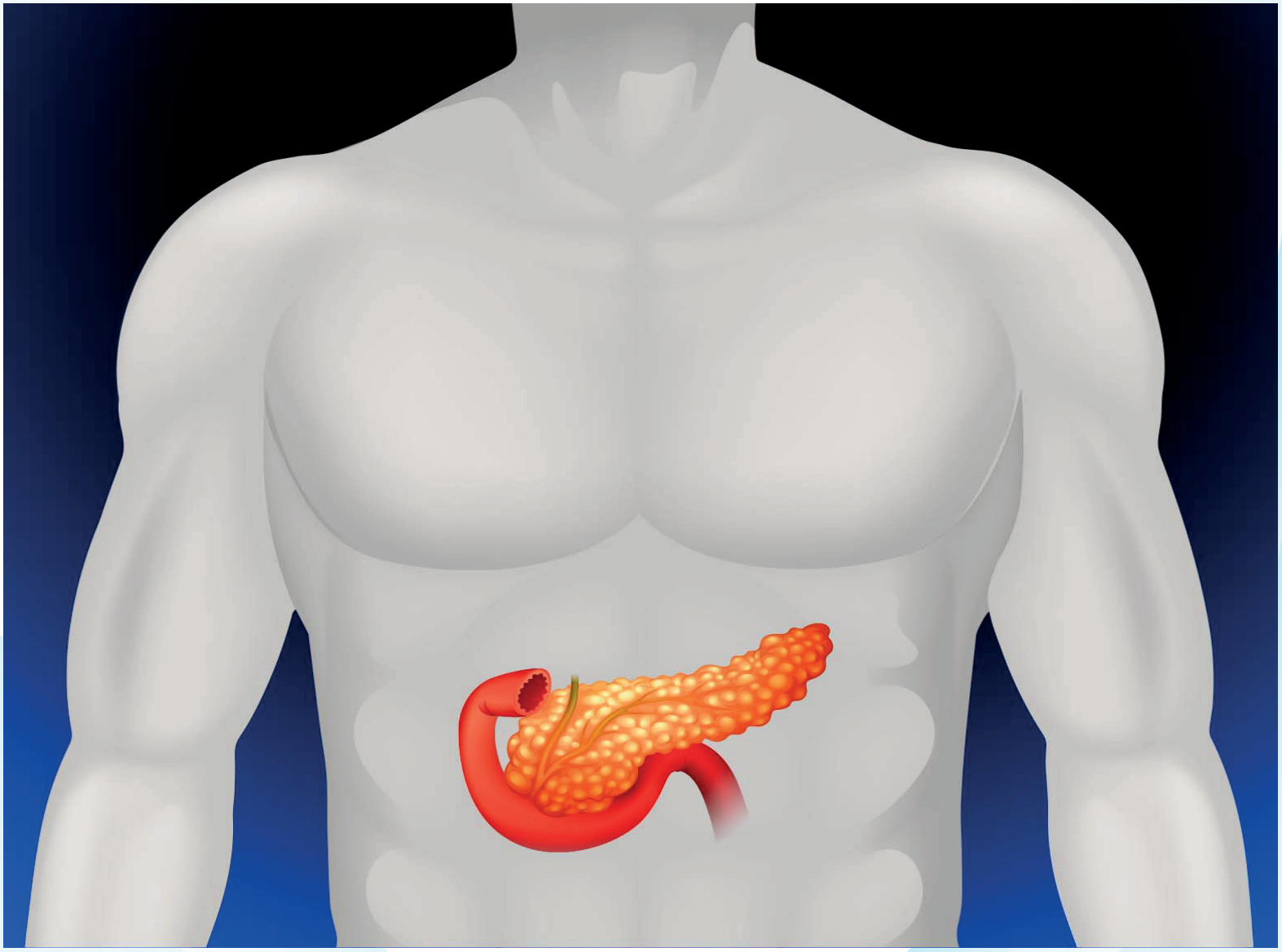
THE REPUBLIC OF UGANDA

MINISTRY OF HEALTH

INTEGRATED DIABETES MANAGEMENT GUIDELINES FOR UGANDA: THE COMPREHENSIVE VERSION



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This Diabetes Management Guideline was developed in close collaboration between the Department of Non-Communicable Diseases Prevention and Control, MOH Uganda, and the Uganda Diabetes Association.

PREFACE

Diabetes is a complex and multifaceted disease that affects millions of people worldwide, imposing a significant burden on individuals, families, and healthcare systems. The prevalence of diabetes continues to rise, driven by factors such as malnutrition, obesity, sedentary lifestyles, unhealthy diets, harmful use of alcohol, use of tobacco-related products, and an aging population. Effective management of diabetes requires a comprehensive approach that incorporates lifestyle modifications, medication, and regular monitoring, as well as patient education, support, and empowerment.

These guidelines aim to provide healthcare professionals with evidence-based recommendations for the diagnosis, treatment, and management of diabetes. Developed by a multi-disciplinary team of experts, these guidelines synthesize the latest research and clinical evidence to inform best practices in diabetes care. Our goal is to improve patient outcomes, enhance quality of life, and reduce the risk of complications, such as cardiovascular disease, kidney damage, and visual loss.

These guidelines cover various aspects of diabetes management, including screening and diagnosis, glycaemic control, blood pressure and lipid management, and prevention and treatment of diabetes-related complications. They also emphasise the importance of patient-centred care, cultural sensitivity, and individualised treatment plans.

I hope these guidelines will serve as a valuable resource for healthcare providers, patients, and caregivers, ultimately contributing to better diabetes care and management. By following these guidelines, we can work together to improve the lives of people living with diabetes and reduce the burden of this disease on individuals, communities, and healthcare systems.

Dr. Diana Atwine
Permanent Secretary,
Ministry of Health

ACKNOWLEDGEMENT

The Ministry of Health is grateful and indebted to the Uganda Diabetes Association for facilitating the development of this first-ever diabetes management guideline for Uganda. The development of these guidelines was made possible through the dedication and expertise of numerous individuals and organisations. We would like to extend our sincerest gratitude to the following:

-The multi-disciplinary team of health care professionals, researchers, and patient advocates who contributed their time, knowledge, and experience to the development of these guidelines. Their expertise in diabetes, primary care, nutrition, and other relevant fields was invaluable in shaping the guidelines.

-The external peer reviewers who provided valuable feedback and insights to enhance the quality and relevance of the guidelines. Their thoughtful comments and suggestions helped to ensure that the guidelines are evidence-based, practical, and effective.

-The organisations and institutions that supported the development of these guidelines (the Uganda Diabetes Association (UDA), the Ministry of Health-NCD Department, and the Uganda NCD Alliance). Their support and resources were essential in facilitating the development process.

-The individuals living with diabetes who shared their experience and perspectives, helping to ensure that the guidelines are patient-centred and relevant to real-world needs. Their input was instrumental in shaping the focus on individualised treatment plans.

-The pharmaceutical companies that provided the UDA with financial support for the development of these guidelines (Ajanta Pharmaceutical Limited, Cipla Pharmaceutical Limited, Denk Pharmaceutical Limited, Microlabs Pharmaceutical Limited, Sanofi Global Health Unit, and Zydus LifeSciences). The investment in this project has enabled the creation of a valuable resource for healthcare professionals, patients, and caregivers.

We appreciate the collective effort and commitment that has gone into creating these guidelines, and we are confident that they will make a positive impact on the lives of people with diabetes and the economy at large.

Prof. Charles Olaro
Director General Health Services
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REMARKS FROM THE PRESIDENT, UGANDA DIABETES ASSOCIATION

The Uganda Diabetes Management Guidelines have come at a crucial time when the burden of diabetes in the country has increased threefold in the last 10 years. Moreover, Uganda is currently facing unique challenges in healthcare delivery due to the compounded phenomenon arising from inadequate financial resources, lack of adequately trained healthcare workers, unavailability of essential medicines and associated technologies, and inequity imposed by public and private sector healthcare. It is probably because of these unresolved challenges that diabetes has an immense impact on morbidity and mortality in our country. With all the constant evolution of diabetes and emerging novel therapeutic choices and technological advancements, there is a need to provide evidence-based, clinical guidance for the best management of different aspects of diabetes to healthcare workers at all levels of healthcare in the country.

These guidelines have been developed by the Uganda Diabetes Association (UDA) guidelines committee, comprised of experts from diverse fields, and cover a wide range of topics that are contextualized to our resources and technologies. Moreover, for effective diabetes care, these guidelines are premised upon the Chronic Care Model and centered around the individual living with diabetes managed by a multi-team of health experts.

Whereas the evidence-based recommendations made in this clinical guideline are consistent with those made in most International guidelines, special attention was paid to resource- and cost-related issues affecting the care of people living with diabetes in Uganda. The guidelines are advisory and are not intended as a set of rigid rules, since individual patients require tailored treatment for their particular condition.

We hope if used appropriately, they will lead to a uniformly high standard and comprehensive management of diabetes in our country.

Dr. William Lumu
President,
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PURPOSE OF THE INTEGRATED DIABETES MANAGEMENT GUIDELINES

Globally, diabetes is one of the leading causes of morbidity and mortality. According to the 2021 International Diabetes Federation estimates, about one in ten adults aged 20-79 years live with diabetes.

In Uganda, the most recently concluded population-based survey reported a two-fold increase in the prevalence of diabetes over 10 years. This survey also reported that about 50% of adult Ugandans are unaware of their diabetes status, resulting in late diagnosis and presentation with debilitating diabetes complications.

One of the most frequently mentioned challenges in clinical practice in Uganda is the presence of significant knowledge gaps in diabetes management among healthcare professionals. To address this challenge, it is important to develop a comprehensive and locally relevant diabetes management guideline.

The purpose of this integrated diabetes management guideline is to provide practical and evidence-based lessons on early diagnosis, optimal management, and detailed prevention of diabetes. We are optimistic that this guideline will ultimately improve the health outcomes of people living with diabetes. Because diabetes is a complex and expensive condition to manage, we are also optimistic that the guideline will provide key tips on how to prevent the condition.

This guideline is not meant to replace one's clinical judgement. Its aim is only to guide healthcare professionals in managing people with diabetes. It also serves to complement the section on diabetes management in the 2023 Uganda Clinical Guidelines.

We hope you find it a valuable resource for managing diabetes in Uganda.

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EXECUTIVE SUMMARY

Background

Despite the growing burden of diabetes in Uganda, we lack a comprehensive, locally adapted clinical guideline for managing diabetes.

Objective

This integrated diabetes management guideline aims to provide healthcare professionals with the latest evidence to inform clinical decision-making when managing individuals with diabetes.

Methods

The Uganda Diabetes Association selected an expert committee to collate, review, and provide an internal peer review of the initial draft of the guideline. This was followed by an external peer review by 11 randomly selected independent African diabetes experts. A working group from the Department of Non-communicable Diseases Prevention and Control, Ministry of Health, Republic of Uganda, conducted an additional external peer review.

Results

This clinical guideline includes these 18 chapters: (1) Epidemiology of diabetes; (2) Definition and classification of diabetes; (3) Screening and diagnosis of diabetes; (4) Organisation of diabetes care; (5) Preventive strategies for type 2 diabetes; (6) Diabetes self-management education, peer support, and medical nutritional therapy; (7) Comprehensive medical evaluation, screening for related comorbidities, and follow-up; (8) Optimal glycaemic targets; (9) Non-insulin pharmacological approaches of glycaemic management in type 2 diabetes; (10) Insulin therapy in type 2 diabetes; (11) Cardiovascular disease risk profiling and management; (12) Management of acute diabetes complications; (13) An overview of chronic diabetes complications; (14) In-hospital management of hyperglycaemia; (15) Diagnosis and management of type 1 diabetes; (16) Management of acute and chronic diabetes complications in type 1 diabetes; (17) Management of hyperglycaemia in pregnancy; (18) Management of diabetes-HIV and tuberculosis comorbidity.

Conclusions

This integrated diabetes management guideline for Uganda provides recent evidence on how to diagnose and manage diabetes, emphasising an individualised and comprehensive approach.

ABBREVIATIONS

2h-BG: 2-hour blood glucose
ACEI: Angiotensin-converting enzyme inhibitor
ACOG: American College of Obstetricians and Gynaecologists
ADA: American Diabetes Association
ARB: Angiotensin II receptor blocker
ASCVD: Atherosclerotic cardiovascular disease
BG: Blood glucose
BMI: Body mass index
BP: Blood pressure
CAD: Coronary artery disease
CCB: Calcium channel blocker
CGM: Continuous glucose monitoring
CCF: Congestive cardiac failure
CKD: Chronic kidney disease
CV: Cardiovascular
CVD: Cardiovascular disease
DASH: Dietary Approaches to Stop Hypertension
DKA: Diabetic ketoacidosis
DKD: Diabetic kidney disease
DM: Diabetes mellitus
DPP-4: dipeptidyl peptidase-4
EADSG: East African Diabetes Study Group
EASD: European Association of the Study of Diabetes
e-GFR: Estimated glomerular filtration rate
FBG: Fasting blood glucose
GLP-1 RA: Glucagon-like peptide-1 receptor agonist
HbA1c: Glycated haemoglobin
HDLC: High-density lipoprotein cholesterol
HT: Hypertension
IADPSG: International Association of Diabetes and Pregnancy Study Groups
IDF: International Diabetes Federation
IFG: Impaired fasting glucose
IGT: Impaired glucose tolerance
ISPAD: International Society for Peadiatric and Adolescent Diabetes
LADA: Latent autoimmune diabetes in adults
LDLC: Low-density lipoprotein cholesterol
MI: Myocardial infarction
MRA: Mineralocorticoid receptor antagonist
NPH: Neutral protamine Hagedorn
OGTT: Oral glucose tolerance test
OSA: Obstructive sleep apnea
PAD: Peripheral arterial disease
PCOS: Polycystic ovary syndrome
PPG: Postprandial glucose
SGLT2i: Sodium-glucose cotransporter 2 inhibitors
SU: Sulfonylurea
TDD: Total daily dose
TGL: Triglyceride
TIA: Transient ischemic attack
TIR: Time in range
TZD: Thiazolidinedione
T1D: Type 1 diabetes
T2D: Type 2 diabetes
UACR: Urine albumin-to-creatinine ratio
The Union: International Union against Tuberculosis and Lung Disorders
VLDLC: very low-density lipoprotein cholesterol
WHO: World Health Organisation

INTRODUCTION

Diabetes mellitus is a complex and chronic metabolic condition whose management requires a multi-sectoral and collaborative approach. To-date, a plethora of evidence on a wide range of therapeutic interventions aimed to improve diabetes outcomes in clinical practice has been published. However, most of this clinical evidence needs to be tailored to local settings, especially in sub-Saharan Africa.

In Uganda, we lack a comprehensive and locally adapted clinical guideline to guide healthcare professionals in managing diabetes. To address this gap, the Uganda Diabetes Association (UDA), working closely with the Division of Non-Communicable Diseases (NCD) Control and Prevention, Ministry of Health, Uganda, set up a guideline expert committee to develop a comprehensive and pragmatic evidence-based clinical guideline for managing diabetes in Uganda. The expert committee was tasked to explore the available published clinical evidence and provide practical recommendations to guide clinical practice and policy in Uganda. This committee comprised executive committee members of the UDA, internists, diabetologists, nephrologists, cardiologists, nutritionists, pharmacists, diabetes education experts, and nurses.

Broadly, the expert committee identified these 18 key areas of interest in diabetes care in Uganda to incorporate into the clinical guideline:

1. Epidemiology of diabetes: Global, African, and Ugandan perspective
2. Definition and classification of diabetes
3. Screening and diagnosis of diabetes
4. Organisation of diabetes at each healthcare level
5. Preventive strategies for type 2 diabetes
6. Diabetes self-management education, peer support, and medical nutritional therapy
7. Comprehensive medical evaluation, screening for related comorbidities, and follow-up in care
8. Optimal glycaemic targets
9. Non-insulin pharmacological approaches of glycaemic management in type 2 diabetes
10. Insulin therapy in the management of type 2 diabetes
11. Cardiovascular disease risk profiling and management
12. Management of acute diabetes complications
13. An overview of chronic diabetes complications
14. In-hospital management of hyperglycaemia
15. Diagnosis and management of type 1 diabetes in children, adolescents, and young adults
16. Management of acute and chronic diabetes complications in children, adolescents, and young adults with type 1 diabetes
17. Management of hyperglycaemia in pregnancy
18. Management of diabetes-HIV and tuberculosis comorbidity

INTRODUCTION

Particular experts were allocated specific areas of interest and tasked with undertaking a literature search, review, and providing additional expert input to initial drafts of the chapters written and shared by the lead member of the guideline development committee. After the internal peer review by the members of the Expert Committee, the final drafts of the chapters of the clinical guideline were shared for external peer review by 11 randomly selected independent experts in the area of diabetes based in six African countries (Uganda, Kenya, Tanzania, Cameroon, Botswana, and South Africa). Based on the submitted comments, each chapter was revised, and a final version of the clinical guideline was drafted for final external peer review by a working group from the Department of NCD Prevention and Control, Ministry of Health, Republic of Uganda.

This integrated diabetes management guideline is intended for a wider audience comprising clinical officers, medical officers, diabetes nurses, diabetes education experts, nurses, physicians, diabetologists, pharmacists, nutritionists, cardiologists, nephrologists, emergency medicine physicians, paediatricians, neurologists, obstetricians and gynaecologists, and ophthalmologists to guide the optimal management of diabetes and its complications at the different healthcare levels. The guideline is also intended to help insurance companies, policymakers at the Ministry of Health, Republic of Uganda, researchers, advocacy groups, and people living with or at risk of diabetes to advocate, develop, and implement policies aimed at preventing diabetes and improving its holistic management in Uganda.

Because medicine is a dynamic field with insightful new evidence being published regularly, this guideline will be periodically updated to incorporate any new published evidence. As a disclaimer, the purpose of these diabetes guidelines is not to fully replace clinical judgement but to provide recent and comprehensive evidence-based recommendations for the management of diabetes.

We hope that this will serve as a guide to healthcare professionals and people living with diabetes in Uganda. This integrated guideline is also meant to complement the section on the management of diabetes in the 2023 Uganda Clinical Guidelines. We hope it will ultimately help in improving the care of people living with diabetes and, therefore, reduce morbidity and mortality related to diabetes.

MATERIALS AND METHODS

To rate the recommendations made in this clinical guideline, we used the American Diabetes Association grading system, whose levels of evidence are either A, B, C, or E, depending on the quality of evidence (summarised in Table 1 below) (1).

Table 1. The ABCE evidence-grading system

LEVEL OF EVIDENCE	DESCRIPTION
A	**Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including:** - Evidence from a well-conducted multicentre trial - Evidence from a meta-analysis that incorporated quality ratings in the analysis **Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including:** - Evidence from a well-conducted trial at one or more institutions - Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	**Supportive evidence from well-conducted cohort studies** - Evidence from a well-conducted prospective cohort study or registry - Evidence from a well-conducted meta-analysis of cohort studies **Supportive evidence from a well-conducted case-control study**
C	**Supportive evidence from poorly controlled or uncontrolled studies** - Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results - Evidence from observational studies with a high potential for bias (such as case series with comparison with historical controls) - Evidence from case series or case reports **Conflicting evidence with the weight of evidence supporting the recommendation**
E	Expert consensus or clinical experience

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CHAPTER 1: EPIDEMIOLOGY OF DIABETES: THE GLOBAL, AFRICAN, AND UGANDAN PERSPECTIVE

SUMMARY

- There is a growing burden of diabetes worldwide, with the majority of people with diabetes living in low- and middle-income countries.
- Despite having the lowest prevalence of diabetes worldwide (4.5%), the greatest increase in the prevalence of diabetes is projected to occur in the African region (129% increase by 2045).
- The 2023 Non-Communicable Diseases Risk Factor STEPs survey in Uganda has reported a twofold increase in the prevalence of diabetes and impaired fasting glucose in adult Ugandans from the 2014 national estimates (3.3% and 4.9%, respectively).
- Socioeconomic, demographic, environmental, and genetic factors may explain this observed increasing trend in the prevalence of diabetes and impaired fasting glucose in Uganda. These factors should be investigated in great detail.

1.1. Global prevalence of diabetes

Current figures show that the burden of diabetes has reached epidemic proportions globally, posing significant public health challenges. The 2021 International Diabetes Federation (IDF) estimates report that about 537 million adults (10.5%) aged between 20 and 79 years are living with diabetes globally. This estimate is projected to rise to 643 million by 2030 and 783 million by 2045. More than 90% of people living with diabetes have type 2 diabetes with about 240 million people living with undiagnosed diabetes. The estimates also show that about 75% of people with diabetes live in low- and middle-income (LMIC) countries (1).

Considering the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) that computed the estimates of diabetes prevalence and burden in 204 countries and territories between 1990 and 2021, about 529 million (95% uncertainty interval [UI] 500–564) people were living with diabetes globally in 2021, with type 2 diabetes making up 96% (95% UI 95.1–96.8) of all diabetes cases. The global age-standardised total diabetes prevalence was 6.1% (95% UI 5.8–6.5). At the super-region level, the highest age-standardised prevalence of diabetes was observed in North Africa and the Middle East (9.3% [95% UI 8.7–9.9]) with country-specific rates of >10% in 11 countries in this region. Oceania had the highest regional age-standardised prevalence of diabetes of 12.3% (95% UI 11.5–13.0) with 15 of 18 countries and territories having a diabetes prevalence > 10%. Eastern sub-Saharan Africa had the lowest regional diabetes prevalence of 2.9% (95% UI 2.7–3.1) (2).

This growing burden of diabetes

globally is mainly driven by socioeconomic advancements or urbanisation, an increasingly aging population, physical inactivity, and increasing rates of overweight and obesity (1).

1.2. Prevalence of diabetes in the African region

According to the 2021 IDF estimates, about 24 million adults (1 in 22 adults or 4.5%) live with diabetes in Africa, with an age-adjusted comparative prevalence of 5.3%. This estimate is projected to increase to 33 million adults in 2030 and 55 million adults in 2045, reflecting the greatest projected increase in all IDF regions of 134% and 129%, respectively.

About one in five (54%) people living with diabetes in Africa are undiagnosed, the highest proportion in all of the IDF regions (1). This calls for increased awareness in communities and healthcare facilities at all levels to ensure early diagnosis of diabetes in the region.

1.3. Prevalence of diabetes in Uganda

The prevalence estimates of diabetes in Uganda vary greatly. Based on the findings from several community-based studies, the reported prevalence of diabetes ranges between 0.4 and 10.6% (3-8). This wide difference in the reported prevalence may be explained by the differences in study settings (rural vs. urban areas), study participants, study sample sizes, and study definitions or diagnostic approaches for diabetes.

