easy fatigability
- Blurred vision
- Unexplained weight loss/Poor growth
- Amenorrhea/ Irregular menses
- Florid fungal or bacterial skin infections /Recurrent mucosal fungal infection (folliculitis, balanitis, vaginal, and oral candidiasis)
- Recurrent urinary tract infection

9.1.2 Physical examination

At the first visit, a thorough physical examination needs to be documented with emphasis on the following;

- General health status (looks well or ill), height, weight, head circumference if less than three years, and body mass index (BMI), plotted on appropriate age and sex-specific centile charts.
- Signs of malnutrition- wasting/ obesity
- Blood pressure using appropriate cuff size, plotted on the centile chart for age and sex.
- Scalp and skin for fungal or bacterial infection, e.g., Taenia corporis / furuncles,
- Neck and axillary flexures for acanthosis nigricans (common in Type 2 diabetes as a marker of insulin resistance)
- Injection sites for signs of inflammation, ulcers, scars, and lipodystrophy[a].

[a]*If already diagnosed and on insulin injections, inspect injection sites*

- *Characteristic symptoms include polyuria (excessive urination), polydipsia, and weight loss. Others include lack of energy/fatigue, bedwetting (enuresis) and failure to thrive*
- *Diagnostic criteria for diabetes in children and adolescents are based on laboratory measurements of plasma glucose. However, capillary blood from finger pricking may be used to diagnose diabetes in locations with poor laboratory support*
- *The differentiation between Type 1, Type 2, monogenic, and other forms of diabetes should be made so that appropriate management can be instituted*

9.1.3 Investigations at Diagnosis

The diagnostic investigations for Type 1 are grouped into specific and ancillary investigations. The ancillary blood investigations might be costly and generally will not alter the acute initial management of the patient. There is the need to discuss with an endocrinologist or a specialist with an interest in diabetes in children or a family physician before requesting the ancillary investigations. These investigations have been further grouped into the levels of care.

Investigations at diagnosis

Level 1 – Facilities without doctors

- Fasting blood glucose (FBG)
- Random blood glucose (RBG)

(Confirmed with plasma samples if possible/available)

Levels 2 & 3
Facilities doctors & specialist doctors
As per Level one
plus

- Glycated haemoglobin (HbA1c)

The following investigations do not alter the initial management but are needed to plan for ongoing care.

- C-peptide, insulin levels (measured before insulin is started)[a], thyroid-stimulating hormone (TSH), free thyroxine (FreeT4), anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies (anti-TPO)[b]
- Coeliac screening-Serum immunoglobulin A(IgA) anti-tissue transglutaminase antibody (anti-tTG-IgA)[c]
- Autoantibodies - markers of beta cell autoimmunity in Type 1 diabetes and can differentiate Type 1 diabetes from Type 2 diabetes.

Involve a paediatric endocrinologist or a paediatrician to assist in decision-making.

- Islet cell antibodies (ICA) against cytoplasmic proteins in the beta cell
- Antibodies to glutamic acid decarboxylase (GAD-65)
- Insulin autoantibodies (IAA)
- Antibodies against protein tyrosine phosphatase (IA-2A)
- Zinc transporter 8 (ZnT8) antibodies

[a] *Measured for those who phenotypically look like Type 2. Involve a Paediatric Endocrinologist*
[b] *Measured at diagnosis, if antibodies are present, monitor the TSH yearly. If antibodies are negative, then follow the ongoing care plan.*
[c] *Measured at diagnosis*

9.1.4 Diagnosis

The diagnosis of diabetes in children and adolescents with Type 1 is made by using either random blood glucose (RBG) or random plasma glucose (RPG) or fasting plasma glucose (FPG), or glycated haemoglobin (HbA1c) in presence of signs and symptoms suggestive of diabetes.

Criteria for diagnosis[2]

- Symptoms and signs suggestive of diabetes with high RBG or RPG (≥11.1 mmol/L)

Or

- Symptoms and signs suggestive of diabetes with FPG ≥ 7 mmol/L (fasting means 8-12 hours without a meal/ caloric intake)[1]

Or

- HbA1c ≥ 6.5%

9.1.5 Management

It is recommended that children and adolescents with Type 1 diabetes be managed by a multidisciplinary team led by a doctor. The team should include, at the minimum, a paediatric endocrinologist/diabetologist or a physician trained in the care of children and adolescents with diabetes, a paediatric/diabetes nurse educator, a dietician, and a clinical psychologist or social worker where possible.[3] The key to management is to adopt a tailored-needs approach and education at each visit.[4]

All patients with Type 1 diabetes need insulin for survival. The usual recommended insulin dose for the pre-pubertal age range is 0.7-1.0 IU/kg/day.[5] However, requirements may rise substantially above this during puberty to about 2 IU/kg/day because of resistance from sex steroids and growth hormone and may decrease during the "honeymoon phase" (before the substantial destruction of beta cells occur) to <0.5 IU/kg/day.[5,6]

The appropriate dose of insulin, therefore, is that which achieves the best attainable glycaemic control for an individual child or adolescent whilst limiting hypoglycaemia, hyperglycaemia, glycaemic swings and resulting in normal growth and development of the child.

Multiple-dose injection regimen mimics the physiological pattern of insulin secretion and is the preferred regimen in managing children and adolescents with type 1 diabetes.

Any child or adolescent to be started on insulin for the first time should be admitted and taught how to inject insulin and monitor the blood glucose level. If the facility does not have the logistics to admit, the patient should be referred to another facitliy that can do so.

No child or adolescent and their caregiver should be discharged home without adequate knowledge on;

- how to correctly draw insulin from a vial or dial an insulin pen
- the injection sites for insulin
- insulin storage
- how to correctly test the blood glucose level and document properly
- how to adjust insulin dose for low and high blood glucose (insulin correction)

9.1.6 Management Goals in Children and Adolescents

- Prevent hyperglycaemia and glucose spikes
- Prevent and adequately correct hypoglycaemia
- Prevent acute complications, e.g., diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS)
- Ensure normal growth and development
- Monitor and prevent long-term complications of diabetes, such as diabetic retinopathy and diabetic nephropathy.

9.1.7 Non-pharmacological management

General

- Diabetes education in age-appropriate language, and well understood by the child or adolescent and caregiver is crucial.[7] It must be started at diagnosis and continued throughout the lifetime. The child or adolescent and their caregivers should be involved in the education tailored towards the age and social settings

- Survival skills must be taught early to every child, including symptoms and management of hypoglycaemia and hyperglycaemia
- Self-monitoring of blood glucose is important in managing diabetes. Children must understand the importance of this and must be encouraged to do it by themselves and document it properly
- Fundamentals of insulin use: the technique of insulin injection, storage of the insulin, proper disposal of insulin syringes and lancets, should be taught at the time of diagnosis and reviewed at each clinic visit
- Psychological assessment and screening, where available, must be done from age 8 years as diabetes distress may be present. In Ghana, children with diabetes may be stigmatized, so it is important to create awareness about the negative effects of stigma on children with diabetes
- Growth monitoring (weight, height, head circumference, body mass index (BMI), pubertal staging) should be carried out for all children and adolescents with diabetes up to age 18 years

The education of patients and caregivers is the key to managing all forms of diabetes in children and adolescents

Dietary management[8]

- Children and adolescents with diabetes need dietary management, so dietician(s) with an interest in diabetes in childhood should be involved early at the time of diagnosis
- There is nothing like a diabetes diet!! However, the diet of a child with diabetes should be a balanced diet, like any growing child. What the child or adolescent requires is a healthy balanced meal appropriate for the age
- Where feasible, children and adolescents should be taught carbohydrate counting plus correction for the glucose level, and encouraged to practise it with each meal
- Education on nutrition should be offered at diagnosis and annually to ensure the child grows within the appropriate weight and height for age

Exercise

Although exercise has many benefits in children with diabetes, including a positive effect on weight, blood glucose, and cardiovascular disease, it

may be associated with hypoglycaemia and hyperglycaemia.[9] The child or adolescent should not be exempted from any school exercise programme. However, the school authorities must be informed and educated on diabetes, particularly hypoglycaemia and hyperglycaemia management pre and post-exercise.[9]

Considerations

- Exercise in children is important. A minimum of 30 minutes to one hour of moderate to vigorous intensity activity at least 5 times a week should be encouraged for those with Type 1 and 60 minutes or more for those with Type 2 diabetes. Activities such as skipping, walking, cycling, jogging, playing "ampe", football, tennis, and basketball, and doing house chores such as sweeping, mopping, weeding, watering flowers, washing cars should be encouraged.
- Certain intense exercises may cause hypoglycaemia; therefore, blood glucose may need to be monitored before, during, and even hours after exercise if a child or adolescent with Type 1 diabetes participates in such intense activity during the day.
- If blood glucose < 5mmol/L before exercise, give a carbohydrate snack and make sure blood glucose is > 5mmol/L before commencing exercise
- If blood glucose > 15mmol/L, exercise may not be advisable until the high glucose level has been corrected. Urine or blood ketones should be checked, and if present, the diabetes team should be consulted immediately. However, in the absence of ketones, hyperglycaemia can be corrected with soluble insulin, 0.01 units/kg every two hours until blood glucose is ≤ 10 mmol/L before exercising.

9.1.8 Pharmacological Management

The ideal goal is to achieve normal or near-normal blood glucose by monitoring the RBG, FBG and HbA1c and adjusting insulin dose appropriately. Blood glucose should be checked before each meal and where indicated, two hours after meals.

Targets in children[10]

Blood glucose levels

- Before meals: 4-7 mmol/L
- 2 hours after meals: 5 – 10 mmol/L
- Bedtime: 5-10 mmol/L
- 3 am: 5-8 mmol/L (monitor when there is persistent early morning hypoglycaemia or hyperglycaemia)

HbA1c targets

Values must be individualized

- 7.5% may be appropriate, but < 7% may be targeted if it can be done safely without hypoglycaemia or in children on continuous glucose monitoring and insulin pumps.
- In younger children below 6 years who may not be able to articulate symptoms of hypoglycaemia and in children with frequent hypoglycaemia, a higher HbA1c of ≥7.5% may be appropriate.

NB: Note that glycaemic control may become difficult during puberty due to insulin resistance and non-adherence

9.1.9 Ongoing care

Three to four monthly reviews are advised after the patient has been counselled and knows what to do. With each review;

- Self-monitoring of blood glucose (SMBG) recordings done at home must be reviewed
- HbA1c should be checked every 3 months
- Inspect injection sites for signs of inflammation, ulcers, scars, or lipodystrophy
- Provide education on Type 1 diabetes, acute management of hypoglycaemia and hyperglycaemia

5 years after diagnosis of Type 1 diabetes or at puberty, the child or adolescent should have a yearly assessment for complications which include; monofilament test, urine for microalbumin, lipid profile, liver function tests, chest x-ray, electrocardiogram (ECG) and fundoscopy.

2 yearly assessment for autoimmune diseases – (Coeliac disease and thyroid dysfunction). If thyroid antibodies were positive at diagnosis of Type 1 diabetes, the patient needs to be screened every year for autoimmune thyroiditis by measuring the TSH, anti-TPO and anti-TG antibodies

In the initial weeks post-diagnosis, 2-4 weekly reviews are recommended to assess the patient's coping mechanisms and glycaemic control. Provide information about the honeymoon phase where insulin requirement is low'
Review earlier than 3 months if major dose changes are made

9.2 TYPE 2 DIABETES AND METABOLIC SYNDROME IN CHILDREN AND ADOLESCENTS

Children at the onset of puberty and adolescents with BMI ≥ 85th percentile for age and sex and with risk factors for type 2 should be screened at least annually for Type 2 diabetes.

Children and adolescents with Type 2 diabetes and any of the following characteristics are at risk of developing of metabolic syndrome, and are predisposed to a higher risk of atherosclerotic cardiovascular disease:

- BMI ≥95th percentile
- Blood Pressure ≥90th percentile
- Triglycerides ≥ 1.7mmol/l
- HDL- cholesterol <1mmol/l

9.2.1 Diagnosis of Type 2 Diabetes

Refer to Chapter 3 on the diagnosis of diabetes in adults.

Diagnosis in children and adolescent are based on symptoms of hyperglycaemia and one of the following laboratory values with negative islet autoantibodies. Type 1 diabetes is common in children and adolescents, so it is advisable to have a discussion with a paediatric endocrinologist before making a diagnosis of type 2 in a child or adolescent.

Diagnostic criteria:

- FPG ≥7.0mmol

Or

- 2-hour plasma glucose after an oral glucose tolerance test (1.75g/kg(Max 75g) anhydrous glucose dissolved in water) of ≥11.1mmol/L

Or

- RPG ≥11.1mmol/L

Or

- HbA1c ≥ 6.5%

9.2.2 Investigations at Diagnosis of Type 2 Diabetes in Children and Adolescents

In Type 2 diabetes, the following ancillary tests must be done at diagnosis and annually thereafter: liver function tests, renal function tests, and lipid profile.

9.2.3 Management of Type 2 in Children and Adolescents[11]

Oral glucose-lowering medications are the drugs of choice. If the HbA1c at diagnosis is <8.5%, metformin is the treatment of choice, together with healthy lifestyle changes. Metformin is given at a dose of 500mg daily and titrated to a maximum of 2g in 2-3 divided doses as required.

However, if in ketosis or HbA1c ≥8.5%, insulin is required initially (starting dose 0.25–0.5units/kg).

Most children and adolescents with Type 2 are obese and have significant insulin resistance. Hence, lifestyle changes such as; a healthy diet, weight loss, and increased physical activity should be encouraged with metformin use. Glucagon-like-peptide -1 (GLP-1) analogues (Liraglutide/Exenatide/Semaglutide) may be used in children 12 years and above. These children and adolescents often require some insulin to maintain the HbA1c within the target range.

- *Glycaemic control of children and adolescents must be assessed by quarterly HbA1c and regular home glucose monitoring*
- *Good glycaemic control with HbA1c ≤ 7.5% reduces the risks of acute and chronic complications*

9.3 OTHER FORMS OF DIABETES IN CHILDREN AND ADOLESCENTS

9.3.1 Monogenic diabetes

Monogenic diabetes is caused by a single gene disorder resulting in defects in beta cells leading to hyperglycaemia. It is rare in children and includes neonatal diabetes, maturity-onset diabetes of the young (MODY), mitochondrial diabetes and diabetes associated with certain syndromes. Chapter 2 describes monogenic diabetes in further detail.

Neonatal diabetes

Neonatal diabetes is a rare form of diabetes that occurs within the first 6 months of life. Early diagnosis is important as it is often due to genetic defects in insulin secretion and glucose metabolism.[12] When hyperglycaemia is noted in the neonatal period, other causes of hyperglycemia must be ruled out, including but not limited to overload of dextrose-containing fluid, sepsis, increased counterregulatory hormones due to stress (especially seen in critically ill preterm or low birth weight infants) and medications such as steroids. Hyperglycaemia is more common in the first 3-5 days of life, often resolving within 10 days. Neonatal diabetes can be classified as transient, permanent, or syndromic.[12]

- **Transient neonatal diabetes**
  This type of diabetes is temporary and may resolve, usually by 13-18 weeks, but there is a high risk of recurrence in adolescence or adulthood.

- **Permanent neonatal diabetes**
  This form of diabetes does not resolve, it often occurs before 6 months of age, but there have been reports of diagnosis after 6 months of life.

- **Syndromic neonatal diabetes**
  Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX syndrome) and Fanconi -Bickel syndrome (hepatomegaly and Fanconi syndrome) due to mutation FOXP3 and SLCA2 respectively, are some of the syndromes known to be associated with neonatal diabetes.

Some of these forms of neonatal diabetes may respond to sulphonylurea therapy but must be done under specialist care. However, insulin is indicated in many of the forms of neonatal diabetes.

A genetic mutation is usually found in 80% of infants with neonatal diabetes, with more than 20 known genetic causes found. These guidelines will not discuss these, but any infant suspected to have neonatal diabetes must be referred to a teaching hospital or tertiary care facility for management.

- **Clinical features**
  - Asymptomatic (Neonatal diabetes may be diagnosed incidentally)
  - Dehydration
  - Small-for-gestational-age or intrauterine growth restriction
  - Failure to thrive
  - Irritability
  - Frequently soaked diapers that may need to be changed frequently
  - Diabetic ketoacidosis (with non-specific symptoms like tachypnea, lethargy, irritability, sunken fontanels, and eyes).

Neonatal diabetes may be associated with extrapancreatic features such as polycystic kidneys, hypothyroidism, liver, cardiac, visual, hearing, skeletal, and neurodevelopmental abnormalities

Laboratory evaluation of neonatal diabetes should be done under specialist care (Level 3)

- Plasma glucose
- C-peptide
- Serum or urine ketones
- Abdominal ultrasound with an emphasis on the pancreas: this may pick pancreatic hypoplasia or agenesis that may occur with some genetic mutations in addition to other renal pathology
- Autoantibodies may be found in infants > 6 months of age
- HbA1c is usually not useful as haemoglobin F is significantly higher in the first 6 months of life compared to Hemoglobin A, which accounts for 10-20% of haemoglobin in the infant < 6 months of age

- Targeted genetic testing may not be available in Ghana but can be done outside the country if necessary. Discuss with a Paediatric endocrinologist

9.4 INSULIN USE IN CHILDREN AND ADOLESCENTS WITH DIABETES

Insulin has been well described in Chapter 5; there are two broad groups: Human insulin and analogue insulins.

Human insulin comes in three forms:

- Short-acting (regular/soluble) - e.g., Humulin R, Actrapid
- Intermediate-acting: NPH insulin, e.g., Humulin NPH, Insulatard, Protophane
- Premixed insulin: a combination of short-acting (regular) and intermediate-acting (NPH) insulins – usually in the combination 30/70 or 25/75, or 50/50.

Analogue insulins are also available but are more expensive. Where available and affordable, analogues should be used in children because of their lower risk of hypoglycaemia. Rapid-acting analogues can be given immediately before meals because of their shorter onset of action, reducing postprandial hyperglycaemia and possibly preventing nocturnal hypoglycaemia. If it is certain that the meal has been eaten, it can also be given immediately after meals in infants and toddlers.

Types of analogue insulin:

- Rapid-acting - e.g., Aspart, Glulisine, Lispro
- Long-acting – e.g., Glargine, Detemir
- Ultra-long-acting insulin, e.g., Degludec, approved for children older than 10 years

Insulin regimens

The two most common regimens used for children and adolescents are:

A. Basal–bolus regimen

Multiple dose injections (basal-bolus regimen) mimic the physiological pattern of insulin secretion in a child or adolescent without diabetes. Basal insulin can either be long-acting or intermediate-acting insulin. The bolus insulin can either be short-acting insulin (human insulin), given 30 minutes before a meal, or rapid-acting insulin (analogue insulin), given at least 10-15 minutes before meals (breakfast, lunch, and supper).[13,14] Note; the rapid-acting insulin can sometimes be given with or immediately after meals in toddlers.

- Approximately 40% of the total daily dose (TDD) of insulin is given as basal insulin (long-acting or intermediate-acting). Long-acting insulin is administered as a single dose, whiles intermediate-acting insulin should be divided into two doses and administered in the morning and evening. Basal insulin can be given without meals.
- The remaining 60% of the TDD of insulin is given as boluses short- or rapid-acting insulin) with the 3 main meals. The boluses are initially divided equally with the meals. The doses can be adjusted depending on the glucose control.
- For example, if the TDD of insulin is 20 units, 8 units (40% of TDD) will be basal insulin and administered once if using long-acting insulin (eg. Glargine), but if using intermediate -acting insulin (NPH) it should be administered in 2 divided doses as 4 units in the morning and 4 units at bedtime. The remaining 12 units (60% of TDD), can be split into 3 doses and administered as 4 units with each main meal.

B. Twice-daily insulin using premixed insulin

When using premixed insulin (70/30), two-thirds of the TDD is usually given in the morning and one-third in the evening. This regimen is easy, but it is not physiological and does not usually give good glucose control. It is always better to do a multiple-dose regimen than twice daily dose for Type 1 diabetes patients

Insulin regimens need to be individualized. Therefore, insulin doses should be adjusted based on the blood glucose profile of each patient.No insulin is superior to the other.

9.5 MANAGEMENT OF CO-MORBIDITIES IN CHILDREN AND ADOLESCENTS WITH DIABETES

Children and adolescents with diabetes mellitus may have co-morbidities such as dyslipidaemia and hypertension.

9.5.1 Management of Dyslipidemia

Levels 1, 2, and 3 facilities

In children, lifestyle modification, including diet therapy, exercise, and weight loss, are to be encouraged to manage dyslipidaemia.

Level 3

Children with LDL cholesterol levels persistently greater than 2.6mmol/L should have the following interventions instituted - dietary changes, increased daily physical activities, and improvement in glycaemic control. If these measures do not improve the LDL cholesterol and the level remains greater than 3.4mmol/L after 6 months, investigations for possible familial dyslipidaemia is needed. Children older than 10 years can be started on a statin.

9.5.2 Hypertension

Children with hypertension must be investigated for secondary causes of hypertension. Blood pressure should be measured at each clinic visit.

Hypertension in children < 13 years is defined as average systolic and/or diastolic blood pressure ≥ 95th percentile for age, sex, and height on 3 or more different occasions.

For adolescents ≥ 13 years, hypertension is defined as average systolic and/or diastolic blood pressure of ≥ 130/80mmHg.

Any of the four classes of major antihypertensive medications listed below can be used as first-line treatment.

- Thiazide diuretics
- Calcium channel blockers
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor blockers

If target blood pressure levels are not achieved after administering the maximum permitted dose of the selected firstline therapy, additional antihypertensive medication should be chosen from a different class in the list above. Consult the paediatric formulary for doses.

9.6 MANAGEMENT OF ACUTE COMPLICATIONS OF DIABETES IN CHILDREN AND ADOLESCENTS

9.6.1 Hypoglycaemia

- Hypoglycaemia is defined as RBG or RPG < 4mmol/L
- With each visit, the management of hypoglycaemia should be discussed[15]
- Chocolate should not be used to manage hypoglycaemia
- Always investigate the cause of hypoglycaemia and address it

If the child or adolescent is conscious:[15];

- Give 0.3g/kg of fast-acting carbohydrate (regular soft drink or sugar or toffee)
- Note: 100mls of coke contains 10.6g of sugar
- 1 tablespoon of sugar is equivalent to 12.5g of sugar
- Follow up the fast-acting carbohydrate with either a meal, if meal time is due, or 15g of a carbohydrate snack (1 tennis ball size of fruit or a slice of brown bread).
- Recheck the blood glucose after 15 minutes, if still less than 4mmol/L repeat the steps above.
- If the child or adolescent is unconscious: give 2ml/kg of IV 10% dextrose and set up IV 10% dextrose as maintenance until the child or adolescent is fully conscious.

9.6.2 Diabetic Ketoacidosis

Diabetic Ketoacidosis (DKA) occurs when there is insulin deficiency. DKA may occur at diagnosis in children and adolescents who are not previously known to have diabetes, or if insulin doses are missed, or if insufficient insulin is given in times of stress, such as during acute illness, surgery, or trauma..[16]

The biochemical criteria for diagnosing DKA are:

- Hyperglycaemia (blood glucose ≥ 11.1mmol/L)

In rare cases, blood glucose can be < 11mmol/L, called "euglycemic ketoacidosis."

- Venous blood pH <7.3 or bicarbonate <15 mmol/l
- Blood ketones ≥ 3mmol/L or ketonuria 2+ or more

NB: High blood glucose and high urine ketones (≥2+) can be used to diagnose DKA in hospitals where blood gases and blood ketones cannot be done.

Symptoms

Nausea, vomiting, abdominal pain, diarrhoea, with or without classical symptoms of diabetes.

Signs

Lethargy, dehydration, respiratory difficulty (Kussmaul breathing), decreased level of consciousness, coma.

Severity of DKA

The severity of DKA is categorised by the degree of acidosis:
Mild DKA - pH 7.2 to < 7.3 / bicarbonate 10 to < 18mmol/L
Moderate DKA - pH 7.1 to <7.2/ bicarbonate 5 to < 10mmol/L
Severe DKA - pH<7.1/ bicarbonate < 5mmol/L

9.6.4 Management of DKA

DKA is a medical emergency; management, history-taking, and examination should be done concurrently.

Fluid replacement is initially more important than insulin therapy, as early complications and mortality are usually due to dehydration and shock. Insulin therapy is needed to correct acidosis and hyperglycaemia. Adequate fluid resuscitation must be initiated at the health facility where the patient is first seen.

The child should then be transferred if the health facility lacks expertise in DKA management and/ or if insulin and potassium are unavailable at the facility. Immediate transfer to the best available healthcare facility with the expertise and necessary resources for DKA management is recommended. The patient should be transferred with IV normal saline running at a maintenance rate if shock has been adequately corrected. The patient must be accompanied by documentation of all treatment, including IV fluids. Do not start insulin enroute to the referral site!!

If significant ketones are present in blood or urine in the presence of high blood glucose, DKA should be considered, and the child should be appropriately assessed and managed

Initial Assessment and Monitoring

The general guidelines for Paediatric Advanced Life Support (PALS) should be followed in the initial assessment and must include measurement of RBG or RPG, blood or urine ketones, serum electrolytes and blood gases where available (Figure 9.2).

Ideally, two peripheral (IV) cannulae should be inserted.

If a laboratory is available on site, carry out the following tests: blood glucose, urea and creatinine, electrolytes, bicarbonate, HbA1c, haemoglobin, and white cell count. Take appropriate microbiological samples if an infection is suspected.

If no laboratory is available, refer to the next level of care.

Fluid replacement

If the patient is referred from another health facility, consider the prior management, including the fluid given.