To date, only two national population-based Non-communicable Disease (NCD) Risk Factors surveys using the WHO STEPwise approach, a sequential process of data collection using a three-step process, have been conducted in Uganda. The initial survey was conducted in 2014, followed by the second one almost ten years later (9). In the 2023 Uganda national NCD risk factor WHO STEPs survey, a total of 3,694 adult Ugandans (1,426 men and 2,268 women) were recruited, giving a response rate of 86%. The median age of the participants was 36 years (age range: 18 – 69 years). The reported prevalence of diabetes and impaired fasting glycaemia (IFG) was3.3% (95% CI: 2.5 – 4.0) and 4.9% (95% CI: 3.9 – 5.9), respectively (10). This reflects an almost two-fold increase in the prevalence of diabetes and IFG reported in the 2014 NCD risk factors STEPs survey of 1.4% (95% CI: 0.9–1.9%) and 2% (95% CI: 1.5–2.5%), respectively (11). In contrast to the 2014 national survey, the prevalence of diabetes and IFG in the urban and rural populations was similar (2.6%, 95% CI: 1.6– 4.2 and 2.6%, 95% CI: 1.9 – 3.5, respectively, for diabetes, and 4.3%, 95% CI: 2.2 – 8.2 and 4.3%, 95% CI:3.5 – 5.3, respectively, for IFG). Nonetheless, sex-based disparities were noted, with women having a greater prevalence of diabetes and IFG in contrast to men (3.9%, 95% CI: 2.7 – 5.1 vs. 2.6%, 95% CI: 1.6 – 3.6, respectively, for diabetes and 5.9%, 95% CI: 4.7 – 7.1 vs. 3.7%, 95% CI: 2.1 – 5.3, respectively, for IFG) (10).

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CHAPTER 2: DEFINITION AND CLASSIFICATION OF DIABETES

SUMMARY

- Diabetes is a complex metabolic condition characterised by disorders in carbohydrate, protein, and fat metabolism due to reduced insulin secretion and action.
- Due to advancements in phenotypic and genetic characterisation, several diabetes subtypes have been identified and the diabetes classification revised.
- Autoimmune type 1 diabetes is marked by the presence of ≥2 islet-cell autoantibodies with or without absolute endogenous insulin deficiency.
- Type 2 diabetes is the most common diabetes subtype. It is a nonautoimmune subtype that develops due to relative insulin deficiency and/or insulin resistance.
- Slowly evolving immune-mediated diabetes is another diabetes subtype characterised by early onset (>30 years), single islet-cell autoantibody positivity, and insulin independence at the time of diagnosis.
- Ketosis-prone type 2 diabetes is an atypical diabetes subtype described mostly in non-White populations. It is characterised by early onset, absence of islet-cell autoimmunity, and presentation with severe hyperglycaemia and ketosis with eventual insulin independence and diabetes remission in some patients.
- Neonatal diabetes and maturity-onset diabetes of the youth are diabetes subtypes caused by single-gene mutations that develop in young patients and are mostly optimally managed with low-dose sulfonylureas.
- Disorders of the exocrine pancreas are associated with endocrine dysfunction and the onset of diabetes.
- Malnutrition-related diabetes or type 5 diabetes is a recently recognised diabetes subtype observed in underweight individuals with a prior history of early-life undernutrition, lean body size, absence of visceral and ectopic adiposity, ketosis resistance, and severe beta-cell dysfunction.

2.1 Definition of diabetes

Diabetes is a constellation of metabolic disorders mainly characterised by hyperglycaemia and dysfunction in carbohydrate, protein, and fat metabolism that develops due to defective insulin secretion, insulin action, or both. Several aetiopathogenic processes are involved in the onset of diabetes. The key processes are either pancreatic beta-cell damage (autoimmune ..relative insulin deficiency or reduced action of insulin on the peripheral tissues, such as skeletal muscle, liver, and adipose tissue, especially in the presence of overweight and obesity (insulin resistance) [1].

2.2 Classification of diabetes

Traditionally, diabetes has been classified into four broad classes, i.e. type 1 diabetes (due to autoimmune beta-cell damage usually resulting in absolute insulin deficiency), type 2 diabetes (characterised by a non-autoimmune related decline in beta-cell insulin secretion and/or insulin resistance), specific types of diabetes due to other causes such as neonatal diabetes, maturity-onset diabetes of the young, pancreatic conditions such as chronic pancreatitis, and hyperglycaemia in pregnancy (pre-gestational and

gestational diabetes mellitus) [1].
However, with the current advancement in phenotypic, genetic, proteomic, and metabolomic characterisation, the classification of diabetes has been widely revised to include additional subtypes. Proper classification of diabetes is integral in guiding the selection of optimal treatment choices, stimulating research to further understand aetiopathogenesis (especially genetic, epigenetic, proteomic, and metabolomic processes involved), and providing a basis for epidemiological studies (mainly to subtype diabetes in population-based studies) [2].

In 2019, the WHO released its revised classification system for diabetes [2]. This replaced the 1999 classification system that had recommended the inclusion of clinical stages of diabetes of normoglycaemia, impaired glucose regulation (IFG and/or impaired glucose tolerance), and overt hyperglycaemia that most individuals progress through [1, 3].
Table 1 below summarises the 2019 WHO revised classification system of diabetes.

Table 1. Different subtypes of diabetes

DIABETES SUBTYPES
Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes o Slowly evolving immune-mediated diabetes of adults o Ketosis-prone type 2 diabetes
Other specific types (see Table 2 below) Monogenic diabetes o Monogenic defects of beta-cell function o Monogenic defects in insulin action Diseases of the exocrine pancreas Endocrine disorders Drug- or chemical-induced Infections Uncommon specific forms of immune-mediated diabetes Other genetic syndromes sometimes associated with diabetes
Unclassified diabetes This category should be used temporarily when there is no clear diagnostic category, especially close to the time of diagnosis of diabetes
Hyperglycaemia first detected during pregnancy Diabetes mellitus in pregnancy Gestational diabetes mellitus
Type 5 diabetes or malnutrition-related diabetes

2.2.1 Type 1 diabetes

Autoimmune type 1 diabetes (T1D), which accounts for 5-10% of diabetes worldwide, is caused by autoimmune destruction of pancreatic beta-cells. Although T1D can occur at any age, the majority of people develop it in childhood and adolescence [2]. The hallmark of T1D is the presence of ≥2 islet-cell autoantibodies such as autoantibodies to glutamic acid decarboxylase (GAD) GAD-65, insulin, tyrosine phosphatase islet antigen 2 (IA-2A), and zinc transporter 8 (ZnT8) with or without absolute insulin deficiency (defined as undetectable or low fasting or random C-peptide levels). The autoimmune destruction of the pancreatic beta-cells in individuals with T1D is associated with specific genetic and environmental factors such as HLA DQB1 and DRB1 haplotypes and early-life exposure to viral infections associated with islet inflammation, such as enteroviruses [2, 4-6].

The progression of T1D has been described to occur in three distinct stages. Stage 1 is characterised by the presence of ≥2 islet-cell-specific autoantibodies, normoglycaemia, and an asymptomatic state. Stage 2 is marked by the presence of ≥2 islet-cell specific autoantibodies and the onset of dysglycaemia (IFG and IGT) but without symptoms suggestive of overt diabetes. Stage 3, which is the final stage of the progression, is characterised by overt hyperglycaemia and symptoms suggestive of diabetes. Some of the islet-cell autoantibodies may be absent in some individuals at this stage [5, 6].

The progression from stage 1 to 3, which can take months to years, is mainly influenced by the presence of multiple islet-cell autoantibodies [5, 6]. Additionally, individuals with T1D are also prone to developing other autoimmune conditions later in life, such as Hashimoto thyroiditis, Graves' disease, Addison's disease, vitiligo, and pernicious anaemia as part of the autoimmune polyglandular syndrome [7, 8]. Because of this, healthcare professionals should be cognisant of these comorbidities during the follow-up of individuals with T1D and promptly assess for them when clinically indicated.

Type 1 diabetes has been documented to occur in children and adolescents in Uganda [9]. The condition in this age group is described in great detail in Chapter 15 of this guideline. In one cross-sectional study, T1D was reported to be extremely rare in adult Ugandans with new-onset diabetes. In this study, autoantibodies to GAD-65, IA-2A, and ZnT8 as markers of islet-cell autoimmunity were screened in 534 adult Ugandans with recently diagnosed diabetes. Only four (0.8%) participants were positive for ≥2 islet autoantibodies (noted positivity for autoantibodies to GAD-65 and ZnT8), reflecting a very low prevalence of T1D in this study population [10].

Because confirmation of T1D in clinical practice requires demonstration of the presence of islet-cell autoimmunity, testing for the islet autoantibodies is essential. However, these tests are not readily available in Uganda, and the cost of testing is prohibitive for an average Ugandan citizen (350,000 Ugandan shillings or 90 US dollars). In the absence of islet-cell autoantibody testing, the measurement of random or fasting C-peptide concentrations to confirm the presence of absolute

endogenous insulin deficiency (which may be absent in some individuals with T1D) can instead be performed [11, 12]. The C-peptide test is readily available in some private hospitals and laboratories in Uganda and is relatively affordable (cost is about 60,000 Ugandan shillings or 15 US dollars).

2.2.2 Type 2 diabetes

Type 2 diabetes (T2D) accounts for 90-95% of diabetes cases worldwide [13]. The condition is a nonautoimmune type of diabetes characterised by the presence of relative endogenous insulin deficiency and/or peripheral insulin resistance [1, 2]. The condition is common in adults and, recently, has been increasingly observed in children and adolescents, especially in the setting of overweight and obesity [2, 13].

The increasing prevalence of T2D reported worldwide is attributed to several factors such as emerging socioeconomic changes, rapid urbanisation, ageing populations, dietary changes (increased consumption of processed foods and sugar-rich beverages), physical inactivity, and increased rates of overweight and obesity [2]. In sub-Saharan Africa (SSA), effects of early-life (in-utero and early childhood) exposures such as chronic malnutrition and tropical infections such as malaria and genetic influences have also been implicated in the increasing prevalence of T2D [14, 15].

Globally, T2D is mainly associated with increasing obesity and overweight. However, it has been widely noted to develop in individuals who are lean in body size (body mass index or BMI <25 kg/m2) in some sub-Saharan African, South Asian, and East Asian populations [16-20]. This atypical lean T2D phenotype has been widely observed in adult Ugandans with new-onset diabetes, exhibiting distinctive phenotypic features [16, 21, 22]. In the Uganda Diabetes Phenotype (UDIP) study, which performed robust clinical, metabolic, and immunologic characterisation of 500 adult Ugandans with recently diagnosed T2D, the lean T2D phenotype was present in 32% (about 1 in 3) of the participants. Compared with the non-lean T2D phenotype, it was largely characterised by a male predominance, presence of serum or urine ketosis at diagnosis, lower surrogate markers of adiposity (BMI, waist: hip ratio, and visceral adiposity) and metabolic syndrome (less co-existing hypertension and lower uric acid and leptin levels), and features of severe beta-cell dysfunction (instead of insulin resistance) [16].

2.2.3 Hybrid forms of diabetes

2.2.3.1 Slowly evolving immune-mediated diabetes

Slowly evolving immune-mediated diabetes (also referred to as latent autoimmune diabetes of adults or LADA) is observed in adult individuals with a T2D phenotype and accounts for 2-12% of adult-onset diabetes, depending on the ethnicity and number of islet autoantibodies screened [2, 23]. The criteria to diagnose this hybrid form of diabetes include onset of diabetes at >30 years of age, presence of a single islet autoantibody (mostly autoantibody to GAD-65, which is positive in about 90% of cases), and insulin independence for at least 6 months from the time of diagnosis [23]. The presence of single islet

autoantibody positivity distinguishes it from the classical autoimmune T1D [23].
Individuals with this diabetes subtype have a personal or family history of autoimmunity and phenotypically present with a lower frequency of metabolic syndrome and a slower rate of deterioration of the beta-cell function, hence the observed insulin independence at diagnosis [23].
Slowly evolving immune-mediated diabetes has been described in adult Ugandans with new-onset diabetes. In a study by Kibirige et al, autoantibodies to GAD-65, IA-2A, and ZnT8 were screened in 534 adult Ugandans with recently diagnosed diabetes recruited from eight tertiary hospitals. Of these, 30 participants (5.6%) were positive for a single islet autoantibody. Autoantibody positivity to GAD-65 was the most prevalent, followed by positivity to IA-2A and ZnT8 [10].

2.2.3.2 Ketosis-prone type 2 diabetes

This novel hybrid form of diabetes is an atypical nonautoimmune diabetes subtype that has been widely described in non-White adult populations (Black Africans, African-Americans, Afro-Caribbean, Hispanics, and Asians) [2, 24-26]. It is characterised by a non-White ancestry, early onset, male predominance, and absence of islet-cell autoimmunity. Human herpes virus type 8, which is highly endemic in sub-Saharan Africa, plays a key role in its pathogenesis by directly or indirectly (via pro-inflammatory cytokine secretion) causing pancreatic beta-cell damage and ensuing relative insulin deficiency [27]. Metabolically, patients present with severe hyperglycaemia and ketosis with eventual insulin independence after the correction of the initial acute hyperglycaemic episode. Most patients achieve diabetes remission, while others only require dietary modification and oral glucose-lowering agents to sustain normoglycaemia [24-26].

2.2.4 Other specific types of diabetes

For this section of the guidelines, we will only discuss monogenic diabetes subtypes (neonatal diabetes and maturity-onset diabetes of the youth or MODY) and diseases of the exocrine pancreas because, compared with other specific types of diabetes, these are encountered more in clinical practice in Uganda.
Table 2 below summarises the other specific types of diabetes [2].

Table 2. Other specific types of diabetes

OTHER SPECIFIC DIABETES SUBTYPES
Monogenic diabetes **Monogenic defects of beta-cell function (a mutated gene followed by a clinical syndrome)** GCK MODY INSR Type A insulin resistance HNF1A MODY INSR Leprechaunism HNF4A MODY INSR Rabson-Mendenhall syndrome HNF1B RCAD LMNA FPLD mtDNA 3243 MIDD PPARG FPLD KCNJ11 PNDM AGPAT2 CGL KCNJ11 DEND BSCL2 CGL 6q24 TNDM
Monogenic defects in insulin action (a mutated gene followed by a clinical syndrome) ABCC8 MODY INS PNDM WFS1 Wolfram syndrome FOXP3 IPEX syndrome EIF2AK3 Wolcott-Rallison syndrome
Other genetic syndromes sometimes associated with diabetes Down syndrome Friedreich's ataxia Huntington's chorea Klinefelter's syndrome Lawrence-Moon-Biedel syndrome Myotonic dystrophy Porphyria Prader-Willi syndrome Turner's syndrome Others
Diseases of the exocrine pancreas Fibrocalculous pancreatopathy Pancreatitis Trauma/pancreatectomy Neoplasia Cystic fibrosis Haemochromatosis Others
Endocrine disorders Cushing's syndrome Acromegaly Pheochromocytoma Glucagonoma Somatostatinoma Hyperthyroidism

Table 2. Other specific types of diabetes

Drug- or chemical-induced diabetes Integrase strand transfer inhibitors Anti-psychotics Glucocorticoids Thyroid hormone Thiazides Alpha-adrenergic agonists Beta-adrenergic agonists Interferon-alpha Others
Infections Congenital rubella Cytomegalovirus
Uncommon forms of immune-mediated diabetes Insulin autoimmune syndrome (autoantibodies to insulin) Anti-insulin receptor antibodies «Stiff man» syndrome
Other clinically defined subgroups Diabetes associated with massive hypertriglyceridaemia

MODY- maturity-onset diabetes of the young; RCAD- renal cysts and diabetes; MIDD- maternally inherited diabetes and deafness; PNDM- permanent neonatal diabetes; TNDM- transient neonatal diabetes; DEND- developmental delay epilepsy and neonatal diabetes, FPLD- familial partial lipodystrophy; CGL- congenital generalized lipodystrophy.

2.2.4.1 Monogenic diabetes

Monogenic diabetes is a genetic form of diabetes caused by a single-gene mutation that affects pancreatic beta-cell function. It is broadly classified into three subtypes, i.e., neonatal diabetes, MODY, and syndromic diabetes seen in patients with monogenic diabetes and extra-pancreatic features [2, 28, 29]. Mandatory genetic testing is recommended to help identify the correct subtype and guide individualised therapy.

Neonatal diabetes (transient and permanent neonatal diabetes) caused by mutations in one of 38 known genes is diagnosed in babies before the age of six months [2, 28, 29]. About 50% of these babies have mutations in genes encoding the ATP-sensitive potassium channel (KCNJ11 and ABCC8). These patients can be optimally managed with high-dose sulfonylureas without increased rates of hypoglycaemic episodes and glycaemic variability. This therapy is also associated with improvement in the neurologic function. Patients with transient neonatal diabetes resulting from

6q24 methylation abnormalities can be managed with low-dose sulfonylureas [28, 29].

In a cohort of paediatric and adolescent Ugandans being followed up in type 1 diabetes clinics, three cases of neonatal diabetes have been registered and are receiving long-term management [9]. In one case report, Nyangabyaki-Twesigye et al described the first case of permanent neonatal diabetes in Uganda in a six-week-old baby who presented with diabetic ketoacidosis and severe hyperglycaemia. The baby had a confirmed mutation in the KCNJ11 gene encoding the Kir6.2 beta-cell subunit and improved on long-term low-dose glibenclamide [30].

Maturity-onset diabetes of the youth (MODY) is a monogenic diabetes that develops due to mutations in one of 11 known genes. It is characterised by early onset (<25 years of age), insulin independence, and an autosomal dominant inheritance [28, 29]. The commonest MODY subtypes are due to mutations in the glucokinase gene (GCK-MODY) and hepatonuclear factor gene (HNF1A-MODY, HNF4A-MODY, and HNF1B-MODY). Each of these subtypes has distinctive clinical features. Patients with GCK-MODY usually have stable pancreatic beta-cell function and, hence, present with mild non-progressive hyperglycaemia that doesn't require treatment. HFN1A-MODY, which is the commonest, is characterised by glycosuria, while foetal macrosomia and neonatal hypoglycaemia are common in children with HFN4A-MODY. HNF1B-MODY is characterised by beta-cell developmental defects, hyperuricaemia, gout, exocrine pancreas defects, and other organ developmental defects such as kidney and genitourinary anomalies. Concerning treatment, patients with HNF1A- and HNF4A-MODY respond adequately to low-dose sulfonylurea treatment. In contrast, patients with HNF1B-MODY require insulin therapy [28, 29].

Other types of monogenic diabetes are shown in Table 2 above. Those types will not be discussed in detail in this section of the guideline.

2.2.4.2 Diseases of the exocrine pancreas

Diabetes can develop in cases of extensive pancreatic damage due to acute or chronic pancreatitis, regardless of cause (alcohol and gallstones being the commonest in the Ugandan context), trauma, infections, pancreatic cancer, and pancreatectomy [2]. Diabetes can also develop in individuals with fibrocalculous pancreatic diabetes (FCPD). This unique secondary form of diabetes has been described extensively in Uganda [31-33] and other low- and middle-income settings [34]. It is characterised by early-onset (in the third decade of life), male predominance, a lean phenotype, recurrent abdominal pain, radiological evidence of pancreatic calcifications, and ketosis-resistant diabetes. These patients also present with features of pancreatic exocrine

insufficiency and are prone to developing pancreatic cancer [34, 35].

2.2.5 Hyperglycaemia first detected during pregnancy

This diabetes subtype includes these two categories of hyperglycaemia: pre-existing or pre-gestational diabetes in pregnancy (defined with the same criteria as in non-pregnant women) and gestational diabetes (diagnosed for the first time during pregnancy in the second or third trimester based on specific blood glucose level cut-offs different from those of pre-gestational diabetes) [2]. The diagnosis, screening, and management of this diabetes subtype are discussed in detail in Chapter 17 of this guideline.

2.2.6 Type 5 diabetes or malnutrition-related diabetes

Type 5 diabetes or malnutrition-related diabetes (MRD) is one of the atypical diabetes subtypes commonly described in Africa, Asia, and the Caribbean [36-48]. This is because these regions have the highest rates of undernutrition globally, mainly aggravated by civil strife and adverse climate change [49].

Despite the removal of MRD in the WHO classification of diabetes in 1999, citing a lack of compelling evidence that malnutrition (undernutrition) can result in diabetes [3], there is now adequate evidence demonstrating that prior early-life (in-utero or childhood) undernutrition increases the risk of onset of diabetes [50-52]. Based on this emerging evidence, the International Diabetes Federation (IDF) officially recognised MRD as a distinct diabetes subtype during its April 2025 World Diabetes Congress in Bangkok, Thailand. The IDF also launched a working group to develop formal diagnostic criteria and therapeutic guidelines for this atypical subtype [53].

Before the IDF World Diabetes Congress, a team of global diabetes experts with an interest in this atypical form of diabetes proposed the term T5D as an alternative name for MRD during an international consensus meeting held in January 2025 in Vellore, India.

Individuals with MRD or T5D exhibit unique phenotypic characteristics that are distinct from those associated with T1D and T2D. These include: evidence of early-life undernutrition (history of maternal undernutrition, low birth weight, or undernutrition during childhood- manifesting as stunting or wasting), early-onset (<30 years), chronic features of undernutrition such as stunting and low BMI <18.5 kg/m 2 (<19 kg/m 2 for Asians), economic deprivation or low socioeconomic status, no strong family history of diabetes, ketosis resistant despite severe hyperglycaemia, and insulin withdrawal, a structurally normal pancreas (no evidence of calcifications, fibrosis, or inflammation), a greater degree of beta-cell dysfunction, and absence of visceral or ectopic adiposity and any underlying autoimmune or genetic cause of diabetes. Additionally, individuals with this atypical diabetes subtype lack clinical features suggesting the presence of insulin resistance, such as acanthosis nigricans [39, 41, 44, 45, 54-56] .

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CHAPTER 3. DIAGNOSIS AND SCREENING FOR DIABETES

SUMMARY OF RECOMMENDATIONS

- Diabetes should be diagnosed based on the glycated haemoglobin (HbA1c) level ≥6.5% (48 mmol/mol), fasting blood glucose level [FBG] ≥7.0 mmol/l (126 mg/dl), 2-hour blood glucose level [2-h BG] after a 75-gram oral glucose tolerance test [OGTT] ≥11.1 mmol/l (200 mg/dl), or random blood glucose level [RBG]) ≥11.1 mmol/l (200 mg/dl), in the presence of the classic symptoms of hyperglycaemia (polyuria, polydipsia, polyphagia, paraesthesia, wasting, and weakness) **(Level of evidence: A).**
- In the absence of the classic symptoms suggestive of hyperglycaemia, the diagnosis of diabetes should be based on two abnormal tests measured at the same time or at two different time points **(Level of evidence: A).**
- The use of new-model calibrated point-of-care glucometers that give plasma glucose-equivalent values is recommended in the absence of laboratory-based glucose measurement **(Level of evidence: B).**
- The HbA1c test should be performed using a method certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complications Trial (DCCT) reference assay **(Level of evidence: B).**
- In the presence of conditions that affect the HbA1c results, FBG, 2-h BG, or RBG should be used to diagnose diabetes **(Level of evidence: B).**
- Screening for type 2 diabetes and prediabetes in asymptomatic adults using a targeted approach by measurement of FBG, 2-h BG, RBG, or HbA1c is recommended **(Level of evidence: B).**

3.1 Introduction

The Uganda Diabetes Association (UDA) fully endorses the World Health Organisation (WHO) (1), International Diabetes Federation (IDF) (2), and American Diabetes Association (ADA) (3) guidelines for diagnosing and screening diabetes and prediabetes in adult non-pregnant individuals. The term "prediabetes", which is an intermediate phase between normoglycaemia and overt diabetes, is adopted to encompass individuals with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (1-3). These will be defined further in the text below.