Correction of Shock

- Ensure appropriate life support. (Airway, Breathing, Circulation)
- Give oxygen to patients in shock or with breathlessness
- Set up a large IV cannula. If this is not possible, set up intraosseous access
- Give IV normal saline bolus of 10ml/kg over 20- 30 minutes.[17] Bolus can be repeated if there is no improvement.

If the only access is by nasogastric tube, give the same volume of fluid over 60 minutes using Oral Rehydration Solution (ORS) until peripheral perfusion improves or cannulation becomes possible.

NOTE:

Shock must be adequately treated before proceeding with insulin infusion. There should be good peripheral perfusion and adequate blood pressure.

Fluid replacement, insulin therapy, and potassium replacement will slowly correct the acidosis, electrolyte deficits, dehydration, and hyperglycaemia over 24 to 48 hours.

If there is no shock but the patient is severely dehydrated, an IV normal saline bolus of 10 ml/kg can be given over 1 hour.[18]

- Replace deficit and maintenance over 48 hours.
- Do not add on the volume of urine output and vomitus to the volume of replacement fluid.

Example: How much fluid will a child of 50 kg in DKA need in 48 hours? (Assuming 10% dehydration). The deficit will be 5 litres. Maintenance in 24 hours is 2.1 litres (1.5 litres + 20 ml/Kg for every Kg over 20, up to a mixiumum of 2.4 litres daily), and in 48 hours will be 4.2 litres. Hence, in 48 hours, this child will need a total of 9.2 litres of fluids.

Once oral fluid is tolerated, IV fluid may be reduced or stopped, and intake of oral fluid should be encouraged.

Insulin treatment in DKA

Insulin treatment can be started once the shock has been corrected and adequate fluid has been given to improve peripheral perfusion. It should be started 1-2 hours after initiating fluid therapy as early insulin treatment without improving peripheral circulation can lead to cerebral oedema.

Short-acting insulin is given intravenously at a dose of 0.1 unit/kg/hour.[18] This reduces blood glucose by approximately 5 mmol/L/hour.

Insulin can be given in two ways:

- Using an infusion pump or a perfuser
  Insulin solution of a concentration of 1 unit/ml is prepared by putting 50 units of short-acting insulin in 50 ml of Normal Saline.

  For example, a child of 50 kg who requires 5 units of units (0.1units / Kg/ hr) will need 5 ml of insulin solution to be delivered every hour to achieve the recommended dose.

You could also put 50 units of short-acting (regular) insulin in 500 ml of Normal Saline – The insulin solution concentration is 1 unit in 10 ml.

For example, A child of 50 kg in DKA will need 50 ml of this solution to run every hour. However, this volume should be calculated and subtracted from the total fluid requirement for the first 48 hours.

An IV bolus of insulin is unnecessary and should not be used at the start of therapy

- Using an intramuscular route (IM);
  Give 0.3 units/kg stat, then 0.1 unit/kg of short-acting (regular, soluble) or rapid-acting insulin every 1 hour.[19]

  For example, a child of 50kg will be given 15 units of insulin intramuscularly stat, then 5 units every hour

When blood glucose is < 15 mmol/l and the patient is still in DKA,, change the normal saline to 5% dextrose saline to run at the same flow rate. The patient still needs hourly monitoring.

When the blood glucose < 8mmol/L and the patient is still in DKA, the dextrose in the maintenance fluid is increased to 10% and run at the same flow rate.

Note: The flow rate of insulin should not be decreased when RBG is decreasing but rather increase the dextrose concentration in the maintenance fluid.

To reduce the risk of cerebral oedema, do not correct for ongoing losses such as excessive urine, vomiting, and diarrhoea.

During the management of DKA, the child needs to be carefully monitored as follows:

- Record hourly: heart rate, blood pressure, respiratory rate, level of consciousness
- Monitor RBG every hour
- Monitor blood ketones every hour
- Monitor pH and bicarbonate every 2-4 hours
- Monitor urine ketones every 2 hours
- Repeat electrolytes and observations such as temperature, respiratory rate, pulses, blood pressure, every 4 hours
- Record fluid intake, insulin therapy, and urine output

Potassium replacement

Start potassium replacement when the serum potassium value is known, or the patient produces adequate urine.

Replace potassium by adding 40 mmol of potassium chloride or potassium phosphate to 1litre of IV fluids (or 20 mmol per 500 ml).[18] The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/hour.

If there is hypokalaemia at presentation, 20 mmol of potassium should be added to the 1litre of the initial fluid resuscitation (or 10 mmol in 500 ml of fluid)

If there is hyperkalaemia at presentation, continue with fluid resuscitation, with no potassium, until the patient produces enough urine of ≥1ml/kg/hour.[17]

Role of bicarbonate

Bicarbonate is rarely used in children and adolescents. Controlled trials have shown no clinical benefit.[7] Acidosis usually corrects with hydration and insulin therapy. If bicarbonate is considered necessary, cautiously give IV sodium bicarbonate 1-2 mmol/kg over 60 minutes. Watch out for hypokalaemia when administering bicarbonate.

Treatment of infection

Any precipitating infection should be identified and treated appropriately. However, in most cases, DKA is due to a lack of insulin from undiagnosed diabetes or non-adherence to insulin therapy.

If an infection is suspected, take appropriate samples for culture and sensitivity and initiate treatment with broad-spectrum antibiotics.

Cerebral oedema

Cerebral oedema is a serious DKA complication that should be considered in all children and adolescents with DKA. It can be idiosyncratic, but its occurrence may be related to various factors, including the degree of hyperglycaemia, acidosis, dehydration and electrolyte disturbance at presentation, and rapid correction of dehydration or hyperglycaemia.

Clinical features of cerebral oedema include headache, vomiting bradycardia, restlessness, irritability, increased drowsiness, incontinence, seizures, and coma.

If cerebral oedema is suspected, TREAT URGENTLY. Involve the Paediatric Critical Care or intensive care team when cerebral oedema is diagnosed.

- Check blood glucose to rule out hypoglycaemia
- Elevate the head of the bed. Reduce the rate of fluid administration by one-third
- Give IV mannitol 0.5-1 g/kg over 10-15 minutes and repeat if there is no initial response in 30 minutes to 1 hour.[6] IV hypertonic saline (3%) 5ml/kg over 30 minutes may be an alternative to mannitol, especially if there is no initial response
- Intubation may be necessary for a patient with impending respiratory failure
- After treatment has been started, if available, a CT scan of the head scan should be done to rule out other possible intracerebral causes of neurological deterioration, especially thrombosis or haemorrhage, which may benefit from a specific therapy

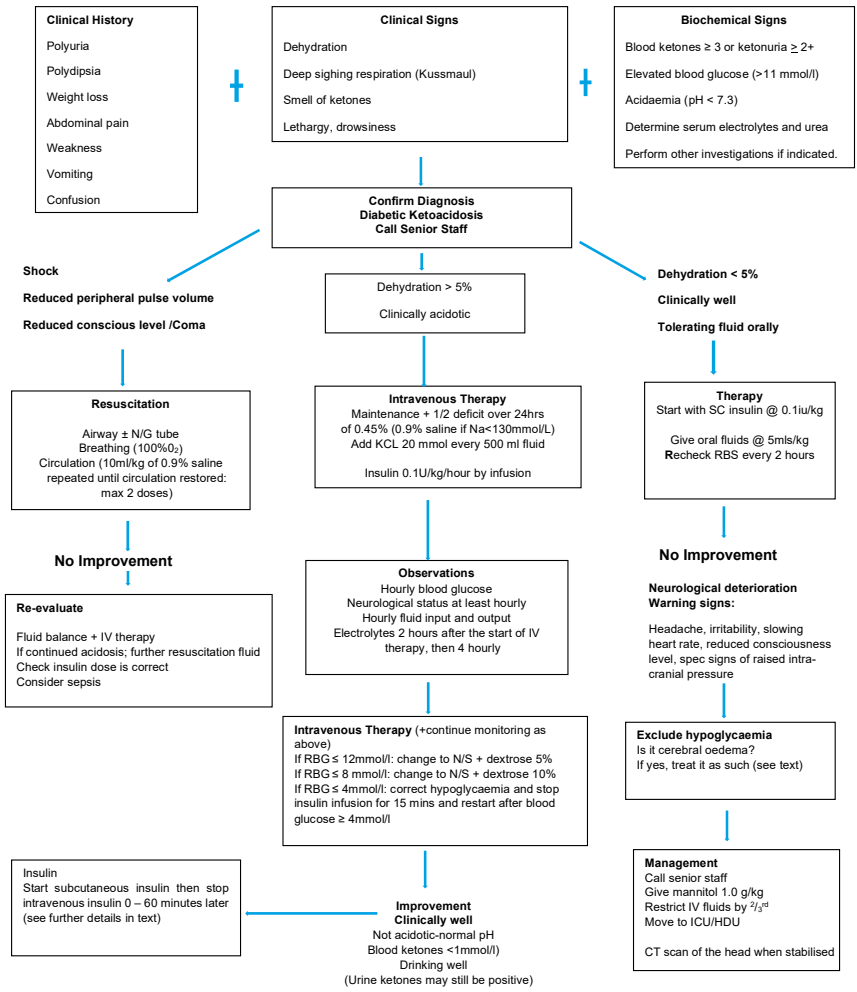

Figure 9.2: Algorithm for the Management of Diabetic Ketoacidosis

Resolution of DKA and Transitioning to SC insulin-

Once DKA has been adequately treated and substantial clinical improvement has occurred, the child can be transitioned to subcutaneous insulin. Mild urine ketones may still be present as the urine test strips detect acetoacetate and acetone and not beta-hydroxybutyrate (B-OH butyrate). Ketonuria persists several hours after blood ketones (β-OH butyrate) levels have returned to normal. Before the switch to SC insulin, ensure the child

or adolescent can tolerate oral fluids. Plan to switch to SC insulin around mealtime.

A long-acting (basal) insulin is given in addition to a short-acting (regular/rapid) insulin. The regimen, dose, and type of insulin used should follow local circumstances and the availability of the insulin (section 9.3.1). The initial insulin dose is 0.6 units/kg/day; however, the dose can be decreased 0.4-0.5 units/kg/day for younger children and increased to 1 unit/kg/day in peri-pubertal ages.

The insulin infusion should run for at least an hour after the first SC insulin injection to prevent rebound hyperglycaemia. It allows sufficient time for the insulin to be absorbed.

Blood glucose should be monitored, and insulin adjusted to attain target values.

9.7 DIABETES IN CHILDREN AND ADOLESCENTS IN SPECIAL SITUATIONS

9.7.1 Pregnancy in the adolescent with diabetes

- It is an example of preexisting diabetes in pregnancy. Insulin management should continue and be adjusted to achieve good glycaemic control. Antenatal care should begin as early as possible and continue throughout pregnancy
- The patient should be reviewed by obstetricians, paediatric endocrinologists, paediatricians, or family physician specialists. Both the dietician and psychologist should review as appropriate
- Patients should keep logbooks for monitoring blood glucose at home to be reviewed at the antenatal care (ANC) and diabetes clinic
- Delivery and post delivery care should be supervised in a health facility by a midwife or an obstetrician
- The baby born to a diabetic mother should be immediately assessed and managed by a neonatologist/paediatrician/medical officer
- Adolescents should be counselled to return to school or learn a vocation

9.7.2 HIV in Diabetes

Children and adolescents with HIV who develop diabetes or vice versa should be managed for both conditions by attending both clinics for antiretrovirals and insulin or oral diabetes medications. The management is the same as any other person without HIV infection. There is a need for both specialty clinics to have round table discussions to plan the comprehensive care for the patient.

9.7.3 Religious Fasting

Children and adolescents with diabetes should be discouraged from fasting, but where patients insist, they should be supported to fast. The basal-bolus regimen, using a basal insulin with a flatter profile, is preferred to avoid hypoglycaemia.[20]

- Reduce basal dose (glargine) by 10% to 20% and give it in the evening or at bedtime. This prevents ketoacidosis during fasting
- Short or rapid-acting insulin should be given at dawn with the morning meal, in the evening when patients break the fast
- Blood glucose should be checked at least every 4 hours during the day
- If the blood glucose rises above 15 mmol/L during fasting, give a correction dose of short-acting or rapid-acting insulin.[21] If blood glucose levels fall below 4 mmol/l, fasting should be stopped and hypoglycaemia treated
- It is advisable to do a 'trial' of fasting before the patient starts the religious fast so that insulin can be adjusted before the start of the religious fast. Refer such patients to a paediatric endocrinologist or a specialist for insulin titration

9.7.4 Drug abuse

Children and adolescents with diabetes who become drug addicts should be referred to addiction centres, psychiatrists, and psychologists for psychotherapy where available. They should continue to come to the diabetes clinic for their insulin and do blood glucose monitoring. A responsible adult relative should be identified to be a focal person to support the patient.