3.2 Diagnosis of diabetes

Diabetes may be diagnosed based on blood glucose and glycated haemoglobin (HbA1c) criteria in the presence of the classic symptoms of hyperglycaemia. These include the 5P's (polyuria, polydipsia, polyphagia, paraesthesia, and pruritis) and 3W's (weight loss, wasting, and weakness). The blood glucose criteria comprise the measurement of the fasting blood glucose (FBG), 2-hour blood glucose (2h BG) after a 75-gram oral glucose tolerance test (OGTT), or random blood glucose (RBG) levels. The OGTT is performed after overnight fasting for at least eight hours using 75 grams of anhydrous glucose dissolved in 250 ml of water and ingested within five to ten minutes (1-3).

Table 1 below summarises the diagnostic cut-offs for normoglycaemia, prediabetes, and diabetes according to the WHO, IDF, and ADA guidelines in nonpregnant individuals (1-3).

Table 1. Diagnostic criteria for normoglycaemia, prediabetes, and diabetes

Diagnostic tests	Normoglycaemia	Prediabetes	Diabetes
Fasting blood glucose (FBG)a	<5.6 mmol/l (<100 mg/dl)	5.6 - 6.9 mmol/l (100 -125 mg/dl)	≥ 7.0 mmol/l (≥126 mg/dl)
2-hour blood glucose (2h BG) after OGTT	<7.8 mmol/l (<140 mg/dl)	7.8 - 11.0 mmol/l (140-199 mg/dl)	≥ 11.1 mmol/l (200 mg/dl)
Glycated haemoglobin (HbA1c)b	≤5.6% (38 mmol/mol)	5.7-6.4% (39-47 mmol/mol)	≥ 6.5% (48 mmol/mol)
Random blood glucose (RBG)	<7.8 mmol/l (<140 mg/dl)	7.8-11.0 mmol/l (140-199 mg/dl)	≥ 11.1 mmol/l (200 mg/dl)

a- Fasting is defined as no caloric intake for a minimum of 8 hours, b- The test has to be performed in the laboratory using a National Glycohaemoglobin Standardization Program (NGSP)-certified method and standardised to the Diabetes Control and Complications Trial (DCCT) assay, OGTT- Oral glucose tolerance test

3.2.1 Use of blood glucose in the screening and diagnosis of diabetes

In cases where a nonpregnant individual presents with the typical symptoms of hyperglycaemia (5Ps and 3Ws) and/or a hyperglycaemic crisis such as diabetic ketoacidosis, a single blood glucose test (RBG ≥11.1 mmol/l or 200 mg/dl or FBG ≥7.0 mmol/l or 126 mg/dl) will suffice to diagnose diabetes (1-3).

In nonpregnant individuals without symptoms suggestive of hyperglycaemia, the diagnosis of diabetes should be based on two abnormal tests measured at the same time or at two different time points. A FBG, 2h BG after an OGTT, or HbA1c should be performed. The only merit of performing FBG and HbA1c measurement over a 2h BG measurement is the convenience (1-3).

Despite its cumbersomeness to perform, cost, and less reproducibility, the OGTT is regarded as the gold standard test for diagnosing diabetes because FBG testing alone misses 30% of cases of previously undiagnosed diabetes and it is the only test that can identify individuals with IGT. It should be used in individuals with IFG (fasting blood glucose levels of 6.1-6.9 mmol/l or 110-125 mg/dl) to determine the glucose tolerance status (1). Individuals should be encouraged to have a mixed diet of at least 150 g of carbohydrates three days before the OGTT because fasting and carbohydrate restriction result in a reduction of insulin secretion and falsely high glucose levels following an oral glucose challenge (4, 5).

Laboratory-based venous plasma glucose measurement is the recommended method of assessment of blood glucose levels (1). Proper

blood collection is important to ensure accurate measurement of blood glucose levels. Collection in blood specimen tubes with glycolytic inhibitors such as sodium fluoride (NaF) and the specimen tube immediately placed on ice packs or centrifuged within 30 minutes is recommended. It is important to note that capillary blood glucose measurement as performed by most point-of-care glucometers is affected by numerous factors such as heat, temperature, hypotension, and hypoxia. Additionally, it may give a higher blood glucose concentration (6, 7). However, to ensure accurate blood glucose measurement in the absence of laboratory methods for blood glucose measurement in resource-limited settings, the use of new-model calibrated point-of-care glucometers such as Accu-Chek Active (Roche Diagnostics, Germany), Freestyle Optium Neo (Abbott Diabetes Care Inc., USA), One Touch Select Plus Flex (LifeScan Inc., Switzerland), and Contour Plus (Bayer Healthcare AG, Germany) that give plasma glucose-equivalent values is recommended (1). Glucometers provide blood glucose levels in two measurement units (i.e. mmol/l and mg/dl). Below are the two formulae that can be used in the conversion of the two units:

1. mmol/l to mg/dl: blood glucose level in mmol/l x 18 (Example: 5 mmol/l is equivalent to 90 mg/dl)
2. mg/dl to mmol/l: blood glucose level in mg/dl / 18 (Example: 220 mg/dl is equivalent to 12.2 mmol/l)

Several free online calculators such as the Diabetes UK blood glucose convertor (8) can also be used in the conversion of blood glucose units.

3.2.2 Use of glycated haemoglobin in the screening and diagnosis of diabetes

The HbA1c test in the diagnosis and screening for diabetes must be performed using a method certified by the National Glycohaemoglobin Standardisation Program (NGSP) and standardised to the Diabetes Control and Complications Trial (DCCT) reference assay. Therefore, point-of-care HbA1c assays are not recommended for the diagnosis of diabetes because they are not NGSP-certified. Additionally, do not perform HbA1c tests in the presence of conditions or clinical factors that affect its accuracy (1, 3). Table 2 below summarises these conditions or clinical factors.

The HbA1c reflects glucose bound to haemoglobin over the 120-day lifespan of a red blood cell. This means that the test is ideal for monitoring glucose control over three months and any condition that affects red blood cell turnover and haemoglobin concentrations will negatively affect its performance (3, 9-11). These conditions will either cause a falsely high or low HbA1c concentration resulting in over-diagnosis or under-diagnosis of diabetes.

Table 2. Conditions associated with a falsely high or low glycated haemoglobin concentration

CONDITION	COMMENT
A: Conditions that falsely elevate the glycated haemoglobin concentration and the apparent reason	
Iron, folate, and vitamin B12 deficiency anaemia	Associated with decreased red blood cell turnover
Asplenia or splenectomy	Associated with increased erythrocyte lifespan
Ureamia in chronic kidney disease	Formation and detection of carbamyl-hemoglobin
Chronic alcohol ingestion	Formation of acetaldehyde-HbA1 compound
Severe hypertriglyceridemia (serum triglyceride levels ≥5 mmol/l)	Cause interference with the assays
Hyperbilirubinemia	
Certain haemoglobin variants such as sickle cell traita	
B: Conditions that falsely lower the glycated haemoglobin concentration and apparent reason	
Anaemia from acute or chronic blood loss (including haemolytic anaemia)	
Splenomegaly	Reduced red blood cell lifespan
Pregnancy	Reduced red blood cell lifespan
Vitamin C and E ingestion	Alter the glycation process
Drugs such as dapsone, ribavirin, trimethoprim-sulfamethoxazole	Increased red blood cell destruction
Chronic liver disease	

a- Depending on the assay used, specific haemoglobin variants may either falsely elevate or lower the glycated haemoglobin concentration

The HbA1c test has some advantages over the FBG and 2h BG measurement. It's more convenient to perform (no need to fast), has greater pre-analytical stability, and has fewer day-to-day variations during acute stressful conditions such as illness. Despite these advantages, its use is limited by its lower sensitivity, cost, and limited availability in most clinical settings, including sub-Saharan Africa (12, 13).

In one prospective study conducted in an outpatient setting in a district hospital in Eastern Uganda, the diagnostic performance of HbA1c and FBG was compared using the OGTT as the reference test (14). In this study, a total of 1659 adult Ugandans were screened for diabetes using a FBG test. Of these, 310 participants underwent both an OGTT and an HbA1c measurement. Based on

the universally recommended cut-off points for diabetes, the HbA1c and FBG tests had comparable sensitivity (69.8% [95% CI 46.3–86.1] vs. 62.6% [95% CI 41.5–79.8], respectively) and specificity (98.6% [95% CI 95.4–99.6] vs. 99.4% [95% CI 98.9–99.7], respectively). The area under curve (AUC) in the receiver operating characteristic (ROC) curves was also similar (0.89 and 0.86 for FBG and HbA1c, respectively) (14). This study showed that, in this study population, HbA1c and FBG were comparable in diagnosing diabetes.

However, it should be noted that the HbA1c test is more expensive and is not widely available. The Access to Cardiovascular diseases, Chronic Obstructive pulmonary disease, Diabetes mellitus, and Asthma Drugs and Diagnostics (ACCODAD) study that was conducted in 2017 to investigate the availability, cost, and affordability of essential diabetes medicines and diagnostic tests in Uganda reported low availability of HbA1c tests especially in the public hospitals (22.7% and 63.6% in the public and private hospitals, respectively). The HbA1c tests were also noted to be unaffordable, costing the lowest-paid government worker an equivalent of 8.6 days' wages (15).

Healthcare professionals should also be cognisant of the clinical factors discussed above that alter the HbA1c results and are highly prevalent in the Ugandan population, such as sickle cell trait and disease (16), and iron, folate, and vitamin deficiencies (17-20).

3.3 Screening for type 2 diabetes or prediabetes in nonpregnant adult individuals

Screening for diabetes or prediabetes in nonpregnant adult individuals can either be performed in a random (involving indiscriminate testing of low-risk individuals) or targeted (selective identification and testing of high-risk individuals, such as individuals with a family history of type 2 diabetes, hypertension, or obesity) approach. Both conditions should be screened jointly because they occur on the same pathophysiological continuum (3, 21).

Because prediabetes reflects an intermediate state between normoglycaemia and diabetes, it is a risk factor for progression to overt diabetes and, similar to diabetes, is associated with cardiovascular diseases, dyslipidaemia, metabolic syndrome, and increased mortality (22, 23).

Screening for type 2 diabetes and prediabetes in asymptomatic adults using a targeted approach is recommended. The screening can be performed by RBG, FBG, post-OGTT 2h BG, or HbA1c measurement (2, 3). The criteria for screening for type 2 diabetes and prediabetes in nonpregnant adults is summarised in Table 3 below.

3.3.1 Frequency of screening for type 2 diabetes and prediabetes

Because of the lack of robust real-world evidence, the precise frequency of screening for type 2 diabetes is unknown. However, a three-year interval of testing is recommended in normoglycaemic individuals. This duration of testing ensures that the number of false-positive tests that will require repeat confirmatory testing is reduced. The period also allows individuals who had false-negative tests to be retested before the onset of diabetes complications. However, for high-risk individuals, the screening should be repeated in shorter periods (preferably every year) (3, 21).

Table 3. Criteria for screening for type 2 diabetes and prediabetes in nonpregnant adults

Indications for screening
A. High-risk individuals: All adults (any age) regardless of the body mass index, with ≥1 of the risk factors below: 1.Physical inactivity 2.Hypertension [Blood pressure (BP) ≥ 130/80 mmHg] or treatment for hypertension 3.Family history (first-degree relative) of type 2 diabetes 4.Dyslipidaemia (High-dense lipoprotein cholesterol level <35 mg/dl or 0.9 mmol/l and/or triglyceride level >250 mg/dl or >2.8 mmol/l) 5.Polycystic ovarian syndrome 6.History of cardiovascular disease (coronary artery disease, stroke, peripheral arterial disease) 7.History of gestational diabetes or delivering a baby weighing >4 kg 8.Presence of conditions associated with insulin resistance (severe obesity and/or acanthosis nigricans)
Individuals with HbA1c ≥5.7% (39 mmol/mol) and/or Impaired fasting glucose or impaired glucose tolerance (testing should be done every year)
Women with a history of gestational diabetes should have lifelong testing every three years.
For all other people, testing should start at the age of 35.
People with HIV, exposure to some high-risk medicines (such as efavirenz, protease inhibitors, dolutegravir, thiazide diuretics, steroids, atypical and typical antipsychotics), and a history of pancreatitis.
B: Frequency of testing • Every three years if screening tests are normal and if there is a history of gestational diabetes. • Once every year for high-risk individuals and in cases of prediabetes.
C: The screening approach • Fasting blood glucose, 2-hour blood glucose following an oral glucose tolerance test (OGTT), or glycated haemoglobin measurement. • The OGTT is the preferred test in high-risk individuals. • Screening should be carried out in healthcare settings because of the need for follow-up and prompt initiation of treatment in individuals with positive tests. • Community-based screening can be considered if referral systems to healthcare centres are present and robust.

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CHAPTER 4: ORGANISATION OF DIABETES CARE AT EACH HEALTHCARE LEVEL

SUMMARY

- Uganda's national health system consists of the public and private (for-profit and not-for-profit faith-based) sectors, with the public sector providing most healthcare service delivery.
- In the outpatient diabetes clinics, individuals with diabetes are best managed by a well-trained multi-disciplinary team of healthcare professionals with adequate resources.
- Outpatient diabetes clinics should have standardised and locally relevant diabetes self-monitoring, education, and screening protocols and equipment.
- At each healthcare level (primary, secondary, and tertiary), there should be the requisite staffing and equipment to provide quality diabetes care (comprehensive clinical examination and biochemical workup for diagnosis and monitoring) at each clinical visit.

4.1 Healthcare Structure in Uganda

Uganda's national health system consists of the public and private (for-profit and not-for-profit faith-based) sectors. The public sector, which contributes about 45% of the healthcare service delivery, is decentralised in structure, overseen by the district administrative teams and the Ministry of Health. About 40% of the hospitals in Uganda are private for-profit, with the remaining being private not-for-profit or community-owned (~15%) (1).

The national public health system consists of National Referral Hospitals, Regional Referral Hospitals, General District Hospitals, referral-level Health Centres IVs, IIIs, and community workers (community health workers and village health teams) at the community level (1, 2). Both primary and secondary healthcare are provided at the referral level health facilities (Health Centres III, IV, District, and Regional Referral Hospitals), while tertiary healthcare is provided at the National Referral Hospitals and subspecialty autonomous public and private hospitals (1, 2).

Despite this well-elaborated hospital structure, Uganda lacks a formal diabetes-specific healthcare delivery framework at the primary level, with glaring knowledge gaps about diabetes management among healthcare professionals.

Furthermore, several studies have documented a lack of accessibility to essential diabetes medications and diagnostic tests, particularly in the public sector, with the majority of these medications and tests being prohibitively expensive (3-8).

As part of our advocacy, we recommend the formal establishment of outpatient diabetes clinics at all primary, secondary, and tertiary healthcare facilities to ensure well-planned and integrated diabetes care, especially in low-level healthcare facilities (Health Centres III and IV). In clinical settings where these outpatient diabetes clinics exist, individuals with diabetes are best managed by a well-trained multi-disciplinary team of healthcare professionals with adequate resources to provide quality diabetes care.

Other requirements of a functional diabetes clinic include standardised and locally relevant diabetes self-monitoring, education, and screening protocols and equipment such as tape measures, weighing scales, stadiometers, functional blood pressure machines, well-calibrated glucometers (with an adequate and reliable supply of glucose strips),

laboratory machines for the assessment of glycated haemoglobin and venous plasma glucose, monofilaments, 128 Hz tuning forks, and clinical care audit forms (to assess the proportions of patients attaining optimal treatment and self-care goals and incident rates of acute and chronic diabetes complications) (9).
Tables 1 and 2 below summarise the minimum staffing and equipment required at each level of healthcare to provide quality diabetes care, and essential workup, plus the time point of assessment recommended for each individual with diabetes.

Table 1. A summary of the requisite staff and equipment for a functional diabetes clinic at each healthcare level

HEALTHCARE LEVEL	STAFF	EQUIPMENT AND MATERIALS
Community level	○ Community health workers ○ Village health teams	○ Diabetes guideline ○ Urine strips for ketones, proteins, pus cells, and casts ○ Digital blood pressure machine ○ Glucometers (preferably calibrated ones) with an adequate supply of glucose strips ○ Weighing scales ○ Stadiometers ○ Tape measures ○ General community register
Primary (Health Centres III and IV)	○ Nurses ○ Clinical officers ○ Health educators ○ Health assistants ○ Laboratory staff ○ Doctors ○ Health information assistants ○ Nutritionists ○ Pharmacy staff	All the above plus ○ Diabetes register ○ Monofilaments ○ Snellen's charts for visual acuity assessment ○ Cardiovascular disease risk assessment charts ○ A biochemical analyser machine (for measurement of venous plasma glucose, glycated haemoglobin, renal and liver function tests, lipid profile) ○ A haematology analyser (to perform full blood counts)
Secondary (District General Hospitals and Regional Referral Hospitals)	All the above plus ○ Podiatrist (foot care expert) ○ Physicians ○ Peadiatricians ○ General Surgeons ○ Obstetricians ○ Ophthalmologists ○ Dentists or dental officers ○ Psychiatric care team ○ Certified diabetes educators	All the above plus ○ Tuning fork ○ Patella hammer ○ Ophthalmoscope ○ A biochemical analyser machine (to perform additional tests such as uric acid, troponin, C-peptide, serum vitamin B12, and microalbuminuria) ○ Electrocardiography (ECG) and echocardiography (ECHO)
Tertiary (National Referral Hospitals and subspecialty autonomous public and private hospitals)	All the above plus ○ Adult diabetologists ○ Paediatric diabetologists ○ Cardiologists ○ Nephrologists ○ Orthopaedic Surgeons ○ Cardiovascular Surgeons	All the above plus ○ Non-mydriatic fundus camera ○ Retinal laser unit ○ Operating theatres ○ Cardiac diagnostic facilities such as cardiac interventional laboratories ○ Haemo/peritoneal dialysis ○ Renal transplant services

Table 2. Essential tests and assessments recommended for each individual with diabetes at each follow-up visit and at each healthcare level

HEALTHCARE LEVEL	WORKUP (History or test)	TIME POINT OF ASSESSMENT		
		Initial visit	3 monthly visits	Annual visit
A: PRIMARY				
	History and diagnosis	x		
	Height and weight measurement (for body mass index calculation)	x	x (weight measurement)	x (weight measurement)
	Waist and hip circumference measurement	x		x
	Resting blood pressure measurement	x	x	x
	Detailed foot inspection	x	x	x
	Oral cavity inspection	x		x
	Monofilament testing	x		x
	Eye examination (for visual acuity)	x		x
	Blood glucose measurement	x	x	x
	Urinalysis for ketones, protein, and casts	x	x	x
	Diabetes education (self-monitoring and care)	x	x	x
	Nutritional counselling	x	x	x
	Psychosocial counselling	x	x	x
	Assessment for drug adherence and adverse events		x	x
B: SECONDARY & TERTIARY	**All the above**	x	x	x
	Eye examination (non-mydriatic fundoscopy)	x		x
	Glycated haemoglobin	x	x	x
	Lipid profile	x		x
	Renal and liver function tests	x		x
	C-peptide	x		
	Microalbuminuria	x		x
	Electrocardiography (if needed)	x		x
	Troponin (if indicated)	x		x
	Serum vitamin B12 (if indicated)			x
	Vibration sense assessment	x		x
	Evaluation for peripheral arterial disease	x		x

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CHAPTER 5: PREVENTIVE STRATEGIES FOR TYPE 2 DIABETES

RECOMMENDATIONS

- Adults who are overweight or obese should be initiated on a comprehensive lifestyle behavior change program to achieve and maintain at least a 7% body weight reduction and ≥150 minutes of moderate-intensity physical activity per week **(Level of evidence: A).**
- Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets that are rich in fruits, vegetables, low-fat dairy products, fish, whole grains, and legumes, with low intake of red meat and alcohol should be encouraged in adults with a high risk of type 2 diabetes **(Level of evidence: A).**
- Several pharmacotherapeutic agents, such as metformin, thiazolidinediones, and incretin therapies such as semaglutide, can be used in lowering the risk of type 2 diabetes in specific patient populations **(Level of evidence: A).**
- Among the above drugs, metformin has the most safety data. It is recommended for the prevention of type 2 diabetes in younger individuals (aged 25-44 years), adults with a body mass index ≥35 kg/m2 and high fasting blood glucose level ≥6 mmol/l (110 mg/dl), glycated haemoglobin (≥6% or 42 mmol/mol), and women with a prior history of gestational diabetes **(Level of evidence: A).**

5.1 Lifestyle behavioural changes in the prevention of type 2 diabetes

Compelling evidence from several randomised clinical trials (RCTs) such as the Diabetes Prevention Programme (DPP) (1), the Finnish Diabetes Prevention Study (FDPS) (2), the Da Qing Diabetes Prevention Study (3), the Indian DPP (4), the European Diabetes Prevention Study (5), and systematic reviews and meta-analyses of RCTs on lifestyle modification (6, 7) have shown that lifestyle behavioural changes that include achieving and maintaining a 7% body weight reduction, low-calorie intake, and ≥150-minutes of moderate-intensity physical activity per week such as brisk walking are highly effective in preventing and/or delaying the onset of type 2 diabetes in high-risk adult individuals in addition to improving the cardiometabolic risk factors such as body mass index (BMI), systolic, and diastolic blood pressure.

For example, in the large DPP that was conducted in the USA, 3,234 adults with impaired glucose tolerance (IGT) were randomised to three arms of a lifestyle intervention (consisting of an individualised plan to achieve at least a 7% body weight reduction and ≥150-minutes of moderate-intensity physical activity per week), metformin therapy (850 mg every 12 hours), and a control arm, and then followed up for at least 2.8 years. Compared with those in the control arm, lifestyle intervention and metformin therapy reduced the risk of type 2 diabetes by 58% and 31%, respectively. The incidence of type 2 diabetes was 39% lower in the lifestyle intervention arm when compared with the metformin arm (1).

A comparable risk reduction of type 2 diabetes using lifestyle modification was also reported by the FDPS. A total of 522 middle-aged overweight participants with IGT were randomised to either lifestyle intervention (healthy diet, weight reduction, and increased physical activity) or a control arm, and then followed up for 3.2 years. Incident diabetes was diagnosed based on an oral glucose tolerance test (OGTT), which was performed annually. The risk of type 2 diabetes was reduced by 58% in the lifestyle intervention group (2).

5.2 Nutritional therapy in the prevention of type 2 diabetes

Nutrition counselling and dietary changes play a pivotal role in the prevention of type 2 diabetes in high-risk adult individuals. Several studies have shown that low-calorie, Mediterranean, and/or Dietary Approaches to Stop Hypertension (DASH)

diets greatly reduce the risk of onset of type 2 diabetes in people with prediabetes (1, 8-10). Mediterranean and DASH diets are essentially plant-based diets (vegetables, fruits, legumes, whole grains) with a high intake of fish, moderate consumption of alcohol, low-fat dairy and poultry products, and low red meat consumption (8, 11).

Therefore, a good nutritional plan should encourage dietary intake of whole grains (such as brown rice and whole-grain bread), fish, legumes (such as soya beans, beans, groundnuts, and peas), low-fat sugar-free dairy products (such as plain yoghurt and low-fat milk), and the use of vegetable-based cooking oils (such as sunflower or olive oil). Dietary intake of refined or processed such as fried fast foods, processed meats, fatty red meat, and high sugar content beverages such as sodas, should be greatly reduced or avoided (8, 11). Alcohol consumption should be in moderation (one drink per day for women and up to 2 drinks per day for men) and avoided in cases of severe obesity and hypertriglyceridemia (8, 11, 12).

5.3 Pharmacological approaches in preventing type 2 diabetes

In adults with a high risk of type 2 diabetes who have difficulty in maintaining lifestyle behavioural changes, specific pharmacotherapeutic options can be used in the prevention of type 2 diabetes. Drugs such as metformin, thiazolidinediones such as pioglitazone, and glucagon-like peptide 1 (GLP-1) agonists such as semaglutide have been shown to lower the incidence of type 2 diabetes in specific patient populations (1, 13, 14).

Among these pharmacological agents, metformin has been extensively investigated in the prevention of type 2 diabetes and has the most safety data (1, 4, 15, 16). Additionally, it is very inexpensive and readily available in most clinical settings. For example, in the DPP, compared with the control arm, metformin was associated with a 31% risk reduction of type 2 diabetes. Metformin therapy was as effective as lifestyle intervention in participants with a BMI ≥35 kg/m2 and those aged 25-44 years (1).

In the Indian DPP, a total of 531 native Asian Indians with IGT were randomised to a control arm, lifestyle modification arm, metformin arm, and a lifestyle modification and metformin arm, and followed up for a median period of 30 months. The relative risk reduction of type 2 diabetes in lifestyle modification and metformin arms was 28.5% and 26.5%, respectively, without an additional benefit using lifestyle modification and metformin in this study population (relative risk reduction was 28.2%) (4).

In the sub-analysis of the DPP to assess the effect of metformin use in women with and without a prior history of gestational diabetes, the use of metformin therapy and lifestyle intervention was associated with a 50% reduction in the risk of type 2 diabetes in 350 participants with a prior history of gestational diabetes. This beneficial effect was maintained over a ten-year follow-up period (17).

This beneficial effect of metformin was also demonstrated in a meta-analysis of 17 RCTs that assessed its effectiveness in preventing type 2 diabetes in 30,474 participants with IGT. Compared with those assigned to the control arm, metformin use was associated with a 35% lower risk of developing type 2 diabetes (15).

5.4 Implementation of effective prevention programs for type 2 diabetes

The implementation of an effective prevention program for type 2 diabetes (T2D) will broadly require these five steps: 1) Increase of awareness about T2D in the general population and healthcare professionals such as doctors, nurses, and community health workers with active engagement of all stakeholders, especially governments; 2) Identification of people at risk of T2D (those with IGT and impaired fasting glucose or IFG) using T2D risk scores and blood glucose tests; 3) Comprehensive planning of a diabetes prevention program that is easy to implement, locally relevant and accepted with active involvement of community health workers; 4) Monitoring and assessing cost and effectiveness of the developed diabetes prevention program (18).

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CHAPTER 6: DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT, PEER SUPPORT, AND MEDICAL NUTRITIONAL THERAPY

SUMMARY

- Diabetes self-management education and support (DSMES) is a structured, multi-disciplinary, and individualised support program that provides comprehensive knowledge about diabetes to individuals at risk or with diabetes to improve their understanding of the condition and ultimately, improve healthcare outcomes and quality of life **(Level of evidence: B).**
- Individuals with diabetes should receive structured diabetes education at diagnosis and throughout the follow-up clinical visits **(Level of evidence: B).**
- Individuals with diabetes should be counselled about these seven essential self-care behaviours: healthy eating, being physically active, self-monitoring of blood glucose, adherence to medicine, good problem-solving skills, healthy coping skills, and risk reduction behaviour **(Level of evidence: A)**.
- DSMES integrated with peer support programs is associated with good health outcomes such as optimal glycaemic control, weight and blood pressure reduction, healthy eating habits, and increased physical activity **(Level of evidence: B).**
- Medical nutritional therapy is important in diabetes prevention and management **(Level of evidence: A).**
- A nutritional plan should be individualised considering one's preferences, culture, religion, health targets, local setting, and financial status **(Level of evidence: B).**
- Carbohydrate intake should be individualised and guided by the glycaemic index, glycaemic load, and patient's treatment targets. Whole-grain starchy food such as brown rice and bread is preferred to refined starchy food such as white rice and bread **(Level of evidence: B).**
- Encourage the intake of foods rich in monounsaturated fats such as fish, nuts, and avocados as opposed to foods rich in saturated fats such as fatty beef and pork **(Level of evidence: B).**
- Alcohol consumption should be in moderation **(Level of evidence: C).**
- Routine vitamin and mineral supplementation in the absence of biochemically confirmed deficiency is not recommended **(Level of evidence: A).**

6.0 INTRODUCTION

Diabetes is a complex metabolic condition whose management requires a multidisciplinary team and a multifaceted approach. Because of its complexity, especially in attaining the optimal treatment goals, individuals with type 1 and type 2 diabetes should play an active personal role in achieving the desired treatment goals and addressing the challenges associated with managing the condition (1).

6.1.0 An overview of diabetes self-management education

Diabetes self-management education and support (DSMES) is a structured, multi-disciplinary, quality-assured, and context-specific support program offered continuously at each healthcare level to deliver comprehensive and personalised knowledge about diabetes to individuals at risk or with diabetes to improve their understanding of the condition and ultimately, improve healthcare outcomes and quality of life (1-3).

This empowers individuals with diabetes to personally manage their condition and make informed choices for self-directed behavioural change and ably integrate

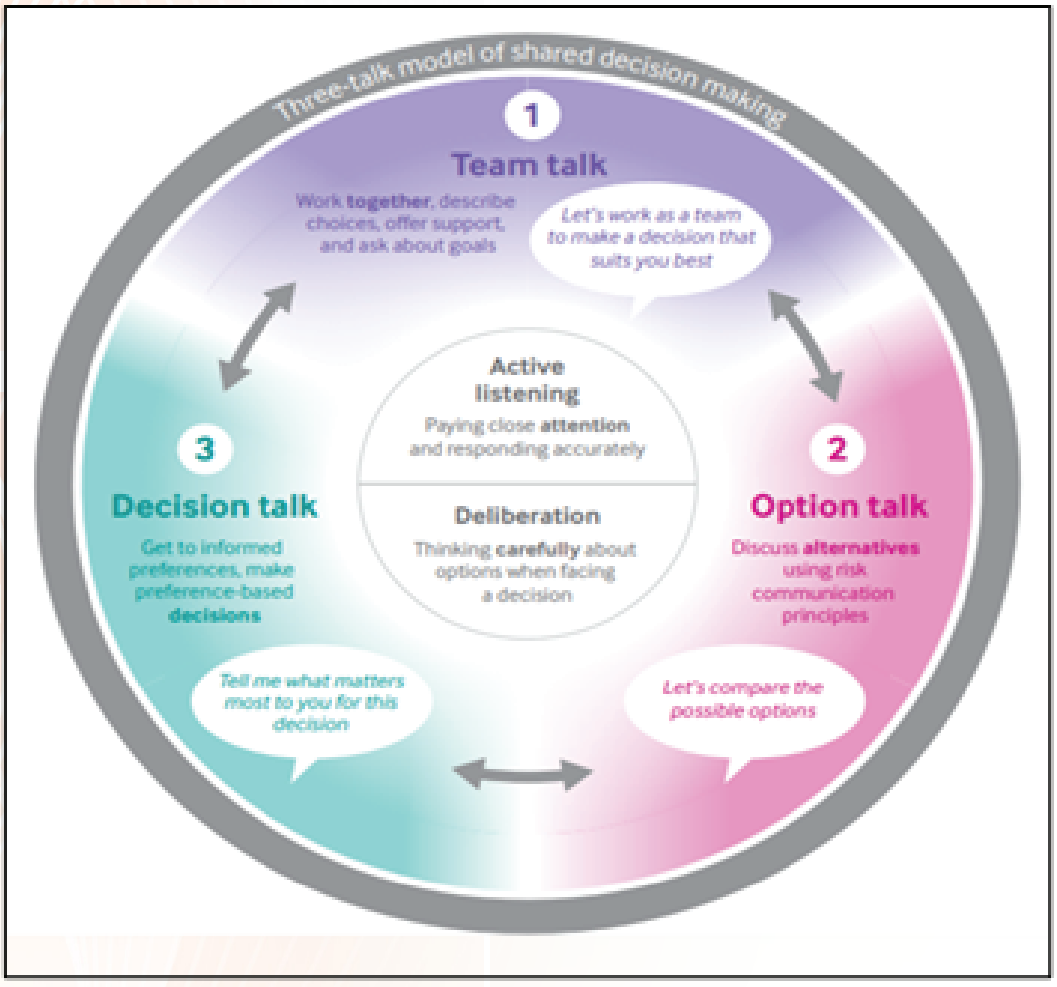
self-management into their daily lives. Therefore, DSMES is the cornerstone of the care of individuals with diabetes who desire to achieve optimal health-related outcomes (1-3).

The model of DSMES is offered by a multi-disciplinary team comprising medical doctors, clinical officers, diabetes educators, pharmacists, nurses, dietitians, and other healthcare professionals who care for individuals with diabetes (1, 2).

At the core of DSMES is the individual living with diabetes. The individual with diabetes going through the education process needs to be assessed for readiness to change whenever a behavioural issue is being tackled. If not ready, the issue can be raised at subsequent visits (2, 4, 5). The individual living with diabetes is an active participant in the care and education process and his/her perspective must be considered when clinical decisions are made in light of the latest research and available management options. Diabetes education must focus on behaviour change or encouragement and should aim at engaging the patient through motivational interviewing and not on didactic lectures (2, 4, 5).

This model of shared decision-making (team talk, opinion talk, and decision talk) is well illustrated in Figure 1 below.

Figure 1. Three-talk model of shared decision-making



Adapted from: Elwyn G, et al. BMJ 2017;359: j4891.

6.1.1 Diabetes self-management education and support tailored to the individual with diabetes

The DSMES process must also take into consideration the specific characteristics of the individual with diabetes such as financial, cultural, and workplace factors, personal preferences and fears, and readiness to change. This is because they have a direct impact on the uptake of education, access to self-care and resources, and behavioural change (6).

Financial factors influence what patients can afford and access. Cultural factors affect behaviour and being culturally sensitive is crucial in implementing an effective DSMES process. Workplace conditions may not support behaviour change and need to be addressed to ensure a supportive environment for individuals with diabetes. Personal preferences and fears should be discussed, options explored, and a consensus reached, with the individual with diabetes making the final decision (6).

Assessing readiness for change is essential and can be done using the Readiness Ruler. This tool helps assess an individual's readiness to change by asking them to rate their willingness, confidence, and commitment on a scale from 0 to 10. When using this scale, 0 means "not prepared to change" and 10 means "already changing." If the response is ≤5, revisit the issue being discussed later. If it is ≥6, ask follow-up questions to encourage change talk and approach (2). Behaviour change is complex, and individuals with diabetes need Diabetes Self-Management Education and Support (DSMES) to achieve it. Diabetes educators are advised to refer them to necessary resources and support groups to aid in behaviour change. The DSMES should adopt a person-centered approach that empowers individuals with diabetes and enhances their self-efficacy (2).

The DSMES process is continuous and its components are vital. A good DSMES program should have these processes below (implemented in this particular order) (2):

1. Assessment of the individual with diabetes at the start of the education program.

2. Set goals that are specific, measurable, achievable, relevant, and time-bound (SMART) once the individual's profile is clear.

3. Plan actions and agree on how to enhance accountability.

4. Implement changes with support from the care center or provider.

5. Regularly monitor, document, and evaluate activities.

Specific outcomes will help provide information about the progress achieved by the individual with diabetes and the DSMES program. This information is vital in improving the quality of the DSMES program.

These specific outcomes are summarised in Table 1 below.

Table 1. Outcomes to evaluate the progress of diabetes self-management education and support programs

Type of outcome	Example
Process outcomes	Referral process Attendance Education mapping Social determinants of health Timing of education sessions
Clinical outcomes	Glycated haemoglobin levels Time in hypoglycemia and time in range if using continuous glucose monitoring (CGM) devices Pregnancy outcomes Low-density lipoprotein cholesterol levels Body mass index and body weight Blood pressure levels
Psychosocial and behavioral outcomes	Healthy coping Healthy eating Being active Taking prescribed medication Monitoring Reducing risky behaviour Problem-solving ability
Patient-reported outcomes	Health-related quality of life Diabetes-related quality of life Diabetes distress Self-efficacy Functional status Patient satisfaction
Patient-generated health data	Blood glucose trends CGM glucose management indicator Weight, activity pattern, and steps Food and/or beverage intake Sleep patterns Blood pressure levels

6.1.2 USE OF APPROPRIATE LANGUAGE IN DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT

It is important to use appropriate words and phrases as you engage individuals with diabetes. This helps one achieve meaningful and fruitful outcomes. Appropriate communication with individuals with diabetes significantly influences their engagement, comprehension of diabetes management, treatment results, and overall psychological and social well-being. When delivering DSMES, the language used affects motivation, behaviours, and outcomes (2, 7). Table 2 below highlights terms and phrases to avoid and suggests better alternatives when interacting with individuals with diabetes.

Table 2. Words to avoid using in diabetes self-management education and support

WORDS YOU SHOULD AVOID USING	WORDS THAT CAN BE USED AS ALTERNATIVES	RATIONALE
Diabetic	○ Child with diabetes ○ Individual or person with diabetes ○ Living with diabetes ○ Child or adult who has diabetes	○ Put the person first ○ Avoids labeling someone as the disease ○ There is much more to a person than diabetes
Controlled or uncontrolled Good or bad control Poor control or poorly controlled	○ Blood glucose levels ○ Elevated or high blood glucose ○ Glucose variability ○ Target glycated haemoglobin or blood glucose ○ Manage diabetes	○ Focus on the physiology and avoid judgement ○ True control of diabetes is impossible
Blood glucose testing	○ Blood glucose checking ○ Blood glucose monitoring	○ A test implies pass/fail or good/bad
Normal blood glucose level	○ Target blood glucose ○ Blood glucose goal(s)	○ In general, it is best to avoid the word normal because the opposite is abnormal

6.1.3 COMPONENTS OF SELF-CARE IN DIABETES

Regarding the self-care of individuals with diabetes, seven essential self-care behaviours have been clearly defined and should be emphasised to every individual with diabetes. These self-care behaviours have been shown to predict better health-related outcomes such as optimal glycaemic control and reduction of incidence and progression of diabetes complications (2, 3). These include:

- Healthy eating
- Being physically active
- Self-monitoring of blood glucose
- Adherence to medicine (glucose-lowering and other ancillary therapies)
- Good problem-solving skills
- Healthy coping skills
- Risk reduction behaviour

Despite the evidence that these self-care behaviours are associated with optimal health-related outcomes in individuals with diabetes, the level of DSMES in sub-Saharan Africa (SSA) is still dismal. One systematic review of 43 observational studies on DSMES in SSA reported that most patients do not regularly monitor their blood glucose levels or engage in physical activity. Additionally, a moderate level of adherence to the recommended diet plans and diabetes medicines was noted. The frequency of use of herbal medicine among the patients was also high (8).

This underscores the need to enhance structured locally-adapted DSMES programs at all healthcare levels in SSA, including Uganda.

6.1.4 EVIDENCE OF EFFECTIVENESS OF DIABETES SELF-MANAGEMENT EDUCATION

Generally, DSMES is recommended as a key component of care for all individuals with diabetes. Several systematic reviews of randomised controlled trials and cross-sectional studies on DSMES in individuals with diabetes have shown that DSMES is associated with improvement in psychosocial outcomes (9), glycaemic control (on a short-term basis) (10-13), diabetes knowledge (13), reduction of risky behaviour (14), and adherence to diabetes medicine (13, 15).

Because of the above favourable outcomes, DSMES programs should be initiated immediately at the time of diagnosis of diabetes and continued throughout the follow-up clinical visits. This helps sustain the desired health-related outcomes (2).

6.2.0 Peer support in diabetes care

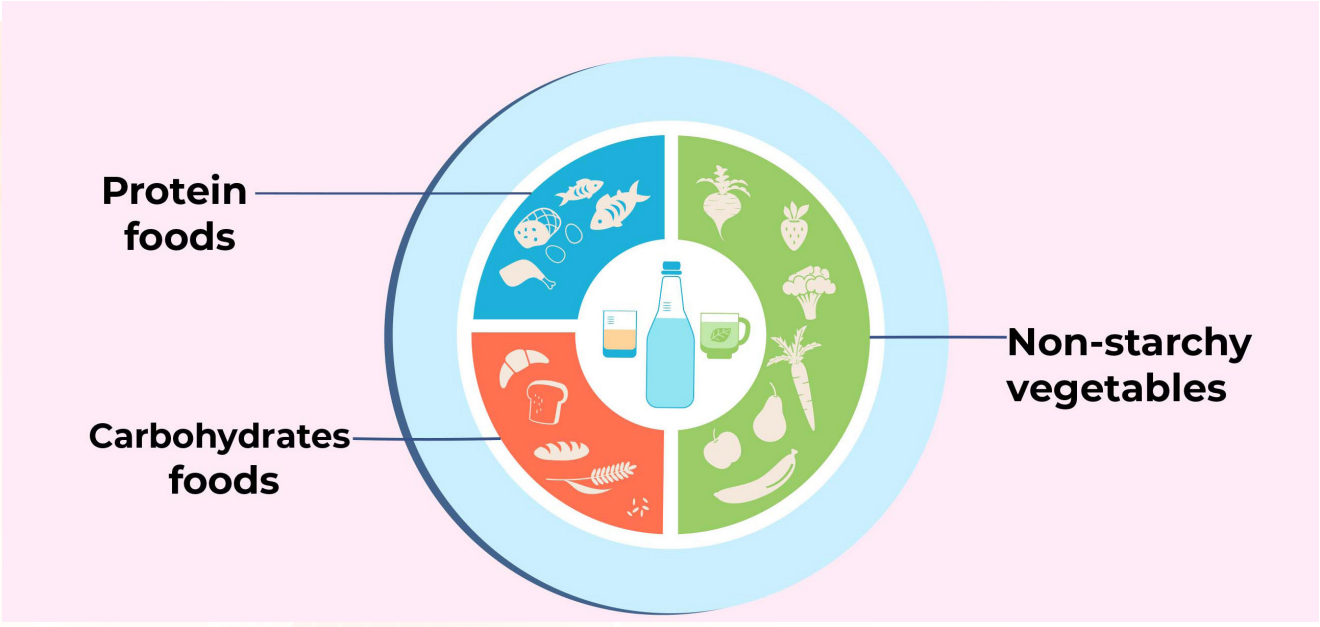
Peer support refers to a process through which non-healthcare individuals or healthcare professionals with common experiences or challenges work together as equals and provide emotional, informational, and instrumental support to each other in a mutually beneficial arrangement (16). In essence, peer support fosters social and emotional understanding through sympathetic listening and encouragement, as well as a strong human connection through shared life experiences. It is also crucial for supporting ongoing long-term follow-up and helping to establish and strengthen linkages to clinical care (16-18).

When integrated with DSMES, evidence shows that peer support programs are associated with optimal diabetes treatment outcomes such as lowering glycated haemoglobin (HbA1c) (19-22), weight (20, 22), blood pressure (22), and improvement in eating habits and physical activity (22). Additionally, peer support programs have extra benefits such as high respect for peers, provision of psychological support, and cost-effectiveness (16).

6.3.0 Medical nutritional therapy in diabetes care

Medical nutritional therapy (MNT) is important in diabetes prevention and management. An optimal nutrition plan aims to encourage an intake of a balanced diet of carbohydrates, protein, fat, vitamins, and minerals to achieve individual treatment goals, maintain an ideal body weight, and delay the onset or progression of diabetes complications (23). Figure 2 below depicts the diabetes plate that should be used to guide the planning of healthy meals. When planning a meal, individuals with diabetes are advised to fill half the plate with non-starchy vegetables (low in carbohydrate content) such as salads, greens, tomatoes, onions, carrots, and spinach. Then, one-quarter of the plate can be filled with lean protein such as fish, chicken, eggs, and lean meat, and the remaining quarter of the plate filled with whole grains such as brown rice or starchy foods such as sweet potatoes, or legumes such as beans, groundnuts, and peas. Portions that are the size of the fist of one's hand are recommended at each serving. It is also advised to add fruits (preferably eaten whole), milk, a calorie-free drink such as water, coffee, or tea, and healthy fat foods such as avocado and nuts (24). The intake of low-fat (preferably unsaturated plant-based), low glycaemic index, low carbohydrate, high protein, and Mediterranean diets have been associated with a significant reduction in body weight and HbA1c (25, 26).

Figure 2: composition of a diabetes plate



6.3.1 Glycaemic index per serving of commonly consumed foods

As part of MNT, individuals with diabetes should be introduced to the concepts of glycaemic index (GI) and glycaemic load (GL) when ranking or selecting the carbohydrates to consume. The GI closely predicts the increase in the postprandial glucose concentrations. Foods with a high GI (defined as a GI ≥70) are carbohydrate-containing foods that are rapidly digested and absorbed resulting in a significant postprandial glucose increase. Because of the slow rate of digestion and absorption, foods with a low GI (defined as GI ≤55) are associated with a gradual increase in postprandial glucose concentrations (27, 28). The consumption of high-GI foods should be discouraged or significantly regulated (both the frequency of consumption and portion). To regulate postprandial glycaemia, individuals with diabetes are advised to have mixed meals containing at least ≥1 low-GI food (28).

Table 3 below summarises the GI of some of the commonly consumed foods in Uganda.