9.8 TRANSITIONING FROM PEDIATRIC TO ADULT CARE

Adolescence is often difficult for most children and even more difficult for children with chronic illnesses who may have established a bond with their paediatrician. Children must be prepared for adult service, where available, as children grow. Where possible, there must be a transition period during which the adolescent is seen by both the paediatrician and the adult physician before they are completely handed over to the adult team. Otherwise, there is the risk of the adolescent dropping out of the health care system and being lost to follow-up. They must be supported to anticipate issues they may encounter in the adult service

During this period, it must be ensured that adolescents are more independent and can function unsupervised as they grow into adulthood. This can be achieved by carefully planning healthcare promotion and patient education sessions. During the transition period, the adolescent also acquires and practices self-management skills. There must be a shift in responsibility from parents to the adolescent, but parents may need to supervise and ensure the child's safety.

9.9 REVIEWS AND APPOINTMENTS

- For the first visit or at diagnosis, the patient must be educated to dispel myths about diabetes, and highlight the importance of insulin and the need to inject insulin frequently to stay healthy. Every child with diabetes and/or their caregiver must monitor blood glucose daily and write values in a logbook that should be reviewed and used to adjust insulin doses accordingly.
- Review patients in the first two weeks to see if they are doing well with their diabetes care. Subsequent visits can be at 2-3 months interval.
- At each visit, review the blood glucose values and insulin doses, inspect injection sites, and advise the patients accordingly and appropriately.
- As much as possible, HbA1C should be done 2-3 months. HbA1c reflects blood glucose values over the past 2-3 months

9.10 CARE PATHWAYS

Level 1 -Facilities without Doctors

Children and adolescents suspected to have diabetes should be referred to a higher facility with a paediatric diabetes clinic or doctors trained in paediatric diabetes management.

Level 2- Facilities with non-specialist doctors

Diagnose and initiate insulin management if doctors have been trained in paediatric diabetes management. Otherwise, refer to the nearest centre with a paediatric diabetes clinic.

Level 3- Facilities with specialist doctors/ paediatricians/ paediatric endocrinologists

Should have a paediatric diabetes clinic to manage and follow up with children and adolescents with diabetes.

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10

Chapter 10

MANAGEMENT OF DIABETES IN SPECIALISED SITUATIONS

LIST OF ABBREVIATIONS

2-HPG	2 Hours Postprandial Glucose
ACE	Angiotensin Converting Enzyme
ADL	Activities Of Daily Living
ANC	Antenatal Care
ARB	Angiotensin Receptor Blocker
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DKA	Diabetic Ketoacidosis
DM	Diabetes Mellitus
DPP-4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
GKI	Glucose Potassium And Insulin
GLP-1 RA	Glucagon-like Peptide-1 Receptor Agonist
HbA1c	Glycated Haemoglobin

HHS	Hyperosmolar Hyperglycaemic State
IFP	Impaired Fasting Plasma Glucose
IGT	Impaired Glucose Tolerance
IV	Intravenous
LDLc	Low-Density Lipoprotein Cholesterol
LFTs	Liver function tests
MR	Modified Release
MVD	Macrovascular Disease
NPH	Neutral Protamine Hagedorn
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovarian Syndrome
PG	Postprandial Glucose
RPG	Random Plasma Glucose
SBP	Systolic Blood Pressure
SC	Subcutaneous
SGLT-2 i	Sodium-Glucose Cotransporter-2 Inhibitor
T2DM	Type 2 Diabetes
TDD	Total Daily Dose
TG	Triglyceride
TZD	Thiazolidinedione
USG	Ultrasonogram

10.0 INTRODUCTION

This chapter discusses the management of diabetes in specialised situations, including hospitalised patients, older adults, pregnancy, religious fasting, and oral health.

10.1 DIABETES MANAGEMENT IN HOSPITALISED PATIENTS

Patients with diabetes are three times more likely to be admitted to a hospital.

Predisposing factors for hospital admissions in a patient with diabetes include:

- Stressful events (acute illnesses such as strokes, myocardial infarctions, infections, and trauma)
- Poor glycaemic control
- Older age
- Multiple comorbidities
- Polypharmacy and adverse drug events
- Patients with previous admissions

Common clinical problems of diabetes patients in hospital

- Hyperglycaemia
- Hypoglycaemia
- Widely fluctuating blood glucose levels
- Chronic diabetes complications
- Perioperative complications

10.1.1 Inpatient hyperglycaemia

Defined as a blood glucose level > 7.8mmol/L[1-3] in patients with or without a prior diagnosis of diabetes. It is associated with an increased risk of in-hospital complications, a longer length of hospital stay, and mortality[2]

- Insulin therapy is the preferred treatment for inpatient hyperglycaemia. It is administered either as an intravenous (IV) infusion or as subcutaneous (SC) using the appropriate regimen, depending on the severity of the illness (Refer to Table 10.1)
- The use of a sliding scale alone, which does not address the basal insulin requirements of patients, and is associated with an increased risk of wide blood glucose fluctuations and hypoglycaemia, is not recommended[4, 5]

Other glucose-lowering agents may only be used in carefully selected patients.

10.1.2 Inpatient Hypoglycaemia

Hypoglycaemia is diagnosed at a blood glucose level of <3.9mmol/L. It can be a result of dysregulated metabolism and /or diabetes treatment. It is a

preventable condition associated with increased mortality.[6] The following factors increase the risk of hypoglycaemia among hospitalised patients:

- Errors in dosing and timing of insulin
- Improper prescription of other glucose-lowering medications
- Inadequate food intake
- Vomiting
- Prior episode of hypoglycaemia
- Older age
- Sepsis
- Kidney failure
- Liver failure
- Malignancy
- Cessation or sudden reduction in glucocorticoid dose
- Altered ability of the patient to sense and/or report hypoglycaemic symptoms

10.1.3 Management

The management of hospitalised diabetes patients may be greatly facilitated by

- Good preadmission glycaemic control in patients due for elective procedures[7]
- A dedicated inpatient diabetes service that applies evidence-based standards of care[8]
- Careful transitioning to an outpatient team for pre-arranged outpatient management[9]

10.1.4 Relevant investigations

- Random blood glucose test – For all patients coming on admission
- HbA1c – For all patients with diabetes mellitus or hyperglycaemia (blood glucose >7.8 mmol/L)
- Urinalysis and culture
- Urine dipstick for ketones (or blood ketones if available),
- Full blood count
- Urea, creatinine, electrolytes
- Liver function tests
- Chest x-ray
- ECG and cardiac enzymes

10.1.5 Treatment goals

- Blood glucose targets for hospitalised patients with diabetes:
  - 7.8 to 10.0mmol/L for most patients
  - More stringent goals (6 to 7.8mmol/L) for selected patients, provided they can be achieved without hypoglycaemia
  - Less stringent goals are 10 to 13.9 mmol/L and > 13.9 mmol/L for those with severe comorbidity and terminal illness, respectively

Bedside blood glucose monitoring must be done:

- For patients with hyperglycaemia and those previously diagnosed with diabetes
- Before meals for patients who are eating and possibly 2 hours after eating
- Every 4 -6 hours for those who are not eating
- Every 30 mins – 2 hours if receiving an intravenous infusion of insulin.

10.1.6 Non-pharmacological management

- ***Education*** of patients and caregivers about the need:
  - To maintain good glycaemic control for best outcomes
  - For glucose monitoring and documentation
  - For prompt recognition and treatment of hypoglycaemia
- ***Medical nutrition therapy in the hospital should aim at the following:***
  - Involving a dietician (where available) whiles on admission until discharge
  - Provision of sufficient calories to optimise glycaemic control and meet metabolic demands
  - Meal plans should be individualised based on blood glucose levels, treatment goals, and medication dose

10.1.7 Pharmacological management

Ideally, a diabetologist or a physician with expertise in diabetes management or the diabetes specialist team should be involved in the treatment of hospitalised patients with diabetes to improve blood glucose control, reduce the length of stay and facilitate the best outcomes.

Insulin therapy

Insulin is the most appropriate pharmacologic agent for effectively controlling glycaemia in hospitalised patients.[2] Refer to Table 10.1 for the treatment regimen for the different categories of hospitalised patients.

Table 10.1 Glucose lowering treatment in Hospitalised Patients

Hospitalised patient	Type of medication	Dosing remarks
Non-critically ill *Eating*	Basal and prandial insulin (with correction component as needed)	Total daily dose of insulin (TDD): • Start from 0.50 units/kg for most patients • 0.25 to 0.30 units/kg for those at high risk of hypoglycaemia (eGFR < 30, low BMI, older adults, on hemodialysis • 0.60 to 1.0 units/kg for insulin-resistant individuals (obese, on steroids) *Give 50% as basal insulin and rest as equal boluses of short or rapid insulin before meals for those who are eating or every 4-6 hours for those on continuous enteral/parenteral feeding* *Correction doses should be used cautiously if preprandial glucose is above the target* *Calculate correction dose = The number of mmol/L of glucose above the target/ Correction factor* *Correction factor = 100 divided by TDD* *Give correction dose as short-acting insulin in addition to bolus doses before meals.*
Not eating	Basal insulin (with or without bolus correction)	Start from 0.1 unit/ kg for those who were not on insulin before admission
Critically ill	Insulin	Continuous intravenous infusion

Perioperative Minor *On insulin*	Basal insulin	Ideally, the patient should be first on the operation list Continue the patient's basal insulin at 80% of the usual dose, which may reduce rebound hyperglycaemia.
	Short or rapid-acting insulin (bolus)	Omit morning dose if no breakfast is eaten. Bolus corrective doses of short-acting insulin may be employed during the procedure Resume normal insulin if eating a normal meal
	Biphasic insulin mixtures	Omit morning dose if no breakfast
Not on insulin	Metformin	Omit morning dose or any dose before the operation
	Sulphonylurea	Omit morning dose
	SGLT-2i	Omit the day before and the day of surgery
Major *(All diabetes patients)*	Use insulin	Continuous variable rate insulin infusion from the morning of operation (with dextrose to prevent hypoglycaemia) or GKI (as summarised below) to keep blood glucose in the suitable range of 5-10mmol/L
DKA/HHS	Refer to Chapter 6	

GKI: Glucose Potassium and Insulin; SGLT-2-i: Sodium glucose cotransporter-2 inhibitor; DKA: Diabetic Ketoacidosis; HHS: Hyperosmolar Hyperglycaemic State

Non-insulin medications

- Generally, in critically ill patients, the use of oral glucose-lowering medications is not recommended
- Metformin is generally not recommended in hospitalised patients with renal, heart or hepatic failure because of an increased risk of lactic acidosis.
- Metformin may be used safely in some hospitalised patients who are not acutely ill or having any procedures
- Consider the profile of other non-insulin medications carefully before use
- Transition the patient to their outpatient non-insulin medication regimen about 2 days before discharge or when deemed suitable by the clinician in charge of the diabetes management

10.1.8 Perioperative care

- Ideally, optimise glycaemic control before elective surgery
- Use continuous variable rate insulin infusion (with dextrose) or GKI (glucose, potassium and insulin).

Typical GKI regimen (may follow the rule of 10):

- 500mls of 10% Dextrose
- 10mmol/L potassium chloride (KCl) (20mmol if potassium deficiency, omit if renal failure or severe hyperkalaemia)
- 10 units insuin (usually soluble insulin; may increase to 16 units if insulin resistant)
- At a rate of 50 – 100mls /hour
    - Resume oral glucose-lowering medications after surgery when the patient has started eating and drinking normally.
    - Monitor capillary blood glucose on admission and hourly during the surgery
    - Refer to Table 10.1 for the treatment regimen for the different categories of patients in the perioperative period.

Transition from intravenous to subcutaneous insulin

- The transition process has been discussed in Chapter 6 under the section on Diabetic Ketoacidosis
- Essentially SC insulin should be administered 1-2 hours (short- or rapid-acting insulin) or 2-3 hours (intermediate- or long-acting insulin) before stopping the intravenous (IV) insulin
- Patients not on insulin previously, needing > 2 units of IV insulin per hour, likely require insulin therapy and can be transitioned to SC insulin therapy
- The initial dose of SC insulin can be calculated by extrapolating the IV insulin requirement over the preceding 8-hour to 24-hour period
- Total daily dose may be divided into basal and bolus insulin components in medically ill patients[10]

10.1.9 Referral and Follow-up

Transitioning from hospital to outpatient setting

Discharge planning should be well structured and tailored to the needs of the patient with diabetes and should begin at admission and be reviewed as the needs of the patient change.

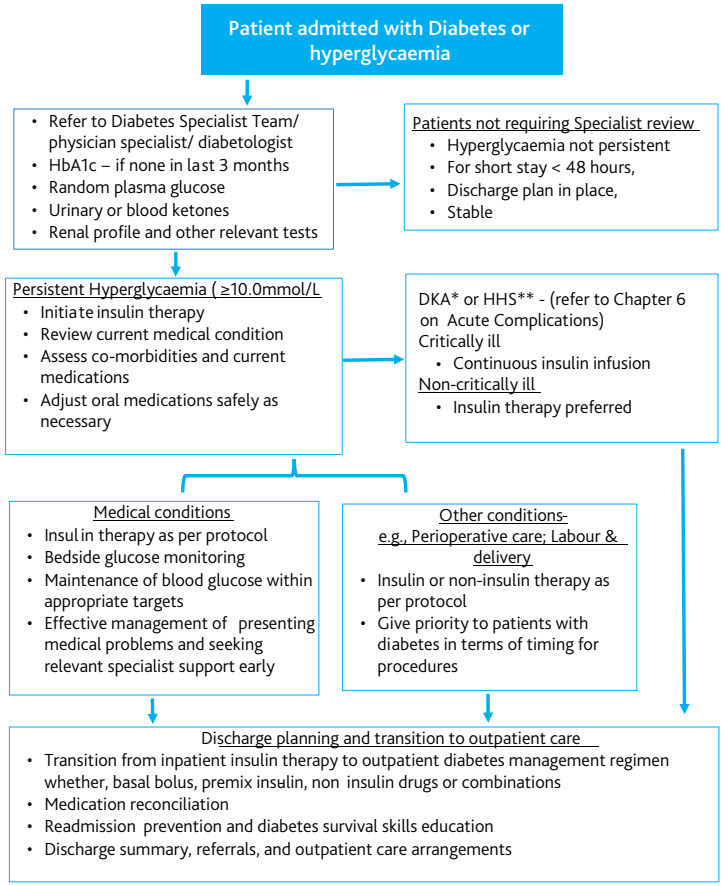
Readmission prevention – hospital readmission rate for patients with diabetes may be reduced by:

- Inpatient education on diabetes survival skills by the diabetes specialist team. The specific diabetes related-problems that led to that admission and how the patient can better manage those problems must be reviewed so that they can cope better at home and prevent frequent readmissions.
- Coordinated speciality care
- Good discharge instructions
- Medication reconciliation before discharge: to review new or changed medications and to ensure no medication is omitted
- Outpatient follow-up within a month of discharge with the patient's primary care physician or physician specialist where available

10.1.10 Level of care for the management of hospitalised diabetes patients

Diabetes patients needing hospitalisation for any complication should be managed in health facilities with doctors (Levels 2 and 3). The broad framework for managing diabetes in Hospitalised patients is set out in Figure 10.1.

Patients should be referred to the next Level where management facilities are inadequate.



*Diabetic ketoacidosis

**Hyperosmolar hyperglycaemic state

Figure 10.1: Flow chart – Broad framework for the management of diabetes in Hospitalised patients

10.2 DIABETES MANAGEMENT IN OLDER ADULTS

10.2.1 Introduction

About 20% of people aged 65–99 years across the world live with diabetes, with the proportion projected to rise rapidly in coming decades.[11]

Cardiovascular risk factors like hypertension and dyslipidaemia are also highly prevalent in older adults. Complications such as stroke, heart attack, kidney disease, eye disease, peripheral vascular disease and cardiovascular disease death are more common in this population.[12]

In the management of older adults with diabetes, their frailty, the presence of multiple comorbidities, and polypharmacy should be taken into consideration. Stringent treatment targets may harm older patients.[13, 14]

Common clinical features

Diabetes in older adults may present uniquely or non-specifically (without the typical symptoms of polydipsia or polyuria) with the following[15]

- Urinary incontinence
- Diabetes-related chronic complications
- Recurrent infections

Relevant investigations

- Baseline investigations are the same for younger adults.
- Investigations for associated comorbidities should be tailored towards the patient's presentation

10.2.2 Related sequelae/complications

Older adults with DM may have similar chronic complications as younger individuals with diabetes but may be at an increased risk of:

- Cognitive decline and dementia (73% increased risk)[16, 17]
- Physical disability[15]
- Hypoglycaemia

  - Older patients are susceptible to hypoglycaemia, partly due to the presence of comorbidities, drug-drug interactions, and a reduced ability to perceive the symptoms and readily communicate their problems.[18, 19] Hypoglycaemia is associated with a greater risk of dementia[19]
- Falls
  - Assess patients for the cause of falls (syncopal, non-syncopal or purely mechanical) and fractures
  - Caution is needed with medications such as pregabalin, amitriptyline, and gabapentin, as side effects may be profound in older adults, leading to delirium, hallucinations, tremors and falls[20]
- Fractures
  - Hip and non-spine fracture risk is significantly increased[21]
  - Fracture risk is increased with some drugs (e.g., pioglitazone and SGLT-2 inhibitors[22, 23]
- Chronic pain
- Erectile dysfunction
- Malignant otitis externa (a necrotising infection usually caused by Pseudomonas)[24]
- Cancers: At an increased risk of several cancers - liver, pancreas, colon, breast, endometrium and bladder[25]

10.2.3 Management

Non-pharmacological management

- Education - teamwork is needed with shared decision-making; education needs to be continual
- Refer to the relevant section on non-pharmacological management
  - There is a need to assess the older patient's ability to self-manage their diabetes: any functional limitations, psychosocial problems, polypharmacy, cognitive impairment, falls, and persistent pain, which may reduce their quality of life and adversely affect self-management.
  - Include family and carers who support older adults in discussions and shared decision-making about diabetes management.
- Individualize nutritionally balanced diet therapy considering their usual eating habits and lifestyle. Refer to a dietician if available.

- Exercise
  - Encourage regular exercise with aerobics and resistance training
  - Sitting or in-bed exercises as the need may be
  - Regular physical activity improves glucose control, prevents loss of muscle mass and reduces cardiovascular disease burden in older individuals.

Pharmacological management

Treatment of diabetes in older persons needs to be individualised. Refer to Chapter 5 for glucose-lowering medications and their dosing recommendations.

Treatment goals

A broad framework for individualising treatment goals for Diabetes in Older Adults is set out in Figure 10.2.

- Keep target blood pressure < 140/90 mmHg if it is tolerated
- Use minimal effective doses of lipid-modifying medications (e.g. statins) to achieve required targets[26]
  - At least a 30% reduction in LDL-C and/ or
  - LDL-C <2.5 mmol/L (patients without established CVD)
  - LDL-C <1.8 mmol/L (patients with established CVD).
- Glycaemic control
  - HbA1c target 7.0 – 7.5% if healthy, have fewer comorbidities, no significant cognitive impairment, and can self-care
  - HbA1c targets 8 - 8.5% if short life expectancy with significant comorbidities and unable to self-care
- Avoid hypoglycaemia by choosing the lowest-risk medications[27]
  - Review insulin or sulfonylurea treatment, which can lead to hypoglycaemia
- Minimise patients' distress and caregiver stress by simplifying complex treatment plans
- Discourage unproven therapies in this most susceptible group of patients
  - Refer to Table 10.2 for precautions in pharmacological treatment

Table 10.2: Precautions in pharmacological treatment in older adults

Medication	Remarks
Metformin	First-line agent for older patients with Type 2 diabetes. Refer to Chapter 5 for cautions and contraindications
Sulphonylurea	Gliclazide is the safest Avoid glibenclamide which is associated with a higher risk of hypoglycaemia and poorer cardiovascular outcomes
Pioglitazone	Low risk of hypoglycaemia Use cautiously in the elderly Weight gain High risk of fluid retention (may worsen heart failure), falls and fractures Potential risk of bladder cancer
Dipeptidyl peptidase-4 (DPP-4) inhibitors	Minimal risk of hypoglycaemia. Lower risk of weight gain Convenient for older adults
Glucagon-like peptide-1 (GLP-1) receptor agonists	refer to Chapter 5 on pharmacological therapy for details
Sodium–glucose cotransporter-2 (SGLT-2) Inhibitors.	Convenient for older adults with T2DM Higher risk of dehydration
Insulin therapy	Patients or their caregivers need good vision, motor dexterity, and intact cognitive function to administer insulin. Where feasible, encourage the use of pen devices

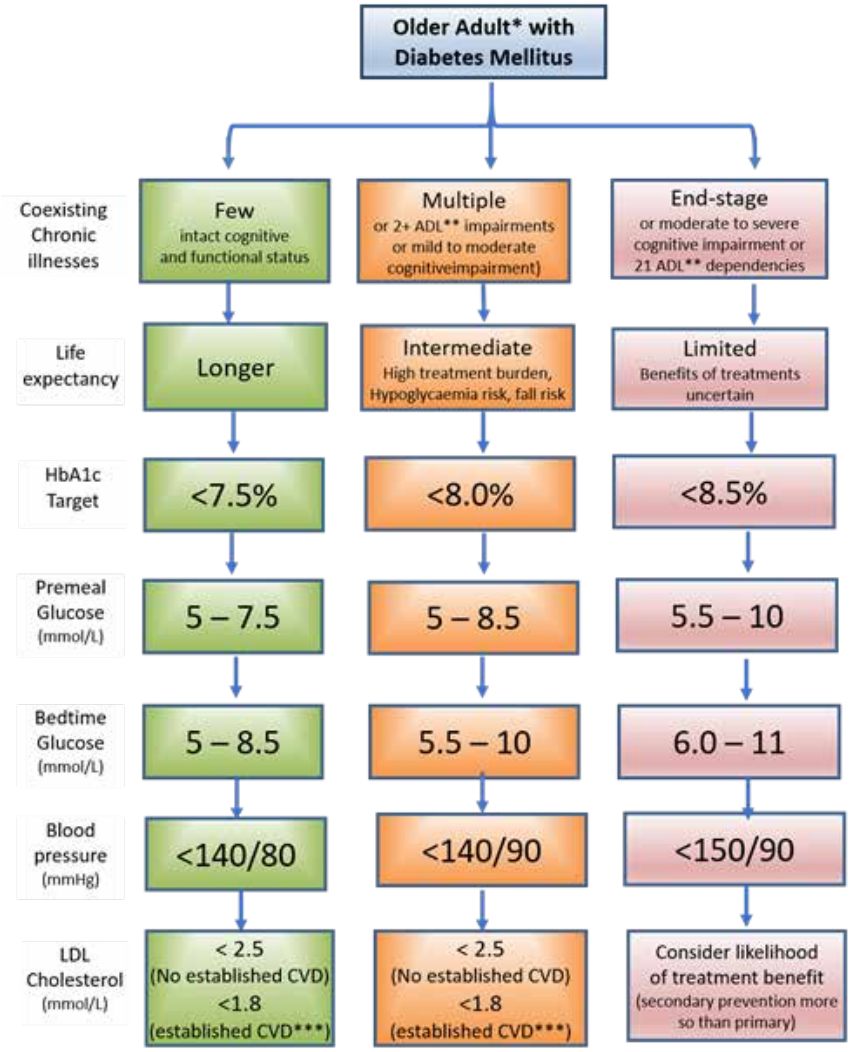
10.2.4 Referral

The following referrals may need to be made to a health facility with a specialist (Endocrinologist or Diabetologist, Physician specialist):

- Recurrent severe or unpredictable hypoglycaemia
- Hypoglycaemia unawareness
- Presence of macrovascular and microvascular complications

Level of care for the management of older diabetes patients

- Older patients with diabetes needing hospitalisation for whatever complication should be managed in health facilities with doctors, preferably by specialists (physicians, family physicians, endocrinologists or diabetologists).



* Older Adult definition: 65 years or more in age

** ADL - Activities of daily living: Personal hygiene (Bathing, oral, nail and hair care), continence (mental and physical control of bladder abd bowel function), dressing, eating, walking independently

*** CVD - Cardiovascular Disease

Figure 10.2: Flow chart – Broad framework for individualising treatments goals for Diabetes in Older Adults[12, 28, 29]

10.3 DIABETES MANAGEMENT DURING RELIGIOUS FASTING

10.3.1 Introduction

Fasting is a voluntary exercise involving abstaining from foods, drinks, and water for medical, dietary, and religious reasons. Christians who form a majority in Ghana undergo variable periods of fasting throughout the year, with the fasting period per day ranging between 12-24 hours. People of the Islamic faith fast annually during the month of Ramadan, and the fasting period can last between 14-16 hours per day.

Persons who are ill or have chronic diseases are discouraged from fasting. However, many of these patients, including those with diabetes, consider fasting an important spiritual exercise and desire to fast.[30]

10.3.2 Related Sequelae/Complications

Risks associated with fasting in patients with diabetes are higher than those without diabetes. Complications associated with fasting include:

- Hypoglycaemia
- Hyperglycaemia
- Diabetic ketoacidosis
- Dehydration
- Thrombosis

10.3.3 Approach to Fasting

At least 6-8 weeks before undertaking a fast, patients must be encouraged to present to health facilities for a clinical assessment and risk stratification to guide them for the fasting period.

Healthcare personnel must assess patients' physical well-being and metabolic control to risk stratify them properly. Recommendations on who can fast, how to fast safely and what to do in case of complications from fasting are essential to optimise care and ensure that people with diabetes who intend to fast do so safely.

People with diabetes intending to fast during Ramadan should be categorised into low, moderate, and high risk groups after a thorough medical evaluation.