Table 3. Glycaemic index of commonly consumed foods in Uganda

Grades of GI		
Low GI foods (GI ≤55))	Medium GI foods (56–70)	High GI foods (>70)
Peanuts <15	Pineapple 59	Honey 73
Low-fat yogurt (no sugar) <15	Ice cream 61	Boiled cassava 74
Tomatoes 15	Table sugar (sucrose) 65	Doughnuts 75
Green lentils 22	Instant porridge 66	French fries or chips 76
Fat-free milk 32	Millet porridge 67	Watermelon 76
Sweet potato 35	Soda or soft drinks 68	Boiled white rice 77
Apple 36	Whole wheat bread 68	Boiled Irish potato 78
Carrots (cooked) 39	White wheat bread 75	White bread 79
Bean stew 44		Cornflakes 81
Long-grain rice 47		Mashed Irish potatoes 87
Green peas 48		Rice, instant 91
Orange juice 50		Lucozade 95
Mango 51		
Yam 51		
Banana 51		
Brown rice 54		
Plantain 55		

GI- Glycaemic index. Adapted from Atkinson FS, et al Diabetes Care. 2008;31(12):2281-3, Mbanya JC, et al. Diabetes Ther. 2021;12(1):37-54, Ebere R et al. Afr Health Sci. 2021;21(2):710-8.

Several studies have investigated the GI of commonly consumed foods in sub-Saharan Africa, with most being conducted in West Africa (29-32). These studies provide insightful lessons in MNT for individuals with diabetes.

In Uganda, similar studies on glycaemic indices of foods are limited. In one unpublished study by Semanda et al conducted in 2018, the glycaemic and insulin responses to three commonly consumed breakfast meals (*katogo, bushera* of about 28 grams of carbohydrates, and milk served with two slices of white bread of 15 grams of carbohydrate and 10 grams of margarine) in Uganda were assessed in six participants with type 2 diabetes and six matched healthy controls. The *katogo* was a mixture of boiled four unripened bananas or plantain (locally called matooke) served with tomato and onion soup with cow butter, while bushera is commercially packaged millet flour.

Serial blood samples were drawn at specific time points following the consumption of each meal and serum glucose and insulin concentrations were measured. Among the three breakfast meals, the Katogo meal, which is widely considered to be healthy locally, was associated with the greatest glycaemic and insulin response in individuals with type 2 diabetes and healthy controls. This was followed by the milk and white bread meal and lastly, by the bushera meal **(Semanda S et al. 2018, unpublished study).** Findings from this study underscore the need to counsel individuals with diabetes in Uganda to avoid or regulate the intake of *katogo* as a breakfast meal.

6.3.2 A summary of the recommended healthy eating patterns

Generally, a balanced individualised nutritional plan that considers an individual's preferences, culture, religion, health targets, local setting (food security), and financial status is preferred. The diets should be individualised and constitute a mixed micro- and macronutrient composition with a major focus on nutrient-dense foods such as vegetables, whole fruits, whole grains, legumes, nuts, and fish. To achieve calorie restriction and avoid postprandial glucose excursions, the quality of carbohydrates (based on the individual food's GI or GL) should be emphasised. Intake of adequate fibre should also be encouraged (23, 33-35).

Low-calorie artificial sweeteners such as aspartame and saccharin used in moderation can act as substitutes for natural table sugar (23, 36). Routine use of micronutrient and herbal supplementation such as chromium, vitamin D, cinnamon, and aloe vera to improve glycaemic control is not recommended due to lack of clinical evidence (23).

Table 4 below summarises the varied healthy eating patterns or recommendations and their nutritional benefits.

Table 4. Healthy eating patterns or recommendation and their associated nutritional benefit

Eating patterns or recommendation	Nutritional benefit
Daily intake of fruits (two servings) and vegetables with each meal (at least three servings per day)	Fruits and vegetables are a rich source of dietary fibre, minerals, vitamins, antioxidants, and are associated with increased satiety.
Encourage intake of whole-grain starchy foods such as brown rice and whole-grain bread as opposed to refined starchy foods such as white rice, white bread, pasta, and other foods made from white flour	Whole-grain starchy foods are rich in vitamins, increase satiety, and improve glycaemic control.
Encourage intake of legumes such as beans, peas, ground nuts, and lentils.	Legumes are good sources of dietary fibre, and protein, and are low glycaemic index foods.
Encourage increased intake of all types of fish such as Nile perch and tilapia (at least twice a week) and other types of white meat such as chicken (without the skin)	These are a rich source of low unsaturated fat, omega-3 fatty acids, vitamin D, magnesium, and calcium.
Encourage intake of low-fat sugar-free dairy products such as low-fat plain yoghurt and low-fat or skimmed milk.	These specific dairy products have a low glycaemic index and are a rich source of calcium, vitamin D, magnesium, protein, and have a low content of saturated fats.
Encourage the use of vegetable oils such as olive and sunflower oil when cooking food. Avoid tropical oils such as coconut oil.	These are rich in unsaturated fats that are associated with a lower risk of cardiovascular diseases.
Reduce the intake of commercially processed foods such as fried foods, chips, baked foods, processed meat, and fatty red meat such as pork, sausages, and beef.	These foods are high in saturated fats, salt, and sugar, and increase the risk of cardiovascular disease, obesity, and other components of metabolic syndrome.
Avoid intake of refined sugar such as table sugar, honey, sugar-sweetened beverages, fresh and processed fruit juices, sweets, and baked foods such as cakes, biscuits, and doughnuts	These are high glycaemic index foods that can result in poor glycaemic control
Avoid or regulate the intake of *katogo* (a traditional breakfast meal consisting of either bean, groundnut, meat, and offal sauce to which a staple food such as cassava or boiled bananas or plantains is added)	It is a high glycaemic index meal
Avoid or consume alcohol (beer, whiskey, and wine) in moderation (Two drinks per day for men and one drink per day for women). Avoid alcohol binge drinking	Excessive alcohol consumption is associated with poor glycaemia, dyslipidaemia (hypertriglyceridaemia mainly), obesity, acute or chronic pancreatitis, and cardiovascular complications such as atrial fibrillation and dilated cardiomyopathy. Alcohol intake can also result in hypoglycaemic episodes if combined with insulin and insulin secretagogues such as sulfonylureas.
Encourage low dietary intake of salt	Excessive salt intake aggravates hypertension and increases the risk of cardiovascular diseases

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CHAPTER 7: COMPREHENSIVE MEDICAL EVALUATION AND SCREENING FOR RELATED COMORBIDITIES

SUMMARY

- A comprehensive medical evaluation at the initial visit is aimed at confirming the diagnosis and type of diabetes, screening for related comorbidities, reviewing any current treatment, and designing an efficient follow-up plan **(Level of evidence: A).**
- Individuals with type 1 and type 2 diabetes present with several co-existing comorbidities that should be evaluated and optimally managed **(Level of evidence: A).**
- Because of the associated high risk of developing autoimmune conditions such as autoimmune thyroid diseases, celiac disease, and pernicious anaemia (vitamin B12 deficiency), individuals with type 1 diabetes should be screened for these conditions at the time of diagnosis and periodically during follow-up **(Level of evidence: A).**
- Individuals with type 2 diabetes should be screened for comorbidities such as hypertension, obesity or overweight, obstructive sleep apnea, dyslipidaemia, depression, metabolic dysfunction-associated steatotic liver disease (MASLD), and vitamin B12 deficiency at the time of diagnosis and periodically during follow-up **(Level of evidence: A).**

7.1 Comprehensive medical evaluation

A comprehensive medical evaluation plan in diabetes care involves several components such as an efficient initial evaluation and follow-up plan, an in-depth assessment for both acute and chronic diabetes complications, optimal screening and management of comorbidities, psychosocial evaluation, self-monitoring, and care, preventive care services, and pro-active engagement of the patient by the multidisciplinary team of healthcare providers (1). This closely follows the widely utilised chronic diseases model in healthcare systems that uses a person-centred approach to inform collective clinical care decisions aimed at improving treatment outcomes (2, 3). Furthermore, a comprehensive medical evaluation plan should be individualised, and healthcare practitioners should be cognisant of the resources at their disposal. Table 1 below summarises the integral components of a focused history taking, physical examination, and laboratory evaluation at the specific clinic visits in routine diabetes care.

Table 1. Components of a comprehensive medical evaluation of an individual with diabetes at the initial visit, follow-up visits, and annual visit

ESSENTIAL COMPONENT	INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
A: FOCUSED SOCIO-DEMOGRAPHIC HISTORY			
Age of diabetes onset	X		
Prevalent symptoms at diagnosis	X		
Social habits: Alcohol ingestion and smoking history	X		
History of diabetes in first-degree relatives	X		
Family history of autoimmune conditions	X		
History of mental health conditions	X		
B: PAST MEDICAL HISTORY			
History of any past hospitalisation	X		
History of common comorbidities and complications such as hypertension, dyslipidaemia, HIV, micro- and macrovascular diabetes complications, thyroid dysfunction	X		
Any supplementary medication such as oral antiplatelet, lipid-lowering, anticoagulant, and antiretroviral therapies	X		
History of long-term use of drugs associated with an increased risk of diabetes such as corticosteroids, anti-psychotics, and older-generation beta blockers	X		
Any drug-related side effects	X		
Date of last dental, foot, eye, kidney, heart, lipid, and blood pressure review	X		
C: PHYSICAL EXAMINATION			
Height and weight measurement (for the calculation of body mass index)	X	X (mainly weight)	X
Waist circumference	X		X
Visual acuity assessment and fundoscopic eye exam (preferably non-mydriatic fundal photography)	X		X
Oral examination for dental caries and gum disease	X		X
Thyroid palpitation	X		
Skin inspection (for insulin injection sites and acanthosis nigricans at the base of the neck- a key sign of insulin resistance)	X		X
Comprehensive foot examination for deformities, ulcers, calluses, skin discolouration, hair, and nail changes. Assess for vibration, pinprick, and temperature sensation	X	X	X
Screen for peripheral arterial disease (palpation for pedal pulses and perform ankle-brachial index assessment if available)	X		X
Assess for any psychosocial disorders such as depression, anxiety, and diabetes distress	X		X
D: LABORATORY WORKUP			
Blood glucose level (preferably measured from a venous blood sample using a clinical chemistry analyser machine)	X	X	X
Glycated haemoglobin	X	X	X

ESSENTIAL COMPONENT	INITIAL VISIT	EVERY FOLLOW-UP VISIT	ANNUAL VISIT
Random or fasting lipid profile (Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides)	X		X
Liver function tests	X		X
Renal function tests (serum creatinine and estimation of the glomerular filtration rate)	X		X
Spot urine albumin creatinine ratio	X		X
Urinalysis (for ketones, pus cells, and protein)	X		X
Serum potassium for individuals on angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and/or diuretics	X		X
Random or fasting serum C-peptide	X		
Thyroid stimulating hormone and free thyroxine levels in individuals with type 1 diabetes and selected individuals with type 2 diabetes	X		X
Electrocardiography and echocardiography (if indicated)	X		X
Serum vitamin B12 levels (if on long-term and high-dose metformin)	X		X
Complete blood count	X		X
HIV serology	X		
Serum total corrected calcium and phosphate (if indicated such as in the elderly and individuals with chronic kidney disease)	X		X
E: OTHER IMPORTANT COMPONENTS			
Structured diabetes education (diabetes self-management education and support)	X	X	
Preconception counselling and family planning	X	X	X
Setting of treatment and self-management goals	X	X	X
Review and adjustment of medication	X	X	X

7.2 Screening for comorbidities

Generally, individuals with type 1 and type 2 diabetes usually present with several medical comorbidities such as hypertension, obesity/overweight, obstructive sleep apnea, HIV, dyslipidaemia, thyroid dysfunction, dementia, hypogonadism, depression, metabolic dysfunction-associated steatotic liver disease (MASLD), gastro-oesophageal reflux disease, polycystic ovarian syndrome, osteoporosis, iron, and vitamin B12 deficiency (1, 4-8). For this section, we will only discuss thyroid dysfunction, iron, and vitamin B12 deficiency reported in individuals with type 1 diabetes, and MASLD, commonly reported in individuals with type 2 diabetes in the setting of overweight or obesity. Other comorbidities such as hypertension, dyslipidaemia, overweight/obesity, tuberculosis, and HIV will be discussed in detail in Chapters 11 and 18 of this guideline.

7.2.1 Screening for thyroid dysfunction and related comorbidities in individuals with type 1 diabetes

Individuals with type 1 diabetes are at increased risk of developing other autoimmune diseases such as autoimmune thyroid diseases, celiac disease, pernicious anaemia (vitamin B12 deficiency), Addison's disease, and autoimmune hepatitis, as part of the autoimmune polyglandular syndrome complex (9-11).

All individuals with type 1 diabetes should be screened for thyroid dysfunction by measurement of the thyroid stimulating hormone (TSH), free thyroxine (FT4), and, if available, thyroid autoantibodies such as thyroid peroxidase autoantibodies (TPOAb), thyroglobulin autoantibodies (TgAb), and

TSH receptor autoantibodies (TRAb), at the time of diagnosis of type 1 diabetes and then periodically (preferably every one to two years) (1, 11).

The presence of elevated TPOAb concentrations helps to identify patients with autoimmune Hashimoto's thyroiditis or those at a higher risk of progression from a clinically and metabolically euthyroid state to overt hypothyroidism requiring thyroxine replacement therapy. Elevated TRAb concentrations in the presence of clinical signs and symptoms of hyperthyroidism confirm the diagnosis of Graves' disease and can also be used to predict disease remission (11, 12).

One hospital-based study conducted on Ugandan children and adolescents with type 1 diabetes receiving outpatient diabetes care from Mulago National Referral and Teaching Hospital, Kampala Uganda, confirmed that thyroid dysfunction is a relatively common comorbid condition in children and adolescents living with type 1 diabetes (13). Muhame et al screened 69 children and adolescents with type 1 diabetes for thyroid dysfunction by measuring the TSH, free T4, and TPOAb concentrations. Thyroid autoimmunity (defined as TPOAb positivity) was reported in five participants, corresponding to a prevalence of 7.3%. One of these participants (20%) had subclinical hypothyroidism (defined as elevated TSH and normal FT4 concentrations). Four participants without TPOAb positivity were also reported to have subclinical hypothyroidism (4/69, 5.8%) (13).

Screening for celiac disease by measurement of the blood tissue transglutaminase IgA levels should be encouraged in individuals with type 1 diabetes with gastrointestinal symptoms such as diarrhoea, abdominal pain, and features of micronutrient deficiency (vitamin B12, folate, iron, calcium, and vitamin D deficiency). In addition to micronutrient supplementation, individuals with confirmed Celiac disease should be counselled to have a gluten-free diet as part of their long-term management (1, 11). Furthermore, screening for vitamin B12 and folate deficiency should be performed in individuals with type 1 diabetes with refractory peripheral neuropathy (with or without optimal glycaemic control) and unexplained anaemia (1, 11).

7.2.2 Screening for metabolic dysfunction-associated steatotic liver disease

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly referred to as non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease in the presence of at least one of the following five cardiovascular risk factors: i) body mass index ≥25 kg/m2 or waist circumference >94 cm for males and 80 cm for females; ii) prediabetes or type 2 diabetes or on treatment for type 2 diabetes; iii) blood pressure ≥130/85 mmHg or on antihypertensive treatment; iv) serum triglyceride concentration ≥1.7 mmol/l (150 mg/dl) or on lipid-lowering therapy; v) serum high-dense lipoprotein cholesterol concentration ≤1.0 mmol/l (40 mg/dl) for men and ≤1.3 mmol/l (50 mg/dl) for women, or on lipid-lowering therapy, in the absence of other factors associated with hepatic steatosis such as chronic heavy alcohol ingestion (1, 14-16).

Screening for MASLD can be performed using imaging modalities such as abdominal ultrasound scan, magnetic resonance imaging, computed tomography scan, and non-invasive online scores such as the fibrosis-4-index (FIB-4) (1, 15, 16). The FIB-4 score which incorporates age, alanine transaminase (ALT) and aspartate transaminase (AST) concentrations, and platelet count has been generally recommended as the preferred non-invasive score to diagnose clinically significant fibrosis (14-16). The score can be determined using free online calculators (17). However, the performance of this score against liver biopsy, which is the gold standard diagnostic method for liver fibrosis, in Black African populations is not well known.

Optimal screening, identification, and management of MASLD in patients with prediabetes or type 2 diabetes is important because of the inherent risk of developing liver-related complications such as cirrhosis and hepatocellular carcinoma, especially in the setting of overweight/obesity and persistently elevated ALT and/or AST concentrations (>30 U/L for six months) (1, 15, 16, 18).

For the Ugandan context, the use of ultrasound scanning and assessment of liver function tests is recommended in the screening for MASLD because of their relatively low cost and easy accessibility in most clinical settings.

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CHAPTER 8: OPTIMAL BLOOD GLUCOSE TARGETS

SUMMARY

- Glycaemic control in clinical practice and studies is mainly assessed based on glycated haemoglobin (HbA1c) levels measured every 3-6 months **(Level of evidence: C).**
- The optimal HbA1c target for nonpregnant individuals with diabetes is <7% (53 mmol/mol) **(Level of evidence: A).**
- In newly diagnosed young individuals with a long-life expectancy, no comorbidities, and a low risk of hypoglycaemia, the target HbA1c level should be <6.5% (48 mmol/mol) **(Level of evidence: A).**
- The HbA1c target can be individualised to <8% (64 mmol/mol) in the elderly with a short-life expectancy and individuals with comorbidities such as cardiovascular disease and recurrent hypoglycaemia, and long-standing diabetes **(Level of evidence: A).**
- A fasting blood glucose level of <7.0 mmol/l (126 mg/dl) and a post-prandial level of <10 mmol/l (180 mg/dl) are recommended as optimal targets (Level of evidence: C).
- Self-monitoring of blood glucose (SMBG) should be offered to every individual with type 1 diabetes and type 2 diabetes **(Level of evidence: B).**
- For individuals receiving 2-4 doses of insulin daily, SMBG is recommended at least thrice daily **(Level of evidence: B).**
- SMBG should be performed at least once a day (preferably in the morning) for individuals on once-a-day basal insulin **(Level of evidence: B).**
- For individuals who are critically ill or with prolonged periods of poorly controlled diabetes and frequent episodes of hypoglycemia, SMBG should be performed more frequently (≥4 times per day) **(Level of evidence: B).**

8.1 Assessment of blood glucose control

Blood glucose control in clinical practice can be assessed by measuring glycated haemoglobin (HbA1c), fasting blood glucose (FBG), post-prandial blood glucose (PPG), or using continuous glucose monitoring (CGM) with emphasis on time in range (TIR) and/or mean CGM glucose (1). For this chapter, we will only discuss the assessment of blood glucose control based on HbA1c, FBG, and PPG measurements.

8.2 Assessment of blood glucose control based on glycated haemoglobin measurement

In clinical practice and randomised controlled trials (RCTs), glycaemic control is mainly assessed by measuring HbA1c level, preferably in the laboratory using National Glycohaemoglobin Standardisation Program (NGSP)-certified assays (1). Point-of-care machines are not recommended in the measurement of HbA1c because their assays are not NGSP-certified. The HbA1c level should be measured at diagnosis or initial assessment visit and repeated every three to six months. In individuals with relatively normal and stable glycaemic levels, the HbA1c can be measured every six months (1). As discussed in Chapter 3 of this guideline, the HbA1c level is affected by several factors that should be considered by clinicians when interpreting a patient's results.

8.2.1 Individualising the glycated haemoglobin results

The HbA1c targets to reflect optimal blood glucose control should be individualised based on a patient's clinical profile. To guide

the clinician in individualising the targets, the mnemonic ACED can be used, i.e. A- Age, C- co-existing Comorbidities or Complications such as renal dysfunction, hypoglycaemia unawareness, or established Cardiovascular diseases (CVD), E- Extra factors such as patient's motivation, family support system, and available resources, and D- Duration of diabetes (newly diagnosed or long-standing) (1).

Generally, the optimal HbA1c target for nonpregnant individuals with diabetes is <7% (53 mmol/mol). However, for newly diagnosed young individuals with a long-life expectancy (>10 years), no comorbidities or CVD, a low risk of hypoglycaemia, and who are highly motivated, an HbA1c target of <6.5% (48 mmol/mol) should be considered. For elderly individuals with long-standing diabetes, a high risk of hypoglycaemia, short-life expectancy, established CVD, and severe comorbidities such as renal dysfunction and cognitive dementia, an HbA1c target of <8% (64 mmol/mol) should be considered (1, 2).

8.3 Assessment of blood glucose control based on fasting and postprandial blood glucose measurement

Generally, most guidelines recommend a FBG and PPG level of <7.0 mmol/l (126 mg/dl) and <10 mmol/l (180 mg/dl) as the optimal targets, respectively. A PPG measurement should be performed at least one to two hours after the beginning of the meal (1, 2).

Healthcare professionals need to know that both FBG and PPG levels have a direct impact on an individual's HbA1c level. These three measurements (FBG, PPG, and HbA1c) constitute the glycaemic triad. Owing to this close relationship, individuals with diabetes should be educated about the advantages of maintaining optimal FBG and PPG levels to attain the recommended HbA1c target. In cases of suboptimal HbA1c levels in a patient with normal FBG levels, the healthcare professional should optimise treatment to achieve normal PPG levels as a priority (3, 4).

8.4 Self-monitoring of blood glucose levels

Self-monitoring of blood glucose (SMBG) is an integral component in diabetes care and should be recommended to every individual with type 1 diabetes and type 2 diabetes especially those on insulin therapy as part of the comprehensive and continuous diabetes education program to guide adjustments in therapy, meal size and type, and physical activity (1, 5, 6).

Several meta-analyses of RCTs assessing the glucose-lowering benefit of SMBG have been conducted (7-9). In one meta-analysis of nine RCTs comparing SMBG versus non-SMBG in participants with type 2 diabetes on oral therapy, SMBG was effective in reducing HbA1c (pooled mean difference: -0.24%; 95% CI: -0.34 to -0.14; p< 0.00001). On subgroup analysis, in participants with a baseline HbA1c of 8.0–10.0% (64-86 mmol/mol) and >10% (86 mmol/mol), SMBG was associated with HbA1c reduction of -0.27 (95% CI: -0.40 to -0.14) and -1.23 (95% CI: -2.31 to -0.14), respectively. However, this beneficial effect of SMBG was sustained at 6 months but not at the 12-month duration or beyond (7).

Regarding the intensity and frequency of SMBG, the approach should be individualised to address a patient's needs and requirements of the healthcare professional (6). For practical guidance, in individuals on insulin therapy, the frequency of SMBG will mainly depend on the type of insulin used and the frequency of its administration. In individuals on a basal-bolus insulin regimen (receiving three pre-meal short-acting or rapid-acting insulin doses and once-a-day basal insulin dose), SMBG should be performed at least three to four times a day. For individuals receiving two pre-meal (pre-breakfast and supper) premixed insulin doses, SMBG should be performed two or three times a day. For those on once-a-day basal insulin at bedtime, SMBG can be done once a day, preferably in the morning, to measure the FBG level. In cases of suboptimal HbA1c control in individuals on once-a-day basal insulin, a second test, to assess the PPG levels, can be introduced mainly to rule out sustained postprandial hyperglycaemia as the cause of suboptimal glycaemic control.