Factors to consider for risk quantification using a patient-centred approach include:

- type of diabetes
- patient's medications
- individual hypoglycaemic risk
- presence of complications and/or comorbidities
- individual social and work-related activities
- previous fasting experiences
- previous hypoglycaemic episodes

Patients are classified into - High risk, Moderate risk and Low-risk groups (Table 10.3)[31]

Table 10.3: Risk Stratification and Scoring for Patients with Diabetes seeking to fast during Ramadan

Risk Element	Risk Score
1. Diabetes type and duration	
Type 1 diabetes	1
Type 2 diabetes	0
2. Duration of Diabetes (years)	
A duration of ≥ 10	1
A duration of < 10	0
3. Presence of hypoglycaemia	
Hypoglycaemia unawareness	6.5
Recent severe hypoglycaemia	5.5
Multiple weekly hypoglycaemia	3.5
Hypoglycaemia<1 time per week	1
No hypoglycaemia	0
4. Level of glycaemic control	

Risk Element	Risk Score
HbA1c levels > 9% (75 mmol/mol)[1]	2
HbA1c levels 7.5–9% (58.5–75 mmol/mol)[2]	1
HbA1c levels < 7.5% (58.5 mmol/mol)[3]	0
5. Type of treatment	
Multiple daily mixed insulin Injections	3
Basal Bolus/Insulin pump	2.5
Once daily Mixed insulin	2
Basal Insulin	1.5
Glibenclamide	1
Gliclazide/MR or Glimepride or Repeglanide	0.5
Other therapy not including SU or Insulin	0
6. Self-Monitoring of Blood Glucose (SMBG)	
Indicated but not conducted	2
Indicated but conducted sub-optimally	1
Conducted as indicated	0
7. Acute complications	
DKA/ HHS in the last 3 months	3
DKA/ HHS in the last 6 months	2
DKA/ HHS in the last 12 months	1
No DKA or HHS	0
8. MVD Complications/Comorbidities	
Unstable MVD	6.5
Stable MVD	2
No MVD	0
9. *Renal Complications/Comorbidities*	
eGFR < 30 mL/min	6.5
eGFR 30–45 mL/min	4

Risk Element	Risk Score
eGFR 45–60 mL/min	2
eGFR >60 mL/min	0
10. Pregnancy[4]	
Pregnant not within targets	6.5
Pregnant within targets	3.5
Not pregnant	0
11. Frailty and Cognitive function	
Impaired cognitive function or Frail	6.5
> 70 years old with no home support	3.5
No frailty or loss in cognitive function	0
12. Physical Labour	
Highly intense physical labour	4
Moderate Intense physical labour	2
No physical labour	0
13. Previous Ramadan Experience	
Overall negative experience	1
No negative or positive experience	0
14. Fasting hours (location)	
≥ 16 h	1
< 16 h	0

DKA—Diabetic Ketoacidosis; HHS - Hyperosmolar Hyperglycaemic State; MVD—Macrovascular disease (Cardiac-cerebral or peripheral);eGFR—Estimated glomerular filtration rate; SU-sulphonylurea.

[1]This measure is equivalent to 11.7 mmol/L average blood glucose.
[2]This measure is equivalent to 9.4–11.7 mmol/L average blood glucose.
[3] This measure is equivalent to 9.4 mmol/L average blood glucose.
[4]Pregnant and breastfeeding women have the right to not fast. regardless of whether they have diabetes or not.

Adapted from Diabetes and Ramadan: Practical Guidelines 2021.[31]

Scoring and Recommendation

Score 0-3	**Low Risk**	SHOULD BE ABLE TO FAST They must be supported to fast
Score 3.5-6	**Moderate Risk**	ADVICE NOT TO FAST If they chose to fast, they must be supported; they need to be cautious and discontinue fasting if any problems arise.
Score >6	**High Risk**	SHOULD NOT FAST If they do still insist on fasting the utmost care and monitoring should be provided alongside other strategies mentioned ealier

Adapted from Diabetes and Ramadan: Practical Guidelines 2021.[31]

This risk stratification may be applied to a structured Christian fast, such as during Lent.

Healthcare personnel must educate patients on the following topics before the commencement of a fasting period:

- Modification of dietary intake
- Modification of medications
- Physical activity
- Knowledge of diabetes emergencies
- Self-blood glucose monitoring
- Recognition of complications

Routine laboratory tests to be reviewed before a fast by diabetes patients may include:

- Records of self-monitoring of blood glucose readings
- HbA1c
- Fasting plasma glucose
- 2hour postprandial readings

10.3.4 Recommended Non-Pharmacological Management for patients who choose to fast

- Dietary advice (similar to non-fasting days); healthy balanced diet
  - Avoidance of overeating when breaking fast
  - Ensure adequate fluid intake
- Maintenance of moderate exercise during fasting
- Self- monitoring of blood glucose during fasting.
  - High-risk patients must check their blood glucose twice daily.
  - Those in the moderate to low-risk group can monitor their blood glucose twice daily.
- The care plan should be individualised

10.3.5 Recommended Pharmacological Management for patients who choose to fast

It is recommended that high-risk patients are switched to relatively newer glucose-lowering medications where possible to reduce the risk of hypoglycaemia.[31, 32] Refer to Table 10.4 for treatment recommendations.

Table 10.4: Treatment recommendation during fasting/Ramadan

Usual treatment before fasting	Treatment during fasting
Diet only	No modification
Oral glucose-lowering medications	
Metformin Once, twice, sustained release 500 mg three times a day	 No dose modification 1000 mg with a sunset meal 500 mg with a pre-dawn meal
Acarbose	No dose modification
Thiazolidinedione (Pioglitazone)	No dose modification
Sulphonylurea Glimepiride, Gliclazide MR - Once a day dosing Gliclazide - Twice a day dosing Glibenclamide*	 To be taken before sunset meal. The dose may be adjusted based on the following: glycaemic control and risk of hypoglycaemia Use half of the morning dose before the pre-dawn meal and full evening dose before the sunset meal.
DPP4 Inhibitors	No dose modification
SGLT-2 inhibitor**	No dose modification; to be taken with evening meal
GLP-1 RA	Titrate the dose appropriately in the pre-fast period. No further dose modification

** To be avoided if possible; ** increase fluid intake in non-fasting hours; avoid this in high-risk individuals.*

Adapted from Diabetes and Ramadan: Practical Guidelines 2021.[31]

Recommended Insulin therapy

Diabetes patients on insulin therapy tend to be at a higher risk of hypoglycaemia in the non-fasting state, and this risk is increased when such patients choose to fast. Insulin analogues are preferred to human insulin due to the lower risk of hypoglycaemia. Switch to insulin analogues where possible. Refer to Table 10.5 for insulin dose modifications.

Table 10.5: Insulin dose modification for Ramadan fasting

Usual insulin regimen prior to fasting	Modification**
Long- or intermediate-acting basal insulin: • Once a day – NPH/detemir/ glargine/degludec • Twice a day – NPH/detemir/ glargine	 • Take at iftar (sunset meal). Reduce dose by 15–30% • Take the usual morning dose in the evening and half the evening dose at dawn.
Rapid- or short-acting prandial/bolus insulin:	Take normal dose before evening meal; Omit lunch-time dose; reduce dawn dose by 25–50%
Premixed insulin: Once a day Twice a day Three times a day	Take normal dose before evening meal Take usual morning dose before the evening meal; 20-50% of evening dose before dawn meal Omit afternoon dose. Adjust evening and morning doses

***Dose titration should be performed every three days according to blood glucose levels*

Adapted from Diabetes and Ramadan: Practical Guidelines 2021.[31]

10.3.6 When to break a fast on medical grounds

- If blood glucose level repeatedly falls within these categories, the fast should end:
- Blood glucose < 3.9 mmol/L
- Blood glucose > 16.7 mmol/L
- Development of symptoms of hypoglycaemia or hyperglycaemia

10.3.7 Referral and Level of care for the management of fasting in diabetes patients

- Pre-Ramadan /Pre-fasting counselling is recommended at all levels of care.
- However, due to the possibility of adjustment of medication concerning meals, it is recommended for patients who desire to fast to visit health facilities with doctors. – Levels 2 & 3
- Patients classified as high risk who insist on fasting should be referred to health facilities with physician specialists, family physicians, diabetologists or endocrinologists for counselling, planning and management- Level 3

10.4 DIABETES IN PREGNANCY

10.4.1 Introduction

The prevalence of diabetes in pregnancy is increasing in keeping with the high prevalence of diabetes globally.

10.4.2 Classification

Diabetes in pregnancy is classified as:

1. Preexisting diabetes in pregnancy
    - o known diabetes mellitus predating pregnancy
    - o may be Type 1, Type 2 or rarely other specific types (e.g. monogenic diabetes)
    - o accounts for 10% of cases of diabetes mellitus in pregnancy

2. Hyperglycaemia first detected in pregnancy:
    i. Gestational Diabetes Mellitus (GDM)
        - usually diagnosed in the second half of pregnancy
        - includes those with blood glucose values within the prediabetes range (used in non-pregnant populations)
        - accounts for about 90% of cases of diabetes mellitus in pregnancy
    ii. Overt diabetes in pregnancy (or "Diabetes in Pregnancy")
        - includes those with blood glucose levels meeting the cut off values for diabetes in non-pregnant population

The prevalence of GDM has been reported to be 10% in Ghana, and 13.6% in Africa.[33, 34] Diabetes in pregnancy is challenging because of the increased risk of adverse pregnancy outcomes associated with maternal hyperglycaemia. [35] Therefore, preconception care for women with preexisting diabetes mellitus is paramount. In contrast, screening of pregnant women without prior diabetes mellitus is recommended at the first prenatal visit and in the second half of pregnancy.

10.4.3 Preconception Care

Organogenesis in the foetus occurs as early as 3-8 weeks of gestation; it is therefore, imperative that women with preexisting diabetes in the reproductive age receive preconception care to attain and maintain good glycaemic control before and throughout pregnancy. It reduces the risk of adverse pregnancy outcomes (see Table 10.6). Preconception care for women with diabetes includes the standard screening done for all women without diabetes in addition to the following:

- Counsel women with diabetes on the effect of diabetes on pregnancy and vice versa, the risks associated with unplanned pregnancies and the benefits of planning their pregnancies.
- Discuss using effective reversible contraception until good glycaemic control is achieved and the patient is ready for pregnancy
- Set glycaemic targets and discuss lifestyle changes and medical nutrition therapy to ensure good glycaemic control. An HbA1c target of <6.5% before and during pregnancy is ideal for reducing the risks of complications[36]

- Review all medications and stop any potentially harmful drugs. Replace angiotensin-converting enzyme inhibitors (ACE) and angiotensin-II receptor blockers (ARBs) with safer alternatives.

In exceptional cases, women with severe renal dysfunction with associated proteinuria may continue ACE inhibitors or ARBs (through shared decision-making) under the guidance of a nephrologist until pregnancy is confirmed[37] In such rare situations, ACE inhibitors or ARBs should be stopped immediately after pregnancy is confirmed

- Stop statins and reinforce dietary and lifestyle management for dyslipidaemia[38]
- Folic acid 5mg should be taken daily at least 3 months before conception to reduce the risk of fetal neural tube defects
- Counselling on the risks of alcohol and nicotine use should be done
- Educate on the risk of development and/or progression of diabetic retinopathy in pregnancy. There is the need to have a retinal assessment before pregnancy, in the first trimester, and every trimester subsequently, or as may be recommended by the eye specialist[39]
- Offer renal assessment and refer to a nephrologist if creatinine ≥ 120µmol/L or urinary albumin: creatinine ratio > 30mg/mmol or estimated glomerular filtration rate (eGFR) < 45 ml/minute/1.73 m^2
- Where possible, a multidisciplinary team approach, including a physician/diabetologist, obstetrician, and nutritionist, should be employed during preconception care and throughout pregnancy[40]

Table 10.6: Adverse outcomes associated with diabetes in pregnancy

Maternal	• Hyperglycaemic crisis (increased risk of DKA even at lower blood glucose levels, especially in Type 1 DM) • Hypoglycaemia • Spontaneous abortion • Hypertension/preeclampsia • Increased likelihood of a caesarean delivery (three-fold) • Retinopathy • Risk of future Type 2 diabetes (those with GDM) • Increased risk of heart disease postnatally
Foetal	• Preterm delivery
	• Two-fold increased risk of severe birth injuries • Foetal malformations (anencephaly, microcephaly, renal anomalies, cardiac anomalies) • Large-for-gestational-age babies • Stillbirth • Growth restriction (less common) • Neonatal hypoglycaemia • Neonatal hyperbilirubinemia • Hypocalcemia • Respiratory distress syndrome • Increased risk of admission to NICU • Increased risk of perinatal mortality • Risk of obesity later in life • Risk of Type 2 diabetes mellitus later in life

10.4.4 Prenatal Screening (Diabetes in Pregnancy)

1. **Screening/diagnosis of overt diabetes mellitus (not previously diagnosed)**

   - Screen women with risk factors for diabetes (see below) at their first prenatal visit (before 13 weeks gestation, or as soon as possible) and

those meeting any one of the standard diagnostic criteria below should be diagnosed with overt diabetes (diabetes in pregnancy)[35] :

- **FPG > 7.0mmol/L OR**
- **2hr 75g OGTT > 11.1 mmol/L**
- **HbA1c > 6.5% OR**
- **An untimed random plasma glucose (RPG) > 11.1mmol/L**

- In the absence of hyperglycemic symptoms or unequivocal hyperglycemia, the diagnosis should be confirmed with a second test (FPG, untimed RPG, OGTT, HbA1c) on another day.
- Although Type 1 diabetes is rarely diagnosed for the first time in pregnancy it may present with significant ketosis and unexpected coma.
- Women with FPG of 5.1 – 6.9 mmol/L should be diagnosed with GDM
- Women not meeting any of the above criteria should be re-screened for gestational diabetes mellitus between 24 and 28 weeks with a 75-g OGTT.

Risk factors for Gestational Diabetes Mellitus

- Overweight or obesity (pre-pregnancy BMI > 25kg/m2)
- History of polycystic ovarian syndrome (PCOS)
- Previous delivery of a macrosomic baby
- Previous history of GDM
- History of prediabetes (IFP, IGT, HbA1C > 5.6)
- Hypertension (BP > 140/90mmHg or on hypertension treatment)
- Triglyceride (TG) levels >2.82 mmol/L and/or HDL cholesterol < 0.9mmol/L
- Family history of diabetes in first-degree relatives
- High-risk ethnicity or race (e.g. African)
- Physical inactivity

2. Screening/Diagnosis of Gestational Diabetes Mellitus (GDM)

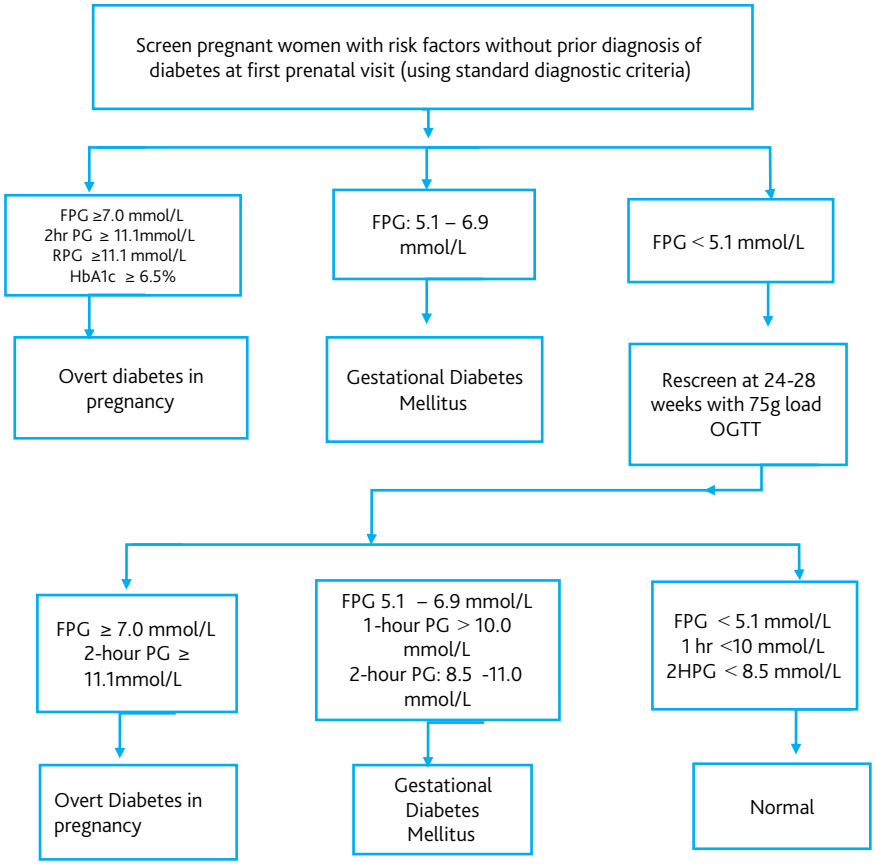
The One-step strategy is recommended in this guideline (Table 10.3).

One-Step-Strategy:

- For women at 24-28weeks gestation with no previous diagnosis of diabetes or GDM, carry out a 75g OGTT with plasma glucose measurements when fasting, at 1 hour and 2 hours
- The OGTT should be carried out in the morning after an overnight fast of 8-14 hours
- The diagnosis of GDM is made if any one of the following is met:
  - **Fasting plasma glucose (FPG) of 5.1 – 6.9 mmol/L**
  - **1-hour Plasma Glucose > 10.0 mmol/L**
  - **2 hours Plasma Glucose of 8.5 -11.0 mmol/L**

NB: Diagnose overt diabetes or diabetes in pregnancy if FPG $\geq$7.0mmol/L or 2-HPG $\geq$ 11.1mmol/L and confirm with a second test (FPG, untimed Random Plasma Glucose (RPG), HbA1c or OGTT) on another day.

3. When OGTT screening is unavailable, screening may be done using fasting plasma glucose (as shown below in Figure 10.4)[41]:



FPG – Fasting Plasma Glucose, RPG – Random Plasma Glucose, GDM – Gestational Diabetes Mellitus, PG - Postprandial Glucose

Figure 10. 3: Diagnosis of Diabetes in Pregnancy

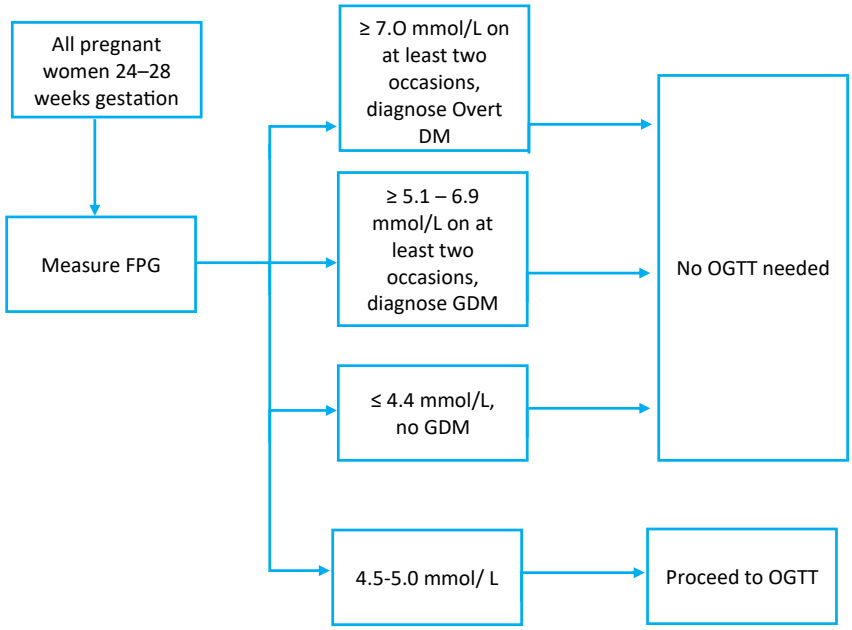


Figure 10.4: GDM screening with fasting plasma glucose

Other Investigations

All routine antenatal tests should be carried out.

1. First trimester
   - HbA1c
   - Thyroid function test
   - Serum urea and creatinine (baseline)
   - Liver function test (baseline)
   - Urine protein to creatinine ratio
   - Ultrasonography (foetal viability and dating)
   - Baseline ECG (women with longstanding diabetes; cardiovascular diseases)
   - Comprehensive ophthalmologic exam (preexisting diabetes)

2. Second trimester
   - Capillary blood glucose levels (4-6 times daily)
   - Repeat HbA1c

- Repeat urine protein-to-creatinine ratio (if 1st trimester value raised)
- Serum urea and creatinine, LFTs, serum uric acid (if preeclampsia present)
- Ultrasonography at 18-20 weeks (for foetal anatomic studies)

3. Third trimester
   - Capillary glucose levels
   - Ultrasonography (for foetal size)
     - Preexisting diabetes: if possible, every 4-6 weeks from 26-36 weeks gestation.
     - GDM: at least once at 36-37 weeks of gestation.

10.4.5 Management of Diabetes in Pregnancy (GDM, Overt Diabetes and Preexisting Diabetes)

Pregnant women on insulin may require lower doses during early pregnancy, and failure to recognise this may lead to hypoglycaemia.

Later in pregnancy, insulin resistance builds up, and frequent insulin dose titrations may be necessary to meet the changing insulin requirements as pregnancy progresses in those with diabetes.

Treatment Goals

Treatment goals are to prevent adverse maternal and foetal outcomes during pregnancy, labour, and postpartum.

Glycaemic targets in pregnancy

- Fasting Plasma Glucose (FPG): 3.9-5.3 mmol/L)
- 1-hour postprandial glucose: 6.1 - 7.8 mmol/L
- 2-hour postprandial glucose: 5.6 - 6.7 mmol/L
- HbA1C: < 6% (ideal, if it can be achieved without significant hypoglycaemia, otherwise allow < 7%)

Monitor capillary blood glucose levels (could be done 4-6 times daily; typically, pre-breakfast, 2hrs post breakfast, pre-lunch, 2hrs post lunch, pre-supper, 2hrs post supper), particularly postprandial levels. To reduce the

risk of adverse outcomes, it is essential to ensure overall good glycaemic control in pregnancy.[42] HbA1c levels fall during normal pregnancy due to physiological increases in red cell turnover.[43] They should be used as a secondary measure of glycaemic control in pregnancy after self-monitoring blood glucose.

Non-Pharmacological Management (For Preexisting DM, Overt Diabetes and GDM)

1. Medical nutrition therapy
    - A nutrition plan should be developed between the patient and a registered dietician familiar with managing diabetes in pregnancy. The food plan should provide a balanced diet with adequate calorie intake while ensuring the attainment of glycaemic targets.
    - A total of 6 meals comprising 3 major meals and 3 snacks are recommended.
    - Carbohydrates - 40% (avoid simple carbohydrates), Protein – 20%
    - Fats – 20% (poly- and mono-unsaturated fats; limit saturated fats and avoid trans fats).
2. Physical activity should be encouraged (specify)
3. Weight management should be based on pre-pregnancy weight
4. For women with GDM with fasting glucose of < 7mmol/L, start on diet and lifestyle modifications, and if targets are not achieved within 2 weeks, offer pharmacological therapy.

Pharmacological Management

1. Gestational Diabetes Mellitus

Indications for pharmacotherapy are

- Glucose levels above target range and foetal overgrowth (macrosomia)
- If fasting plasma glucose is < 7mmol/L at diagnosis, and targets are not met within 2 weeks of non-pharmacological therapy, add metformin
- After a week of non-pharmacological therapy plus a maximum dose of metformin (2500mg) if treatment targets are not met, add insulin
- If fasting plasma glucose > 7mmol/L at diagnosis offer immediate treatment with insulin and lifestyle modification, with or without metformin

- For women with fasting plasma glucose 6.0-6.9mmol/L and complications such as macrosomia and polyhydramnios, consider immediate treatment with insulin and lifestyle changes, with or without metformin.

Insulin therapy

- Lispro and aspart (rapid-acting), regular (soluble), neutral protamine hagedorn (NPH) and, detemir insulin, glargine are safe and effective and may be used.
- If fasting blood glucose is the only component elevated (>7mmol/L), start basal insulin (NPH, glargine, or determir) at 0.2 units/kg or 6-8 units before bedtime.
- If postprandial blood glucose is the only component elevated, start 4-8 units of rapid-acting or regular insulin before meals (bolus insulin).
- If preprandial and postprandial glucose concentrations are high, start a combination of basal and bolus or premixed insulin to control fasting and postprandial hyperglycaemia.
- Titrate insulin doses based on blood glucose levels to achieve glycaemic targets.
- Consult a specialist physician/diabetologist for assistance in insulin initiation.

2. Preexisting diabetes in pregnancy (Type 1 and Type 2) and Overt diabetes in pregnancy
    - Insulin is the preferred drug for Type 1 and Type 2 diabetes in pregnancy.
        - Basal/bolus (multiple daily injections) or premixed insulin can be used in Type 1 diabetes in pregnancy.
        - To reduce the risk of preeclampsia, women with Type 1 or Type 2 diabetes in pregnancy should be prescribed a low dose of Aspirin (100-150mg/day) starting at 12-16 weeks of gestation.

In pregnant women with diabetes and chronic hypertension, treat blood pressure to a target of SBP: 110-135 mmHg and DBP: 85 mmHg to prevent accelerated maternal hypertension.