For individuals on oral glucose-lowering therapy alone and stable glycaemic control,

SMBG can be performed at least two to three times a week. Frequent SMBG (≥4 times per day) may be required in individuals who are critically ill, those with prolonged periods of poorly controlled diabetes, frequent episodes of hypoglycemia, and risk factors of hypoglycaemia such as chronic kidney disease.

8.5 Clinical benefits of intensive glycaemic control on microvascular and macrovascular diabetes complications

Several large RCTs comparing intensive and standard glycaemic control in people with type 1 and type 2 diabetes such as the Diabetes Control and Complications Trial (DCCT) (10), United Kingdom Prospective Diabetes Study (UKPDS) (11), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (12), Action to Control Cardiovascular Risk in Diabetes (ACCORD) (13), Veterans Affairs Diabetes Trial (VADT) (14), and the Kumamoto study (15) have consistently demonstrated that intensive glycaemic control is associated with a reduction in the rates of microvascular complications.

For example, in the UKPDS, 3,867 individuals with newly diagnosed type 2 diabetes were randomised to intensive and standard glycaemic control and followed up for a median period of 10 years. Compared with standard glycaemic control, intensive glycaemic control was associated with a 12% reduction in any diabetes-related endpoint (such as (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, etc), a 10% reduction in diabetes-related mortality, and 25% reduction in microvascular complications (11).

In the DCCT, 1,441 participants with type 1 diabetes were randomised to intensive (mean HbA1c of 7% or 53 mmol/mol) and standard glycaemic control (mean HbA1c of 9% or 75 mmol/mol) and followed up for a mean period of 6.5 years. Intensive glycaemic control was associated with a 76% risk reduction of developing retinopathy, slowing of progression of retinopathy by 54%, a 47% risk reduction of developing proliferative or severe nonproliferative retinopathy, a 39% risk reduction of developing nephropathy, and a 60% risk reduction of developing neuropathy (10).

On longer follow-up of participants enrolled in the UKPDS and DCCT, the beneficial effects of intensive glycaemic control in reducing the rates of microvascular complications were noted to be maintained over a prolonged period (16, 17). This is referred to as the legacy effect or metabolic memory that demonstrates intensive glycaemic control in the early stages of diabetes confers a clinical benefit of reducing the rates of microvascular complications sustained over a long period (18).

Regarding the effect of intensive glycaemic control on macrovascular diabetes complications, no clinical benefit was initially observed in the ADVANCE (12), ACCORD (13), and VADT (14) trials. However, with a longer follow-up in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDICT) and the UKPDS, and in additional RCTs, intensive glycaemic control has been reported to have long-term cardiovascular disease (CVD) benefits (19). In the DCCT/EDIC, intensive glycaemic control reduced the incidence of any CVD and major cardiovascular events (nonfatal myocardial infarction, stroke, or cardiovascular death) by 30% and 32%, respectively (17). In the UKPDS follow-up of 10 years, in the sulfonylurea–insulin arm, intensive glycaemic control was associated with a 15% risk reduction of myocardial infarction and a 13% risk reduction of all-cause mortality. In the metformin arm, intensive glycaemic control reduced the risk of myocardial infarction and all-cause mortality by 33% and 27%, respectively (16).

These long-term cardiovascular benefits of intensive glycaemic control reported in the two studies above may be related to lower HbA1c levels and reduction in the rates of some cardiovascular risk factors such as microalbuminuria and hypertension (19).

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CHAPTER 9: NON-INSULIN PHARMACOLOGICAL APPROACHES OF GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

SUMMARY OF RECOMMENDATIONS

- An individualised approach based on an individual's age, body mass index, prevalent comorbidities or complications, duration of diabetes, and external factors should be used in clinical practice to guide the selection of glucose-lowering therapies **(Level of evidence: A).**
- Early initiation of combination glucose-lowering therapy is recommended to ensure early attainment and sustainment of optimal glycaemic control and delay of disease progression **(Level of evidence: A).**
- For the elderly and individuals at risk of hypoglycaemia, use drugs associated with a low risk of hypoglycaemia, such as metformin, dipeptidyl peptidase IV (DPP-IV) inhibitors, sodium-glucose cotransporter-2 inhibitors (SGLT2i), and glucagon-like peptide 1 receptor agonists (GLP-1 RA) **(Level of evidence: A).**
- Individuals with a lean type 2 diabetes phenotype should be treated using mainly sulfonylureas (SU) and/or DPP-IV inhibitors, while those with a non-lean type 2 diabetes phenotype should be treated using mainly metformin, SGLT2i, GLP-1 RA, and thiazolidinediones (TZD) **(Level of evidence: B).**
- Individuals with type 2 diabetes and co-existing atherosclerotic cardiovascular diseases should be initiated on GLP-1 RA or SGLT2i as the first-line glucose-lowering agents, while those at risk or with heart failure (regardless of the ejection fraction) and renal dysfunction should be initiated on SGLT2i as the first-line glucose-lowering agent **(Level of evidence: A).**

9.1 Approach to the selection and initiation of appropriate individualised non-insulin glucose-lowering therapies

Several classes of non-insulin glucose-lowering therapies are approved for the management of type 2 diabetes. These include biguanides such as metformin, sulfonylureas (SU) such as gliclazide, glibenclamide, and glimepiride, dipeptidyl peptidase IV (DPP-IV) inhibitors such as sitagliptin, teneligliptin, linagliptin, and vildagliptin, thiazolidinediones (TZD) such as pioglitazone, sodium-glucose cotransporter-2 inhibitors (SGLT2i) such as dapagliflozin, canagliflozin, and empagliflozin, alpha-glucosidase inhibitors such as acarbose, and glucagon-like peptide 1 receptor agonists (GLP-1 RA) such as semaglutide and liraglutide (1-3).

A holistic, individualised, or person-centred approach should be used in clinical practice to guide the choice of which of the above non-insulin glucose-lowering therapies will be used in the management of type 2 diabetes. This forms the basis of personalised or precision medicine currently recommended in diabetes care (4). Broadly, the individual-based factors to consider as guiding principles for the selection of non-insulin glucose-lowering treatment in type 2 diabetes include understanding the predominant underlying pathophysiologic defects, the status of pancreatic beta-cell function, individual glycaemic targets, individual's age, and body mass index, the prevalent diabetes complications and comorbidities, duration of diabetes (newly diagnosed or long-standing diabetes), and external factors such as availability and cost of the drug, side effect profile, and patient preference (1, 4-8). These constitute the ABCDE and 2Ps approach, which is described in the sections below.

9.2 The ABCDE and 2Ps approach in the management of type 2 diabetes

Because glycaemic management in

individuals with type 2 diabetes is not a "one size fits all", the ABCDE approach uses simple clinical characteristics to guide healthcare professionals towards an individualised approach for managing type 2 diabetes, hence selecting effective and relatively safe glucose-lowering treatment. This approach entails knowing the patient's Age, Body mass index (BMI), prevalent diabetes Complications and/or Comorbidities, Duration of diabetes, and assessing for External factors that can influence which glucose-lowering drugs are to be selected (5, 6, 8). For the Ugandan context, we add the 2Ps to guide the selection of diabetes therapy, including knowing the predominant underlying Pathophysiologic defect (pancreatic beta-cell dysfunction or insulin resistance) and the status of Pancreatic beta-cell function.

9.2.1 Using age to guide the selection of non-insulin glucose-lowering therapy

Advanced age is associated with an increased risk of hypoglycaemia and complications or comorbidities such as atherosclerotic cardiovascular disease (ASCVD), renal dysfunction, and cognitive dysfunction. Because of this, drugs with a well-documented low risk of hypoglycaemia, such as metformin, SGLT2i, GLP-1 RA, and DPP-IV inhibitors, are preferred (6, 8). If a healthcare professional opts to use a SU, gliclazide is preferred because it is associated with the lowest risk of hypoglycaemia among the SU (9). Do not prescribe glibenclamide for elderly individuals (age ≥60 years) due to its high risk of hypoglycaemia when compared with other SU (10).

Metformin is known to lower serum vitamin B12 levels, resulting in worsening of cognitive function. Therefore, all elderly individuals on metformin should be screened annually for vitamin B12 deficiency. Pioglitazone should be avoided in the elderly because it is associated with an increased risk of osteoporosis and fluid retention exacerbating heart failure (6, 8).

The use of SGLT2i in the elderly may be associated with an increased risk of volume depletion and genital infections in elderly females and males with co-existing benign prostatic hypertrophy (11). Therefore, all elderly individuals on SGLT2i should be counselled about increased fluid intake.

9.2.2 Using body mass index to guide the selection of non-insulin glucose-lowering therapy

The assessment of an individual's BMI (weight in kilograms divided by height in metres2) helps in stratifying patients into lean (BMI <25 kg/m2) and non-lean (BMI ≥25 kg/m2) type 2 diabetes phenotypes. These two phenotypes have distinct clinical and metabolic phenotypic characteristics that directly influence glucose-lowering therapy selection. In the Uganda Diabetes Phenotype (UDIP) study that performed robust phenotypic characterisation of 500 adult Ugandans with recently diagnosed type 2 diabetes, 32% of the participants were lean in body size (BMI <25 kg/m2). Compared with those with the non-lean subtype, the lean type 2 diabetes subtype was characterised by features of pancreatic beta-cell failure (lower fasting and 120-minute C-peptide and oral insulinogenic index levels) and minimal insulin resistance (lower homeostatic model assessment 2-insulin resistance level) (12).

Because of these striking phenotypic differences and from a pathophysiologic perspective, drugs that stimulate insulin secretion by the pancreatic beta-cells, such as SU and DPP-IV inhibitors, may be the ideal first-line non-insulin oral agents in individuals with the lean type 2 diabetes phenotype. Additionally, these oral agents are not associated with weight loss. For individuals with the non-lean type 2 diabetes phenotype, adding GLP-1 RA, SGLT2i, or TZDs to metformin and lifestyle modification would be the preferred option. This is because these therapies are associated with weight loss and improve peripheral insulin sensitivity (3, 5-8).

It is important to note that while TZDs are important in improving peripheral insulin sensitivity, this class of drugs is associated with weight gain due to fluid retention and osteoporosis (13, 14). Because of these adverse events, there is a need to reconsider their use in non-lean individuals with type 2 diabetes. However, you may consider prescribing them for non-lean individuals with metabolic dysfunction-associated steatotic liver disease (15).

Studies conducted on White Europeans and

Asians with type 2 diabetes have demonstrated optimal response to DPP-IV inhibitors and SU in individuals with a non-obese phenotype (BMI <30 kg/m2) and those with an obese phenotype (BMI ≥30 kg/m2) responding better to TZDs such as pioglitazone (16-19). This confirms differential response to these oral glucose-lowering therapies based on an individual's baseline BMI. However, studies to assess the differences in therapeutic response to these oral glucose-lowering drugs in Black Africans are still lacking to date.

9.2.3 Using prevalent diabetes complications and comorbidities to guide the selection of non-insulin glucose-lowering therapy

As discussed in detail in Chapter 7 on comprehensive medical evaluation and screening for related comorbidities, the initial (at diagnosis or first contact) and annual follow-up visit should involve a detailed cardiovascular risk stratification and screening for diabetes complications and comorbidities, notably ASCVD (coronary heart disease, cerebrovascular disease, and peripheral arterial disease), renal dysfunction, heart failure, hypothyroidism, cognitive dysfunction, and psychiatric disorders (20).

The WHO CVD risk charts (21), the pooled cohort risk equations score (22), and the Framingham risk score (23), which are freely available for use online, can be used in ASCVD risk stratification. In individuals at high risk for ASCVD (presence of overweight or obesity, hypertension, dyslipidaemia, hyperuricaemia, albuminuria, 10-year risk of ASCVD >20% on using the pooled cohort risk equations score or Framingham risk score), established ASCVD, renal dysfunction, and heart failure (regardless of the ejection fraction), SGLT2i and GLP-1 RA should be used as the first-line glucose-lowering therapies in combination with metformin or other agents (1, 6, 8).

Findings from several large meta-analyses assessing the cardiovascular and renal benefits of SGLT2i and GLP-1 RA have consistently reported that these two classes of glucose-lowering therapies are associated with reducing the risk of cardiovascular (CV) and all-cause mortality, major adverse CV events or MACE (incident myocardial infarction, stroke, heart failure, coronary revascularization, atrial fibrillation, or CV mortality), hospitalisation due to heart failure, progression of renal disease, and acute kidney injury (24-26).

In individuals with comorbidities that increase the risk of hypoglycaemia such as autonomic neuropathy, renal dysfunction, and hypoglycaemia, non-insulin therapies with a low risk of hypoglycaemia such as metformin, SGLT2i, GLP-1 RA, and DPP-IV inhibitors are preferred. Avoid TZDs and metformin in individuals with or at risk of heart failure and those with an estimated glomerular filtration rate <30 ml/min/1.73 m2, respectively (6, 8).

9.2.4 Using duration of diabetes to guide the selection of non-insulin glucose-lowering therapy

A long duration of diabetes increases the risk of developing complications such as ASCVD, renal dysfunction, autonomic neuropathy, progressive decline of beta-cell mass and eventual secretory dysfunction, and lower life expectancy. Because of this, therapies such as SGLT2i, GLP-1 RA, DPP-IV inhibitors, and metformin may be preferred as the first-line glucose-lowering therapies (6, 8).

9.2.5 External factors that can guide the selection of non-insulin glucose-lowering therapy

Several external patient-, family-, or healthcare setting-related factors such as availability and cost of the drug, side effect profile, and patient preference should also be considered while selecting which non-insulin glucose-lowering therapy to use in managing type 2 diabetes.

9.2.6 Using the 2Ps to guide the selection of non-insulin glucose-lowering therapy

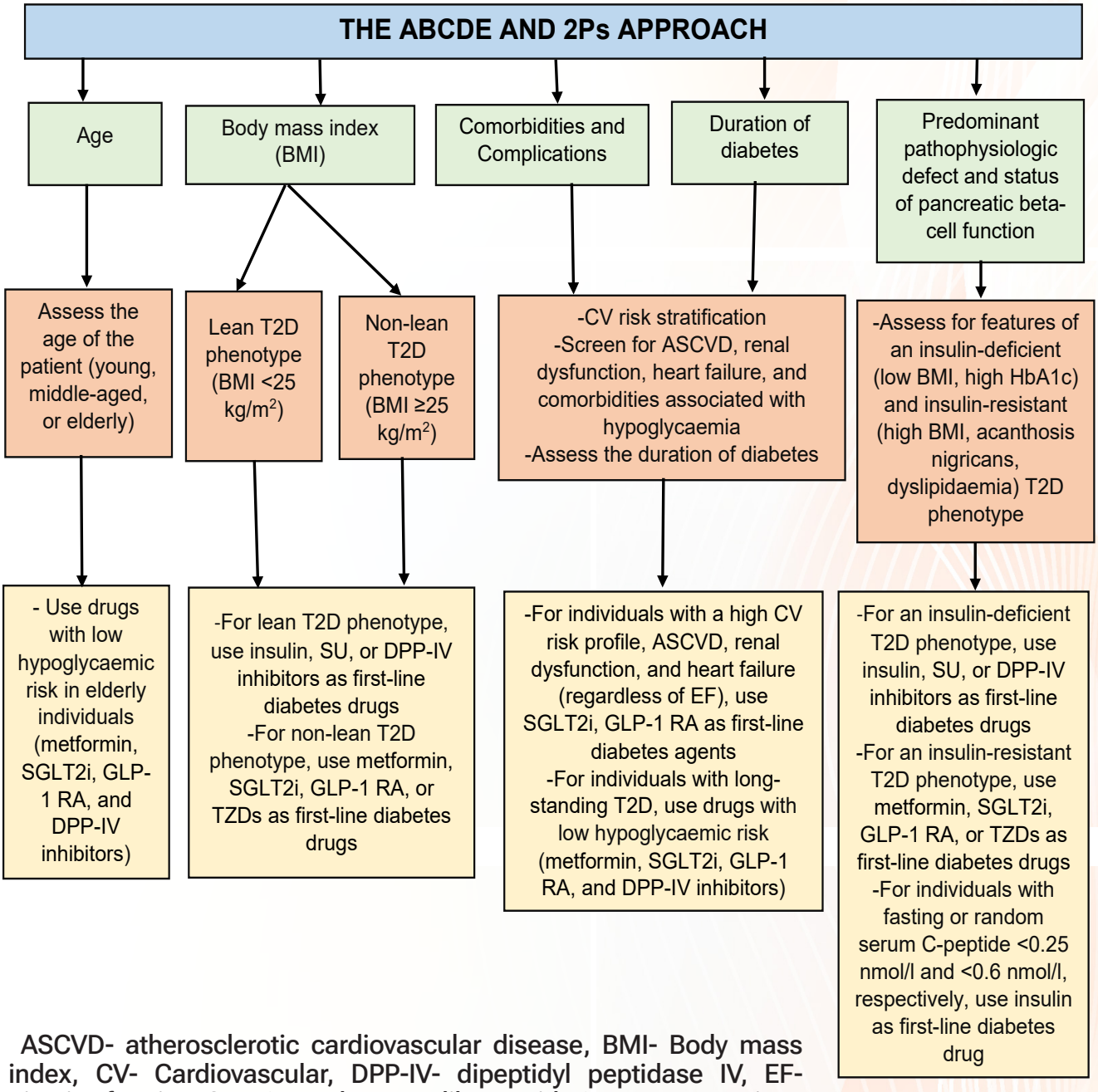
The 2Ps approach involves understanding the predominant underlying pathophysiologic defect and the status of pancreatic beta-cell function to guide the selection (5, 6). Because type 2 diabetes is characterised by multiple pathophysiologic defects, understanding these defects is important because each glucose-lowering therapy targets a specific

underlying defect(s) (5, 7, 27).
In the clinical evaluation of a patient with type 2 diabetes, it is important to establish whether the predominant underlying pathophysiologic defect is pancreatic beta-cell dysfunction or insulin resistance. Clinically, the presence of a low or normal BMI (<25 kg/m2), frequent presentation with ketosis, severe hyperglycaemia on assessment, and early-onset of secondary oral hypoglycaemic failure may reflect a predominant profile of pancreatic beta-cell dysfunction (28, 29). Predominance of insulin resistance is characterised by the presence of overweight or obesity, atherogenic dyslipidaemia, hypertension, mild hyperglycaemia, and the presence of clinical signs such as acanthosis nigricans (cutaneous hyperpigmentation and thickening at the base of the neck and armpits) (29, 30).
Individuals with a predominance of pancreatic beta-cell dysfunction will require therapy with insulin or oral agents that stimulate beta-cell secretion of insulin such as SU and DPP IV inhibitors as the ideal first-line therapies while those with a predominant insulin-resistant phenotype will require therapies that induce weight loss and improve peripheral insulin sensitivity such as metformin, GLP-1 RA, SGLT2i, and TZDs (5-7).
Studies conducted on adult Ugandans with new-onset and long-standing type 2 diabetes have demonstrated a predominant insulin-deficient phenotypic picture characterised by low BMI and surrogate markers of beta-cell function such as fasting and 120-minute C-peptide and insulinogenic index levels (12, 28, 31-33). Because of this, baseline assessment of the status of pancreatic beta-cell function, either by measurement of the fasting, random, or stimulated serum C-peptide concentrations, should be encouraged in clinical practice mainly to confirm the diagnosis of type 2 diabetes, and guide the selection of optimal glucose-lowering treatment (either insulin or oral therapy) (34, 35). In clinical settings without access to serum C-peptide tests, the presence of phenotypic characteristics such as low BMI and persistently suboptimal glycaemic levels should influence the clinical decision of timely initiation of insulin therapy.
Fasting and random (or stimulated) serum C-peptide concentrations <0.08 nmol/l (0.24 ng/ml) and <0.2 nmol/l (0.6 ng/ml), respectively, suggest absolute insulin deficiency and requirement. Individuals with type 2 diabetes and fasting and random (or stimulated) serum C-peptide <0.25 nmol/l (0.76 ng/ml) and <0.6 nmol/l (1.8 ng/ml), respectively, will most likely fail to achieve optimal glycaemic control with non-insulin therapies, hence necessitating a switch from oral glucose-lowering therapies to insulin therapy (34).
Figure 1 below summarises the ABCDE and 2Ps approach in individualising non-insulin glucose-lowering therapy in the management of type 2 diabetes. Figure 2 summarises how to select the optimal glucose-lowering therapy based on the predominant underlying pathophysiological defect.

9.3 Use of combination glucose-lowering therapy in the management of type 2 diabetes

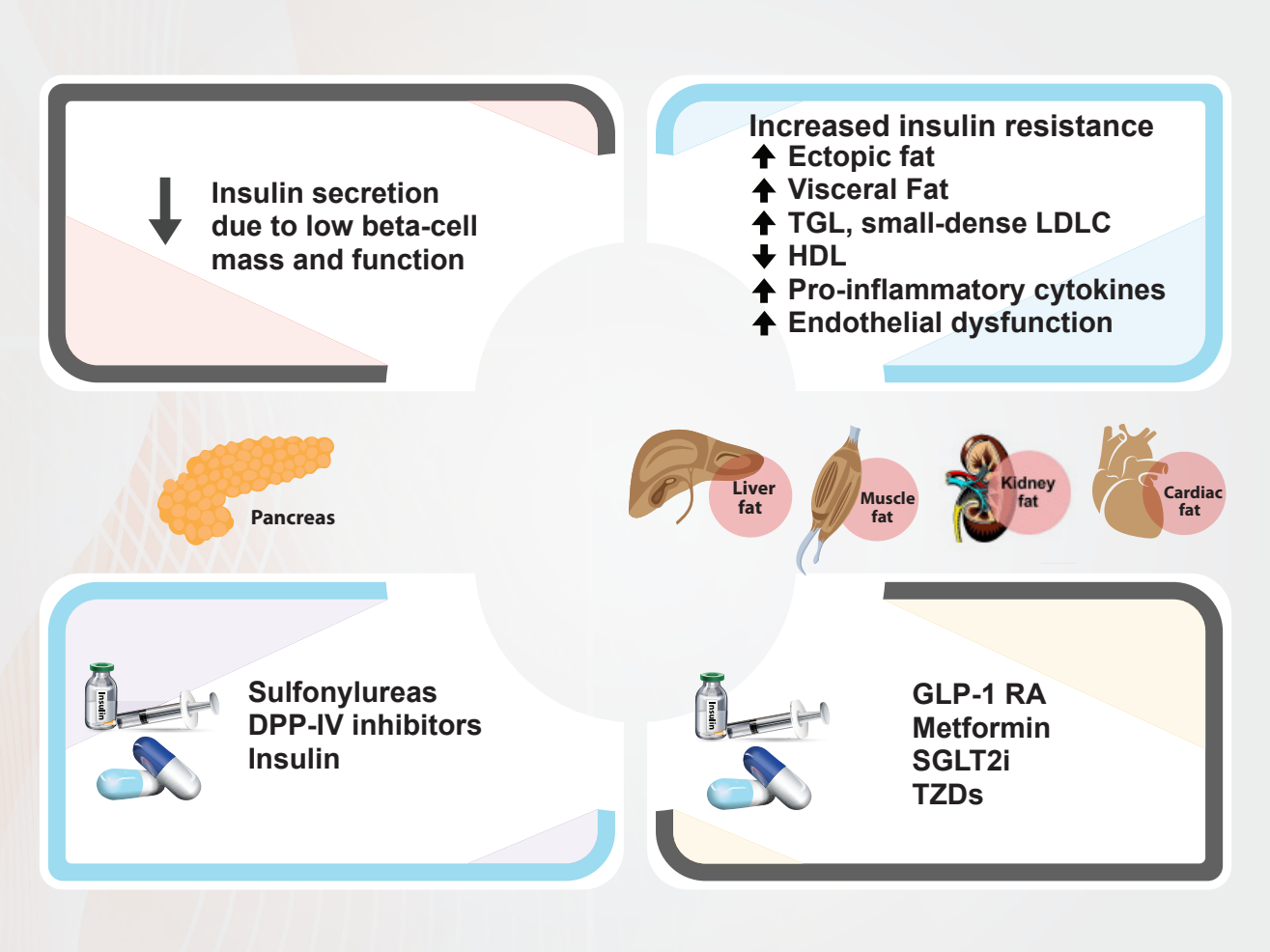
Type 2 diabetes is characterised by heterogeneity in pathophysiology, disease progression, and therapeutic response to glucose-lowering therapies (27, 36, 37). Because of this, achieving and maintaining optimal glycaemic control may require combination therapy in some individuals. This approach of combination therapy is recommended by most professional societies such as the American Diabetes Association, European Association of the Study of Diabetes, International Diabetes Federation, and American Association of Clinical Endocrinology in individuals with newly diagnosed type 2 diabetes with HbA1c ≥ 7.5% or 58 mmol/mol or those presenting with HbA1c levels 1.5-2.0% above target (1, 38-40). Additionally, initial glucose-lowering combination therapy, as opposed to sequential addition of glucose-lowering medication, is also recommended in the management of type 2 diabetes to address the multiple underlying pathophysiologic mechanisms involved, sustain optimal glycaemic decline and control, delay disease progression, and avert the high oral hypoglycaemic failure rate associated with long-term use of monotherapy (41-46).

Figure 1. The ABCDE and 2Ps approach to guide the selection of individualised glucose-lowering therapy for managing type 2 diabetes



ASCVD- atherosclerotic cardiovascular disease, BMI- Body mass index, CV- Cardiovascular, DPP-IV- dipeptidyl peptidase IV, EF- Ejection fraction, GLP-1 RA- glucagon-like peptide 1 receptor agonists, SGLT2i- sodium-glucose cotransporter inhibitors, SU- sulfonylureas, T2D- Type 2 diabetes, TZDs- thiazolidinediones

Figure 2. Selection of the optimal glucose-lowering therapy based on the predominant underlying pathophysiologic defect



Adapted from Tanabe H et al. Diabetes Res Clin Pract. 2021;180:109067

9.4 An overview of the pharmacology of non-insulin glucose-lowering therapies

9.4.1 Metformin

Drug class and mode of action

Metformin is the only biguanide currently used in diabetes care. It is often recommended as the first-line therapy in the management of type 2 diabetes because of its low cost, effectiveness, and relatively good safety profile. Its glucose-lowering properties are achieved mainly through its effect of activating the adenosine monophosphate-activated protein kinase in the liver, resulting in hepatic uptake of glucose and inhibiting gluconeogenesis. It also improves insulin sensitivity by activating insulin receptor expression and enhancing tyrosine kinase activity (2, 3).

Metformin has been shown to induce modest weight loss in overweight and obese patients with type 2 diabetes and is associated with a low risk of hypoglycaemia.

Commonly associated side effects

These include gastrointestinal side effects such as nausea, vomiting, abdominal pain, bloating, and loss of appetite. These can be reduced by using an extended-release formulation. Although lactic acidosis is often cited as one of its side effects, it is rarely encountered in clinical practice.

Metformin use is contraindicated in patients with advanced renal insufficiency if e-GFR is <30 ml/min/1.73 m2 (2, 3).
Long-term use of high-dose metformin therapy (≥5 years) is associated with vitamin B12 deficiency, especially in the elderly and vegetarians (47-49). This is because the drug inhibits the calcium-dependent intrinsic factor-vitamin B12 binding, hence impairing vitamin B12 absorption (47, 48). Therefore, measurement of serum vitamin B12 levels at the initial visit and periodically (especially in the presence of suboptimal glycaemic control and peripheral neuropathy) is recommended in all patients on long-term metformin therapy (1).
Healthcare professionals in Uganda should be cognisant of the relatively high prevalence of vitamin B12 deficiency in adult Ugandans with type 2 diabetes. In one hospital-based study conducted at Mulago National Referral Hospital and Teaching Hospital, Kampala Uganda, the prevalence of vitamin B12 deficiency (defined as serum vitamin B12 concentrations <200 pg/ml) was 10.7%. A haemoglobin level<12 g/dl and glycated hemoglobin≥7 % were reported to be independent predictors of vitamin B12 deficiency in this study population (50). This further underscores the need to screen for vitamin B12 deficiency in the adult Ugandan population with type 2 diabetes.

Recommended dose
The recommended dosing range of metformin is 500 mg/day to a maximum of 2000 mg or 2 g per day given in two divided doses after meals.

9.4.2 Sulfonylureas
Drug class and mode of action
Sulfonylureas (SU) such as glimepiride, gliclazide, glipizide, and glibenclamide are insulin secretagogues and act by binding on the sulfonylurea receptor located on the pancreatic beta-cell, resulting in the closure of the K+ ATP channels, depolarization of the beta-cell, intra-cellular influx of calcium and eventual insulin release.

Commonly associated side effects
These include weight gain and hypoglycaemia, especially in specific patient subgroups like the elderly, and patients with liver, renal, and thyroid dysfunction (2, 3).
Recommended dose
The dosing of the commonly available SU is as shown: gliclazide- 30-60 mg once a day after a meal, glimepiride- 1-4 mg once a day after a meal, glipizide- 5-20 mg per day after a meal, glibenclamide 5-10 mg per day after a meal.

9.4.3 Dipeptidyl peptidase IV inhibitors
Drug class and mode of action
The DPP-IV inhibitors, such as teneligliptin, vildagliptin, linagliptin, and sitagliptin, are incretin mimetics and act by inhibiting the activity of the enzyme DPP-IV, which rapidly degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), hence increasing their circulating concentrations. These incretin hormones are important in enhancing glucose-dependent insulin secretion from the pancreatic beta-cells, inhibiting glucagon release from the pancreatic alpha cells, reducing gastric emptying, reducing appetite, and promoting satiety. They also promote pancreatic beta-cell differentiation and mass. Because they stimulate beta-cell insulin secretion dependent on the circulating glucose levels, they are associated with a lower risk of hypoglycaemia. Unlike the GLP-1 RA, they are not associated with weight loss and are cardiovascular-neutral.

Commonly associated side effects
These include nasopharyngitis, headache, skin reactions, and acute pancreatitis. They are contraindicated in acute, chronic, or recurrent pancreatitis or at high risk for pancreatitis, pancreatic cancer, and severe liver disease (2, 3).

Recommended dose
The dosing of the commonly available

DPP-IV inhibitors in Uganda is as shown: sitagliptin 50-100 mg once a day, vildagliptin 50-100 mg per day, teneligliptin 20-40 mg once a day, and linagliptin 5 mg once a day.

9.4.4 Glucagon-like peptide 1 receptor agonists

Drug class and mode of action

The GLP-1 RA such as exenatide, liraglutide, lixisenatide, semaglutide, dulaglutide, and albiglutide exhibit increased resistance to enzymatic degradation by the DPP IV enzyme, hence mimicking the action of endogenous GLP-1 to enhance glucose-dependent insulin secretion by the pancreatic beta-cells and inhibit glucagon secretion by the pancreatic alpha-cells (2, 3).

They are associated with a low risk of hypoglycaemia, potent weight loss effects, and cardiovascular and renal protective benefits as shown in several large landmark randomised controlled trials.

Commonly associated side effects

The drugs are generally well-tolerated, with mild gastrointestinal side effects (nausea and vomiting) being the commonest (2, 3).

Currently, these drugs are not readily available in Uganda, and their cost is prohibitive. For example, a monthly dose of the once-weekly original brand semaglutide injection is about 2,500,000 Uganda shillings (660 US dollars).

9.4.5 Sodium-glucose cotransporter-2 inhibitors

Drug class and mode of action

The SGLT2i such as empagliflozin, dapagliflozin, and canagliflozin lower blood glucose in an insulin-independent method by inhibiting glucose reabsorption in the proximal renal tubules through blockade of the SGLT2 channels, resulting in urinary glucose excretion (glycosuria). Because of its insulin-dependent mechanism of action, it is not associated with hypoglycaemia unless used with insulin secretagogues such as SU. Similar to GLP-1 RA, they have weight and blood pressure reduction properties, and cardiovascular, and renal protective benefits.

Commonly associated side effects

These include recurrent urinary tract infections, genital candidiasis, dehydration, especially with low oral intake, and euglycaemic ketoacidosis, especially in patients also on insulin therapy. Patients should be advised to maintain good general hygiene and adequate hydration (at least three litres per day) to avoid most of these side effects (2, 3).

Recommended dose

The dosing of the only two available SGLT2i in Uganda is as shown: dapagliflozin 5-10 mg per day and empagliflozin 10 mg or 25 mg per day.

9.4.6 Thiazolidinedione

Drug class and mode of action

The TZDs, such as pioglitazone, are agonists of nuclear receptors called peroxisome proliferator-activated receptor-gamma (PPARγ), facilitating increased transcription of proteins that augment the post-receptor actions of insulin, resulting in improved insulin sensitivity and glucose uptake in numerous tissues, including adipose, muscle, and liver, and improving beta-cell function and mass. Additionally, they reduce free fatty acid accumulation and pro-inflammatory cytokines and increase adiponectin levels.

Commonly associated side effects

These include a dose-dependent weight gain due to fluid retention, oedema, worsening or precipitating heart failure, and increased risk of osteoporosis (2, 3).

Recommended dose

The dose of the only available TZD in Uganda is pioglitazone. Its recommended dose is 15-30 mg per day.

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CHAPTER 10. INSULIN THERAPY IN THE MANAGEMENT OF TYPE 2 DIABETES

SUMMARY OF RECOMMENDATIONS

- One of the hallmarks of type 2 diabetes is the progressive decline in pancreatic beta-cell mass and secretory function. Because of this, insulin therapy may be required either at the time of diagnosis or later in the course of the condition **(Level of evidence: A).**
- Some of the indications of insulin therapy in adults with type 2 diabetes include persistently high HbA1c levels (HbA1c ≥10% or 86 mmol/mol) despite being on maximum doses of ≥2 oral hypoglycaemic agents, symptomatic individuals with newly diagnosed type 2 diabetes and fasting blood glucose (FBG) >14 mmol/l (250 mg/dl) or random blood glucose (RBG) >16.7 mmol/l (300 mg/dl) **(Level of evidence: B).**
- Early initiation of insulin therapy ensures rapid and sustained glycaemic control (and its related benefits of legacy effect), and improves pancreatic beta-cell mass and function, and peripheral insulin sensitivity **(Level of evidence: B).**
- Despite similar efficacy, analogue insulins are preferred to human insulins due to their superior safety profile (less hypoglycaemia and glycaemic variability) and meal-time convenience in administration **(Level of evidence: A).**
- The preferred approach to insulin initiation is to start with a once-a-day basal insulin regimen. If optimal glycaemic targets are not met, then switch to using basal-bolus insulin or premixed insulin regimens **(Level of evidence: B).**
- The approach of using basal-bolus insulin regimens, as opposed to premixed insulin regimens, is the preferred approach for insulin administration because it closely mimics the normal insulin secretion pattern of the body **(Level of evidence: B).**
- The use of sliding scale in managing hyperglycaemia in inpatient clinical settings should be generally avoided due to its related complications such as the increased risk of glycaemic variability and cardiovascular events **(Level of evidence: B).**

10.1 Introduction

The Uganda Diabetes Association fully endorses the East African Diabetes Study Group (EADSG) guidelines on insulin therapy in diabetes (1) and insulin storage and optimisation of injection techniques in diabetes management (2). For this chapter, we will discuss the normal physiology of insulin secretion, the rationale for initiation of insulin therapy in individuals with type 2 diabetes, the pharmacology of commonly available insulin types in Uganda, algorithmic initiation of insulin therapy in individuals with type 2 diabetes, insulin use in specific patient populations, common side effects associated with insulin, insulin storage, recommended delivery devices, and injection techniques. Insulin therapy in individuals with type 1 diabetes will be addressed in detail in Chapter 15 of this guideline.

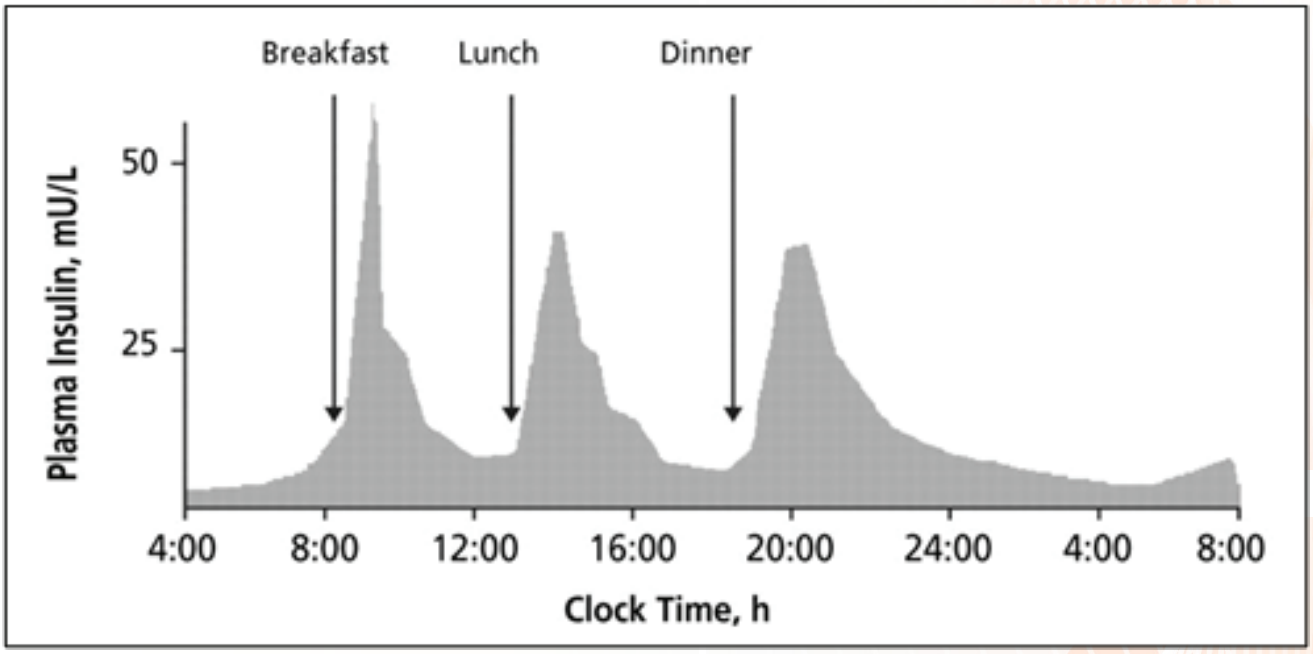
10.2 Overview of the normal insulin secretion physiology

Insulin, a peptide hormone secreted by the beta-cells of the pancreas, plays a pivotal role in maintaining glucose homeostasis, cell growth, and metabolism (3, 4). It was discovered in 1921 by Dr. Frederick Banting, Charles Best, and James Bertram Collip under the supervision of John James Macleod at the University of Toronto, Canada. The first patient to successfully use insulin was Leonard Thompson in 1922 (5).

In healthy individuals without diabetes, the plasma glucose concentrations are maintained within a narrow range of 4.0-7.0 mmol/l (72-126 mg/dl) even after a large carbohydrate-based meal. The plasma glucose should not reduce below 4 mmol/l (72 mg/dl) even after an overnight fast. In addition to insulin, this glucose homeostasis

is also tightly maintained by an interplay of several other hormones, such as glucagon, cortisol, growth hormone, and incretin hormones (glucagon-like peptide 1 or GLP-1 and glucose-dependent insulinotropic polypeptide or GIP) (3, 4).
Figure 1 below summarises the physiological pattern of insulin secretion.
Following ingestion of food, the plasma glucose rises to a peak in 30-60 minutes and returns to basal or below basal concentrations in two to three hours in response to the insulin released post-prandially. This postprandial insulin release (first-phase and late-phase occurring within 30 minutes and after 30 minutes, respectively) is also influenced by the postprandial release of GLP-1 and GIP, which are incretin hormones that stimulate insulin secretion from the pancreatic beta-cells in a glucose-dependent manner. In addition to the postprandial insulin, insulin secretion also occurs during basal periods. This secreted basal insulin helps in the sustained suppression of lipolysis and glycogenolysis. Postprandial and basal insulin is secreted by the pancreatic beta-cells in a 50%:50% ratio (3, 4).
The hyperglycaemia in individuals with type 2 diabetes characteristically develops due to loss or blunting of the first- and late-phase of insulin secretion, which results due to reduced pancreatic beta-cell mass and/or function and loss of the incretin effect (6).

Figure 1. The normal physiological pattern of insulin secretion



10.3 Rationale for initiation of insulin therapy in individuals with type 2 diabetes

The hallmark of type 2 diabetes is the progressive decline in the beta-cell mass and secretory function with worsening glycaemic control, secondary oral hypoglycaemic agent failure, and the eventual need for insulin therapy (7, 8). Because of this progressive feature, many adults with type 2 diabetes will eventually require and benefit from insulin therapy later in the course of the condition.
For the Ugandan context, a relative proportion of adults with new-onset type 2 diabetes have insulin deficiency requiring insulin therapy right from diagnosis. As part of the Uganda Diabetes Phenotype (UDIP) study, fasting serum C-peptide concentrations, as a marker of pancreatic beta-cell function, were measured in 494 adult Ugandans with recently diagnosed type 2 diabetes (diagnosed in the preceding three months without evidence of islet autoimmunity). Insulin deficiency (defined as a fasting serum C-peptide concentration <0.76 ng/ml or 0.25

nmol/l) was noted in 22% (about 1 in 5) of the participants. Predictors of insulin deficiency in this study population were high glycated haemoglobin (HbA1c) concentrations, low body mass index (BMI), and non-high-dense lipoprotein cholesterol concentrations (9).
Insulin therapy is indicated in adults with type 2 diabetes in these clinical situations:

1. Biochemically confirmed insulin deficiency (fasting serum C-peptide <0.76 ng/ml [0.25 nmol/l] or random serum C-peptide concentration <1.80 ng/ml [0.6 nmol/l]). Generally, serum C-peptide should be measured after correction of an acute hyperglycaemic episode, ideally >3 weeks from the time of diagnosis in patients with newly diagnosed type 2 diabetes or after an acute hyperglycaemic crisis (diabetic ketoacidosis or hyperglycaemic hyperosmolar state).
2. Persistently high HbA1c levels (HbA1c ≥10% or 86 mmol/mol) or uncontrolled diabetes concerning the glycaemic goals.
3. Clinical presentation in diabetic ketoacidosis.
4. Presence of secondary oral hypoglycaemic agent failure (failure to attain optimal glycaemic control despite using maximum doses of >2 oral hypoglycaemic agents).
5. Symptomatic patients with newly diagnosed type 2 diabetes and fasting blood glucose (FBG) >14 mmol/l (250 mg/dl), random blood glucose (RBG) >16.7 mmol/l (300 mg/dl), and/or HbA1c ≥10% (86 mmol/mol).
6. In cases of surgery (pre-, intra-, and post-operative periods).
7. Patients on high-dose steroids for management of any medical condition.
8. Patients with acute illnesses necessitating inpatient management, such as sepsis and post-myocardial infarction.
9. Patients with comorbidities or complications that deem the use of oral hypoglycaemic agents as contraindicated, such as end-stage renal and hepatic dysfunction and acute or chronic pancreatitis.
10. Pre-gestational and gestational diabetes.

In the case of the above clinical situations, adult individuals with type 2 diabetes should be counselled and initiated on insulin therapy to attain the desired glycaemic goals (as discussed in Chapter 8 of this guideline) (1, 10-13).

10.3.1 Benefits of early initiation of insulin therapy

The benefits of early initiation of insulin therapy in individuals with type 2 diabetes have been demonstrated in randomised controlled trials (RCTs) and meta-analyses (14-17). Generally, early initiation of insulin therapy has been shown to rapidly improve glycaemic control, hence reducing the glucotoxic and lipotoxic effects of hyperglycaemia on the pancreatic beta-cells. This helps to preserve beta-cell mass and function, in addition to improving peripheral insulin sensitivity (18, 19).

Early initiation of insulin therapy with rapid and sustained optimal glycaemic control in individuals with type 2 diabetes is associated with metabolic memory or legacy effect and long-term benefits of reducing the risk of microvascular and macrovascular diabetes complications (18-20).

10.4 Mode of action of insulin

Once secreted by the beta-cells of the pancreas, insulin regulates endogenous glucose production and utilisation. Insulin suppresses hepatic glucose production, lipolysis (by inhibiting the insulin-sensitive lipase), and stimulates peripheral glucose uptake mainly by the skeletal muscle and fat cells, and promotes protein synthesis by inhibiting proteolysis (3, 4).

10.5 Pharmacology of Commonly Available Insulin Types in Uganda

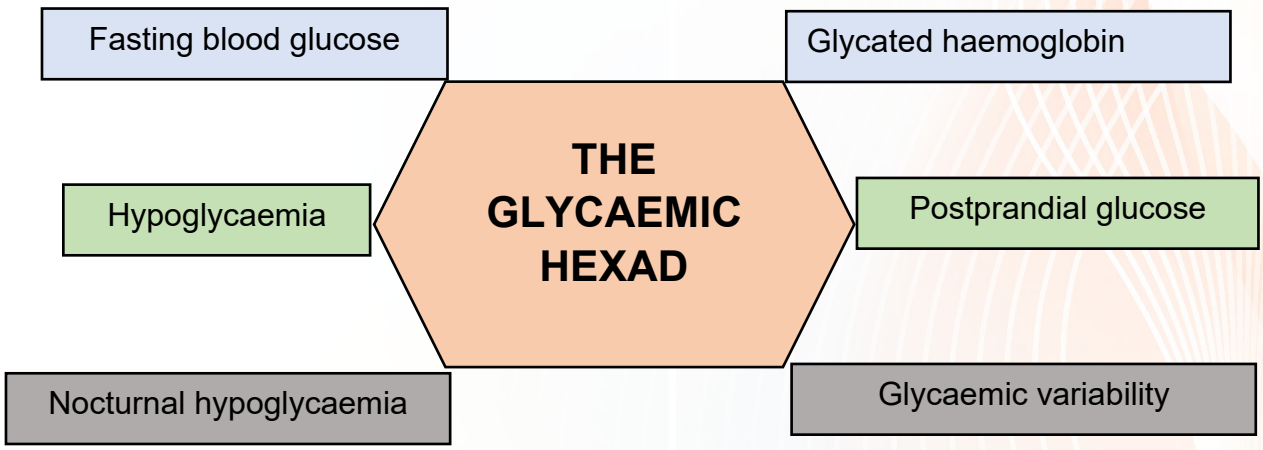
Both human and analogue insulins are available in Uganda, although the latter is relatively more expensive and not readily available. The available human insulin types include short-acting or regular U100 insulin,

intermediate-acting insulin such as neutral protamine Hagedorn (NPH) insulin, and premixed insulin containing regular and NPH insulin in a 30:70 ratio. The available analogue insulin types include rapid-acting insulin aspart, long-acting insulins such as insulin glargine U100 and insulin detemir, and premixed biphasic insulin aspart in a 30:70 ratio of aspart and protamined aspart.