Intrapartum Management

- Optimising intrapartum glucose metabolism reduces neonatal hyperinsulinaemia and subsequent hypoglycaemia.
- Maternal blood glucose should be maintained in the range: of 4.0 – 7.0 mmol/L.
- Combined use of insulin and glucose infusions can be employed in labour
- 5% Dextrose in normal saline (or in ringer lactate) solution at a rate of 100ml/hour and regular insulin at a rate of 0.5-1.0 U/hour can be used with frequent capillary glucose monitoring (preferably hourly).
- Patients with diet-controlled Gestational diabetes do not require this regimen

Neonatal Care

- Unrecognised and uncorrected hypoglycaemia in the newborn can lead to neonatal seizures, brain damage and death.
- Early oral feeding (breastfeeding) is encouraged; infuse intravenous glucose if early feeding is not possible.
- Monitor newborn babies of mothers with diabetes every 4-6 hours for hypoglycaemia and correct it appropriately.
- Monitor serum calcium levels

Postpartum Care

- Insulin requirements must be re-assessed and doses adjusted to match the decline in insulin resistance after delivery
- Re-screen women with GDM at 6-12 weeks postpartum with 75g OGTT using nonpregnancy diagnostic criteria
- If prediabetes is found in women with a history of GDM, they should receive intensive lifestyle interventions and/or metformin to prevent Type 2 DM
- Women with a history of GDM should have lifelong annual screening to detect prediabetes/Type 2 DM
- Effective contraception should be discussed and prescribed for all women with diabetes in the postpartum period

- Preconception care should be discussed if they desire another pregnancy in the future to ensure good outcomes
- Psychological assessment and support should be provided where appropriate

10.4.6 Referrals

- Refer cases of preexisting Diabetes Mellitus who desire to be pregnant for preconception care (in level 2 or 3 facilities)
- All women with diabetes in pregnancy (preexisting Types 1 and 2, Overt diabetes and GDM) should be managed in level 2 or 3 facilities
- Refer women with preexisting diabetes in pregnancy at first contact to an Ophthalmologist for a dilated eye examination to assess for retinopathy
- Refer all women with diabetes during pregnancy to a registered dietician for dietary counselling
- Refer women with diabetes in pregnancy who are not achieving glycaemic targets to a specialist physician/diabetologist for control
- Refer newborns of women with diabetes with complications for neonatologist/paediatrician's attention
- Refer women with preexisting diabetes who are planning a pregnancy to the Nephrologist if:
  - Serum creatinine >120 µmol/L
  - Urine albumin: creatinine ratio >30mg/mmol
  - Estimated glomerular rate(eGFR) < 45ml/min/1.73 m^2
- Refer pregnant women with preexisting diabetes to the Nephrologist if
  - Serum creatinine >120 µmol/L
  - Urine albumin: creatinine ratio > 30mg/mmol

10.4.7 Levels of Care Recommendations

Care pathways for diabetes in pregnancy is summarized in Figure 10.5.

- Pregnant women with well-controlled diabetes can be managed in a health facility with a doctor knowledgeable in diabetes care (Levels 2 & 3)
- Pregnant women with poorly controlled blood glucose should be managed in a health facility with an obstetrician in conjunction with a physician specialist, diabetologist, or endocrinologist (Level 3)

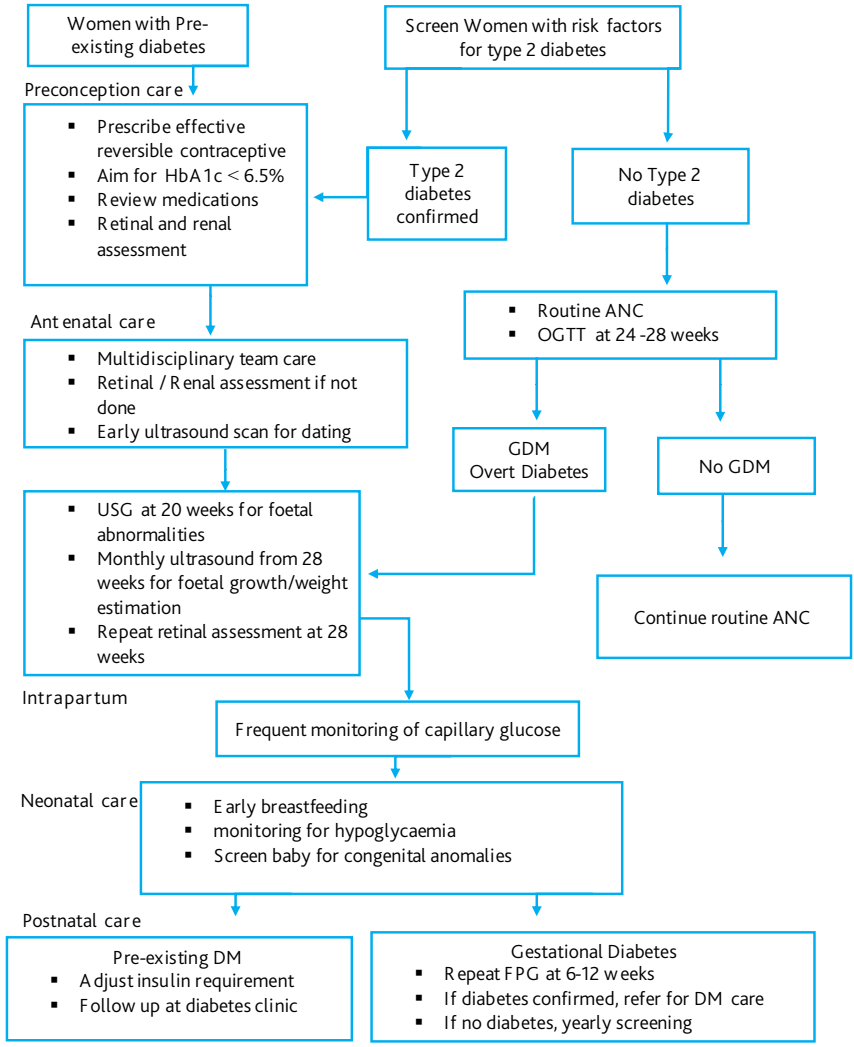


Figure 10.5 : Care Pathways for Diabetes in Pregnancy

10.5 DIABETES AND DENTAL CARE

10.5.1 Introduction

Poor glycaemic control in diabetes may be associated with oral diseases. Due to the plethora of oral manifestations and complications of diabetes, practicing dentists are likely to face it frequently. As a result, oral health

professionals can be crucial in diagnosing and managing diabetes. This can be achieved through proactiveness in assessing the quality of blood glucose control and any existing symptoms and complications resulting from diabetes.[44]

Dental visits should be used for patient education, stressing the interlinkages between diabetes and oral diseases. The benefits of adequately managed diabetes on oral health outcomes and oral health quality of life must also be highlighted to patients. This preventive approach will reduce the onset and incidence of treatment complications and medical emergencies linked to poor glycaemic control.

The oral health practitioner should be keenly aware of the cardinal pathophysiological changes in the quality and quantity of saliva, together with the possibility of increased glucose concentration in the saliva. These upstream problems will significantly impact on saliva buffering components, the antibacterial effect of saliva, levels of cariogenic bacteria, and bacterial plaque biomass. The trickle-down effects become evidenced in higher incidence and severity of complications in oral diseases like periodontitis and dental caries.[44] These and other common oral manifestations, including peculiar steps necessary and recommendations for the care of the diabetic dental patient, are discussed below.

10.5.2 Oral Complications of Diabetes

These include:

- Increased risk of dental caries due to salivary hypofunction
- Gingivitis
- Periodontitis
- Salivary gland dysfunction leading to xerostomia
- Impaired or delayed wound healing
- Taste dysfunction
- Oral candidiasis
- Higher incidence of lichen planus

10.5.3 Periodontal disease

Periodontitis is an infectious disease resulting in inflammation of the tissues surrounding and supporting the tooth with progressive loss of connective tissue attachment and alveolar bone.[45] Periodontal disease and diabetes are interrelated and have a bidirectional relationship.[46] Diabetes has a detrimental effect on periodontal disease, increasing its prevalence, extent, and severity.

Treatment of periodontal disease in diabetics has been identified to aid glycaemic control.[47, 48] The risk of periodontitis is increased by approximately threefold in diabetic individuals compared with non-diabetic individuals, and the severity of periodontitis is much greater in uncontrolled diabetes.[49] The changes seen in the microvasculature of the retina, glomerulus, and other end organs in people with diabetic complications also occur in the periodontium.[50, 51] Untreated, periodontal diseases may serve as initiators or propagators of insulin resistance similar to what happens in obesity, thereby aggravating glycaemic control. Also, periodontal treatment improves glycaemic control in diabetic patients. Poor glycaemic control in diabetes may lead to microvascular, macrovascular, and neuropathic complications, leading to oral diseases, such as periodontitis, caries, oral thrush, and dry mouth (xerostomia).

Signs and symptoms of periodontal disease:

- Swollen gingiva, bright red, dark red, or dark purple gums. Gums that feel tender when touched and the presence of pain on chewing. Gums also bleed easily and have areas with significant recessions
- Bad breath (halitosis) can also supervene
- Purulent discharge from the gum, drifting of teeth, mobile teeth, and loss of teeth are also witnessed
- Xerostomia which can lead to caries, burning sensation in the mouth
- Impaired/delayed wound healing
- Increased incidence and severity of infections, secondary infection with candidiasis, parotid salivary gland enlargement, gingivitis, and periodontitis

10.5.4 Diagnosis of dental conditions

Diagnosis of oral diseases can be achieved through evaluation of the patient's history (medical, drug, social, family), in-depth extra and intra-oral examinations (probing pocket depth, tissue inflammation, clinical attachment loss, dental caries), radiographic examination (bitewing, periapical, orthopantomogram) and laboratory testing (microbiological)

10.5.5 General Consideration in treating patients with Diabetes

Take the following into consideration[52]:

- Ensure good glycemic control at the time of the appointment time
- Good blood glucose control is key to controlling and preventing oral health complications of diabetes
- Schedule patients with diabetes for early morning appointment; patients should eat and take their medication before the appointment. Also ensure that patents take their medications before coming for any dental procedure
- Check vital signs at the time of appointment and do a random blood glucose level check before any surgical procedure.
- Have a source of glucose readily available in the office to correct hypoglycaemia, if needed
- Consult patient's physician if you need medication altered for dental procedures (including patients with hypertension, those recovering from embolic strokes and taking blood thinners)
- The patient's diabetic protocol must be maintained after surgical treatment under local anaesthesia.

10.5.6 Hypoglycaemia in the dental chair

- Hypoglycaemia is defined as blood glucose < 3.9mmol/L.
- Signs and symptoms of hypoglycaemia: shakiness or tremors, confusion, agitation and anxiety, sweating, tachycardia, dizziness, a feeling of "impending doom," unconsciousness, and seizures

Management of hypoglycaemia

- Have a source of glucose (intravenous or oral). As soon as signs or symptoms are present, blood glucose should be checked by the dentist, and appropriate action taken:
- Provide approximately 15 g of oral glucose to the patient: e.g., juice, soda
- If the patient is unable to take food or drink by mouth, or if the patient is sedated: give 25 to 30 ml of 50% dextrose intravenously (which provides 12.5 to 15.0 g of dextrose), or
  Give 1 mg of glucagon intravenously (glucagon results in rapid release of stored glucose from the liver), or
  Give 1 mg of glucagon intramuscularly or subcutaneously (if there is no intravenous access).

10.5.7 Recommendations

Facilities without a Dentist (Physician Assistant-Dental)

- Rule out acute orofacial infection or severe dental infection; if present, provide care immediately
- Establish the best possible oral health through nonsurgical debridement of plaque and calculus (scaling and polishing) and institute oral hygiene instruction. Limit more advanced care until a diagnosis has been established and good glycemic control is obtained.
- Refer appropriately

Facilities with a Dentist

The dentist should inquire about the attending physician, medications, the type, severity, and control of diabetes, and the last appointment by the patient.

Investigate the patient's recent glycaemic results

- HbA1c < 7% - relatively good control; HbA1c > 7.5% - poor control
- Fasting blood glucose 4.4-7.2 mmol/L-good control
- Random blood glucose <10mmol/L-good control

Action to take depending on glycaemic control

- Assess for glycaemic control and treatment should be limited to palliation in patients with unknown levels of glycaemic control
- Prophylactic antibiotics in patients taking high insulin doses to prevent postoperative infection
- Best to do procedures when blood glucose is in the normal range
- *Refer for specialist consultation when needed*

10.5.8 General Measures for Good Oral Health in Patients with Diabetes

To help prevent or control oral diseases, it is important to:

- Brush your teeth twice daily with fluoride-containing toothpaste and floss to remove bacteria containing plaque in between your teeth
- Chlorhexidine-containing mouthwash may be used when needed as an adjunct to mechanical teeth cleaning (not to be used for more than 14 days)
- Visit your dentist twice a year or more frequently if you have periodontitis
- Patients who wear removable dentures should get education on oral hygiene, dental prosthetic maintenance, and the necessity of replacing them
- Smoking cessation helps ensure and maintain oral and dental health
- Ensure good management and control of diabetes

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