10.5.1 A comparison between human and analogue insulin types

In the management of individuals with type 1 and type 2 diabetes, healthcare professionals must consider both the efficacy and safety of the insulin type being used. These two aspects in diabetes care are incorporated in the glycaemic hexad which includes the glycaemic triad (HbA1c, FBG, and postprandial glucose [PPG]) representing the efficacy component and glycaemic variability, hypoglycaemia, and nocturnal hypoglycaemia, representing the safety component (21). Figure 2 below comprehensively illustrates the glycaemic hexad.

Figure 2. Components of a glycaemic hexad



Both human and analogue insulins have comparable effects on the HbA1c. Despite being less available and more expensive in Uganda compared with human insulin types, analogue insulins are generally preferred due to their better safety profile as a result of structural modifications. They are associated with a lower frequency of hypoglycaemia, nocturnal hypoglycaemia, and glycaemic variability. Because of this advantage, analogue insulins are preferred in elderly patients and individuals with conditions associated with glycaemic variability and frequent hypoglycaemic episodes such as long-standing diabetes, renal and liver dysfunction, and autonomic dysregulation. They are the preferred insulins during fasting periods such as Ramadhan. Additionally, analogue insulins are preferred to human insulins because of the convenience of administration (administered 10-15 minutes before a meal), faster onset of action, better control of postprandial hyperglycaemia, and glycaemic control (1, 22-24).

Human and analogue insulins have varying onset of action, peaks, and duration of action once administered subcutaneously or intravenously. Table 1 below summarises these varying properties of the types of insulin.

Table 1. Pharmacological properties of the different types of insulin

Generic name	Onset of action	Peak	Duration of action	Effect of glycaemia
A: Human insulins				
Regular or short-acting insulin	30-60 minutes	2-4 hours	6-8 hours	Controls PPG levels
Intermediate-acting insulin, e.g. NPH insulin	1-2 hours	6-12 hours	18-24 hours	Controls FBG levels
Premixed insulin (30% regular insulin and 70% NPH insulin)	30-60 minutes	2-8 hours	10-16 hours	Controls both FBG and PPG levels
B: Analogue insulins				
Rapid-acting insulin e.g. insulin aspart and lispro	5-15 minutes	4 hours	3.5-4.5 hours	Controls PPG levels
Premixed insulin analogues e.g. biphasic insulin aspart (30% aspart and 70% protamine)	5-15 minutes	1-4 hours	10-16 hours	Controls both FBG and PPG levels
Long-acting insulin glargine	60-90 minutes	No peak	20-26 hours	Controls FBG levels
Long-acting insulin detemir	60-90 minutes	No peak	20-26 hours	Controls FBG levels

FBG- Fasting blood glucose, NPH- Neutral Protamine Hagedorn, PPG- Postprandial glucose

10.6 Algorithmic approach of initiating insulin therapy in individuals with type 2 diabetes

10.6.1 Introduction

Before the initiation of insulin therapy, a patient-centred or the ABCDE approach as discussed in Chapter 8 of this guideline has to be fully considered. This ensures that the right insulin type, regimen, dose, delivery device, and strategies for intensifying and optimising insulin doses are closely followed. Before initiating insulin therapy in individuals with type 2 diabetes, structured diabetes education and self-monitoring of blood glucose (SMBG) should be emphasised as integral components. This is because the choice of insulin type and dose will also be influenced by the FBG and PPG measurements as illustrated in Table 1 above.

10.6.2 Initiation of insulin therapy with a basal insulin

Figure 3 below summarises the algorithmic approach to initiating insulin therapy.

Most professional societies such as the EADSG, American Diabetes Association, American Association of Clinical Endocrinology, and the International Diabetes Federation recommend initiation of insulin therapy with a basal (long-acting) insulin (1, 11-13). Basal insulin regimens are important in suppressing hepatic glucose production in meals and during sleep, hence optimally controlling the FBG level (1). Examples of basal insulins that can be used include the long-acting insulin glargine, insulin detemir, and the intermediate-acting NPH insulin.

The recommended starting dose of basal insulin is 10 units/day or 0.1-0.2 units/kg/day administered subcutaneously at bedtime (10 or 11 pm). Increase the dose by 2-4 units once or twice weekly until you attain the target FBG level of <7 mmol/l (126 mg/dl) without episodes of nocturnal or early-

morning hypoglycaemia. However, in case the total administered basal insulin dose is >30 units/day or 0.5 units/kg/day (overbasalisation), then the insulin therapy approach has to be intensified and optimised (1).

10.6.3 Intensification and optimisation of insulin therapy after the initiation of basal insulin

In cases where the optimal FBG and HbA1c targets (as discussed in Chapter 8) are not met, a prandial short-acting or rapid-acting insulin can be added to the basal insulin regimen (basal-bolus regimen) or premixed insulin regimen introduced (1). The recommended step-by-step approaches are discussed below:

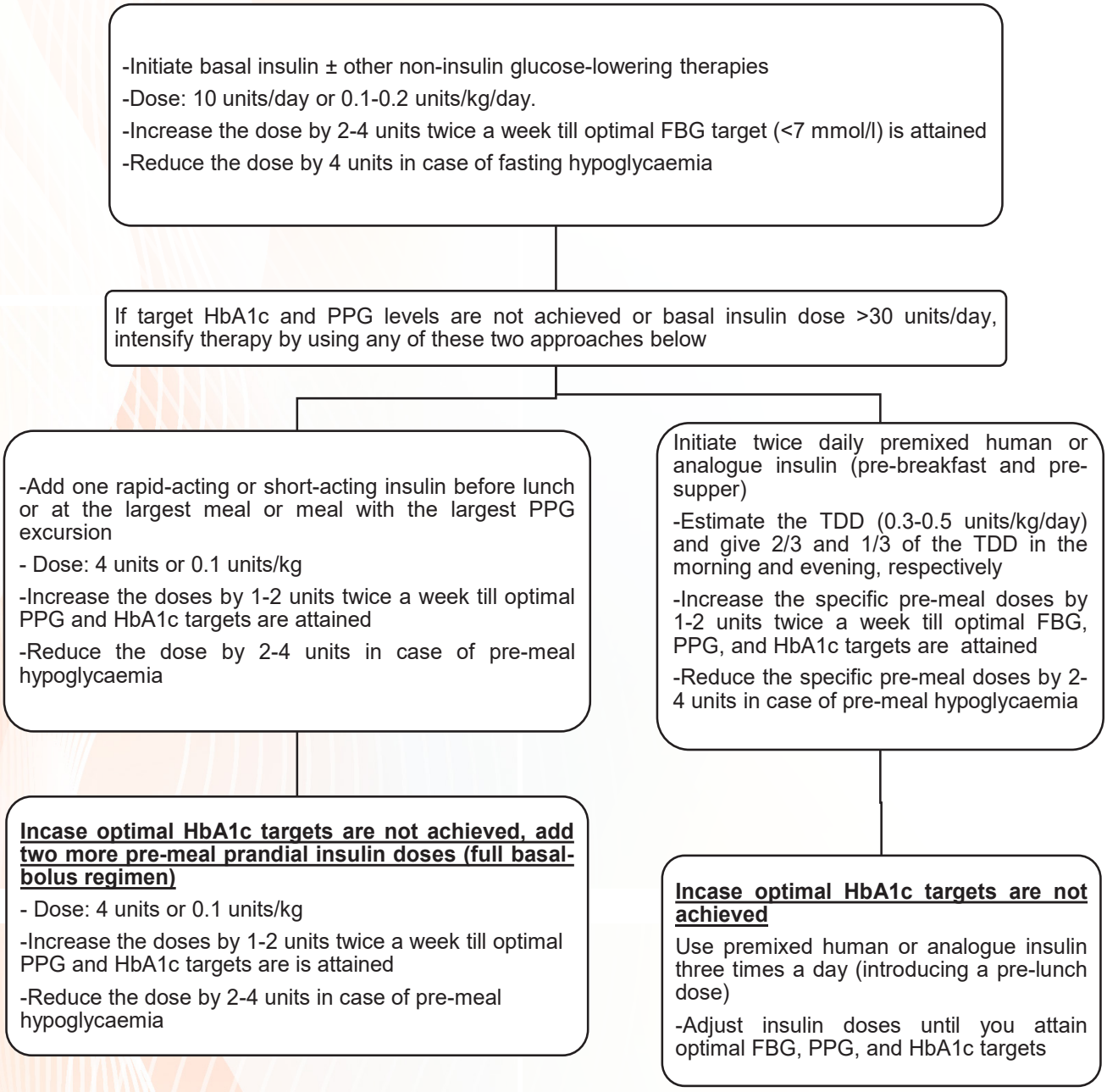
1. Introduce one short-acting or rapid-acting insulin before lunch, or at the largest meal, or meal with the greatest postprandial glucose excursion. The dose can be individualised. However, you can start with 4 units per day or 10% of basal insulin dose and increase the dose by 1-2 units once or twice weekly till you attain optimal FBG, PPG, and HbA1c levels. Reduce the insulin dose by 2-4 units or 10-20% in cases of episodes of hypoglycaemia.

2. If optimal HbA1c target is not achieved, introduce two additional postprandial insulin doses and proceed to a full basal-bolus regimen (three premeal or prandial insulin doses and one basal insulin dose). In this case, the calculated total insulin daily dose (TDD) is 0.3-0.5 units/kg/day. About 40-50% and 50-60% of the TDD should be allocated to the basal and prandial insulin dose, respectively.

3. In case the basal-bolus insulin dosing is not appropriate for the patient due to specific external factors such as irregular meal and work patterns and lack of motivation, consider a twice-daily premixed human or analogue insulin regimen. The TDD remains 0.3-0.5 units/kg/day, with 2/3 and 1/3 of the TDD being administered in the morning (pre-breakfast dose) and night (pre-supper dose). Increase the premeal doses by 1-2 units until the SMBG targets (FBG levels <7.0 mmol/l or 126 mg/dl and PPG levels <10.0 mmol/l or 180 mg/dl) are reached. In cases of episodes of hypoglycaemia, reduce the responsible premeal insulin dose by 2-4 units. If the optimal HbA1c targets are not met, then administer premixed insulin three times daily, adding the third dose before lunch.

However, in patients with type 2 diabetes who are poorly controlled on oral agents (HbA1c >9% or 75 mmol/mol), initiating premixed analogue insulin therapy is preferred and superior to basal analogue or premixed human insulins. In critically ill hospitalised patients with type 2 diabetes, a basal-bolus insulin regimen is preferred to premixed insulin (1). The use of a sliding scale in the management of hyperglycaemia in hospitalised individuals with type 2 diabetes is a very common practice in clinical settings in Uganda and should be generally avoided. This is because studies have shown that it is associated with poor inpatient glycaemic control and harmful effects such as glycaemic variability (25), hence increasing the risk of cardiovascular events.

Figure 3. Algorithmic approach of initiating insulin therapy in a patient with type 2 diabetes



10.6.4 Self-monitoring of blood glucose in patients on insulin therapy: how to monitoring and manage hyperglycaemia and hypoglycaemia

Initiating insulin therapy and modifying the insulin doses is important in attaining and maintaining optimal glycaemic control and averting insulin-related complications such as hypoglycaemia. Healthcare practitioners should also be fully familiar with the different aspects of insulin pharmacokinetics as summarised in Table 1 above. The frequency of SMBG in patients on insulin therapy is also discussed in Chapter 8.

Prandial and basal human or analogue insulins mainly control the PPG and FBG levels, respectively. Premixed human and analogue insulins control both PPG and FBG levels. This

should always be considered while selecting which insulin type to use.

Additionally, early morning (pre-breakfast) and late-night (2-4 am) blood glucose levels are determined by the administered pre-supper and bedtime prandial, premixed, and basal insulin dose. In individuals on prandial (meal-time) insulin, the pre-lunch and pre-supper blood glucose levels are determined by the pre-breakfast and pre-lunch insulin doses, respectively. For patients on premixed insulin only, the blood glucose levels throughout the day and pre-supper level are determined by the morning pre-breakfast insulin dose. These basics of insulin action should always be considered when adjusting insulin doses to attain the recommended glycaemic targets (1).

In cases of early-morning hypoglycaemia, the dose of the basal insulin has to be reduced by 2-4 units, while in cases of late-night hypoglycaemia, the doses of the pre-supper prandial or premixed insulin and the basal insulin dose should be reduced. In cases of pre-meal hypoglycaemia, reduce the previous premeal short-acting or rapid-acting prandial insulin.

In case of fasting hyperglycaemia, before increasing the pre-supper prandial, premixed, and basal insulin doses, first rule out episodes of late-night hypoglycaemia by encouraging the patient to measure his or her blood glucose levels at 2 or 3 am. Late-night episodes of hypoglycaemia are associated with fasting hyperglycaemia due to a surge in the levels of counter-regulatory hormones such as glucagon and cortisol in response to hypoglycaemia. This is called the Somogyi phenomenon (26). It is managed by reducing the pre-supper prandial or premixed insulin doses. In case no episode of late-night hypoglycaemia is reported, then increase the pre-supper and bedtime basal insulin doses. In cases of pre-meal hyperglycaemia, increase the previous premeal short-acting or rapid-acting prandial insulin. In case of evening or pre-supper hyperglycaemia in patients on premixed insulin, increase the morning or pre-breakfast insulin dose (1).

10.6.5 Use of insulin therapy in specific patient populations

10.6.5.1 Insulin therapy in elderly people

As discussed in Chapter 9 of this guideline, elderly people are at an increased risk of hypoglycaemia and have comorbidities that increase the risk of hypoglycaemia such as renal dysfunction. Because of this, analogue insulins with convenient dosing such as once a day are preferred to premixed or basal-bolus human insulin. Regular SMBG in this patient category should be encouraged (1).

10.6.5.2 Patients with renal and cardiac dysfunction

Chronic kidney disease is an independent risk factor for hypoglycaemia due to reduced renal gluconeogenesis and clearance of insulin and other glucose-lowering drugs, in addition to the presence of a blunted counter-regulatory response to hypoglycaemia (27). Studies such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) (28) and Veterans Affairs Diabetes Trial (VADT) (29) showed that hypoglycaemia is associated with increased cardiovascular events. Hypoglycaemia is associated with endothelial dysfunction (reducing vasodilatation), increased sympathoadrenal response (increasing rhythm abnormalities and haemodynamic changes), and an augmented pro-inflammatory and coagulant state (increased levels of C-reactive protein, vascular endothelial growth factor, and factor VII, with platelet activation) (30). Collectively, these events result in increased cardiovascular events such as myocardial infarction, angina, arrhythmias, and stroke.

Because of the above reasons, premixed or basal analogue insulins are preferred to human insulins in individuals with renal and cardiac dysfunction because of their better safety profile (associated with less hypoglycaemia and glycaemic variability) (1). However, the selection of the insulin analogue of choice and its dosing should be individualised.

10.6.5.3 Individuals with type 2 diabetes on insulin therapy during Ramadhan and other fasting periods

Individuals on insulin therapy who are clinically stable and wish to fast should receive comprehensive counselling about the associated risks, how to adjust the insulin doses and timing of administration, and the need for regular SMBG. Because of their superior safety profile when compared with human insulins, analogue insulins are preferred (basal or premixed). Closely following the healthcare professional's guidance, the insulin doses have to be reduced by 40-60% and administered at the breaking of the fast and early-morning meal. For individuals on prandial insulin, the pre-lunch insulin dose has to be omitted (1).

10.6.5.4 Individuals with type 2 diabetes preparing for surgery

Before any surgical procedure, ensure optimal glycaemic control to ensure good surgical outcomes (safe induction, maintenance, and reversal of anaesthesia, quick wound healing, etc.). The pre-operative HbA1c level should be <7% (53 mmol/mol) and the random blood glucose ranging between 4.4-10 mmol/l (79-180 mg/dl) (1).

The usual dose of insulin and oral hypoglycaemic agent should be administered on the day before the surgery and then the patient is allowed to fast overnight. The morning dose of insulin and oral hypoglycaemic agent has to be omitted on the day of surgery. Intra-operatively, start a continuous intravenous 5% dextrose glucose infusion with hourly blood glucose monitoring. Intravenous insulin therapy (preferably short-acting or rapid-acting insulin 0.1 units/kg) should be started if intraoperative blood glucose levels are >10 mmol/l (180 mg/dl) (1, 31).

Postoperatively, continue the 5% dextrose glucose infusion, along with both intravenous short-acting or rapid-acting prandial insulin administered every 6-8 hours and basal insulin administered once a day, accompanied by 6-8 hourly blood glucose monitoring. Restart subcutaneous insulin and/or oral hypoglycemic agents if the patient can tolerate oral feeding (1, 31).

10.6.6 Insulin storage, delivery devices, injection sites, and techniques

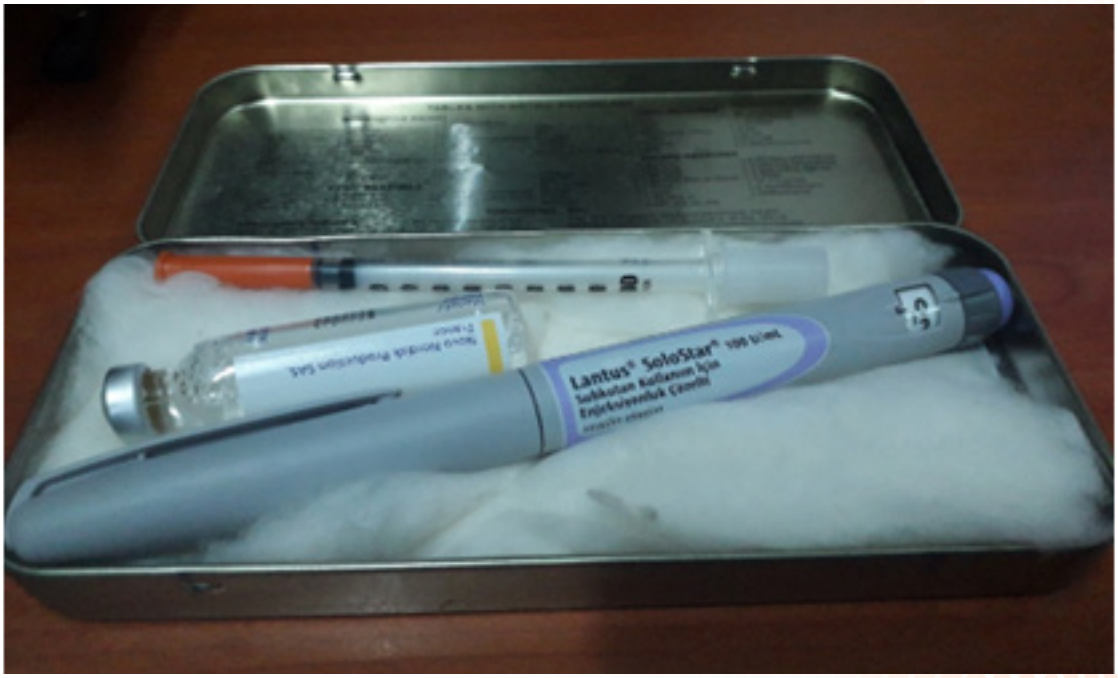
10.6.6.1 Recommendations for insulin storage

According to the manufacturer's guidelines, it is recommended to store insulin in a cool environment of temperatures <30°C, away from exposure to extremes of temperature. If stored at temperatures <30°C and <25°C, it can last 28 days and 45 days, respectively (1, 2).

A recent Cochrane review of 17 studies analysing the effects of storing human insulin above or below the manufacturer's recommended insulin temperature storage range and time, or both, showed that unopened short-acting and intermediate-acting human insulin vials and cartridges stored at 25°C and 37°C can be kept for a maximum of six months and two months, respectively, without losing its potency. Additionally, unopened short-acting, intermediate-acting, and premixed human insulin vials and cartridges stored at temperatures between 25°C and 37°C can remain viable without loss of potency for three months (32). This evidence is compelling and reassuring for individuals with diabetes, especially in low-resource settings where refrigerators and a constant supply of electricity are not readily available.

The practice of storage of insulin in water, on the floor, and/or on sand, as a cooling improvisation, is very common in Uganda, especially in rural areas. This should be discouraged because of the increased potential of contamination of insulin resulting in repeated injection abscesses. In the absence of a refrigerator, individuals on insulin therapy should be advised to store their insulin in a simple clean plastic container with dry cotton wool in a cool environment at room temperature (Figure 4) (1, 2).

Figure 4. Insulin storage in a clean mathematical set with dry cotton wool



Picture by Davis Kibirige

10.6.6.2 Optimal Insulin Delivery Devices

Regarding the optimal insulin delivery devices in clinical practice, insulin is commonly administered using syringes or prefilled insulin pens in Uganda. A very small number of individuals with type 1 diabetes are on continuous subcutaneous insulin infusion using insulin pumps. The choice of the delivery device to be used should be individualised, considering the issues of access, ease in insulin administration, and cost to the patient.

For individuals using insulin vials, the recommended insulin syringe for use in insulin administration is a U100 0.5 ml or 1 ml insulin syringe with a 6 mm needle length. Needle lengths that are more than 6 mm are too long and are associated with an increased risk of intramuscular injections, excruciating pain at the site of injection, and erratic blood glucose levels due to rapid absorption of the insulin when administered intramuscularly. For individuals using prefilled insulin pens, the recommended insulin pen needle length is 4 mm (especially for children, adolescents, and lean adult individuals). Prefilled insulin pen needle lengths of 5 mm can be considered for individuals who are overweight or obese (1, 2).

10.6.6.3 Recommended insulin injection sites and techniques

Figures 5 and 6 below illustrate the recommended insulin injection sites and techniques.

The recommended insulin injection sites are the abdomen, thigh, buttocks, and outer aspect of the arms. These sites should be rotated to avoid excessive pain and lipohypertrophy associated with injecting insulin in the same spot. It is advised that the insulin be injected perpendicularly with or without a gentle skin pinch to avoid intramuscular administration of insulin. The insulin syringe or prefilled insulin pen needle should ideally be changed daily (1, 2).

Figure 5. Recommended insulin injection sites

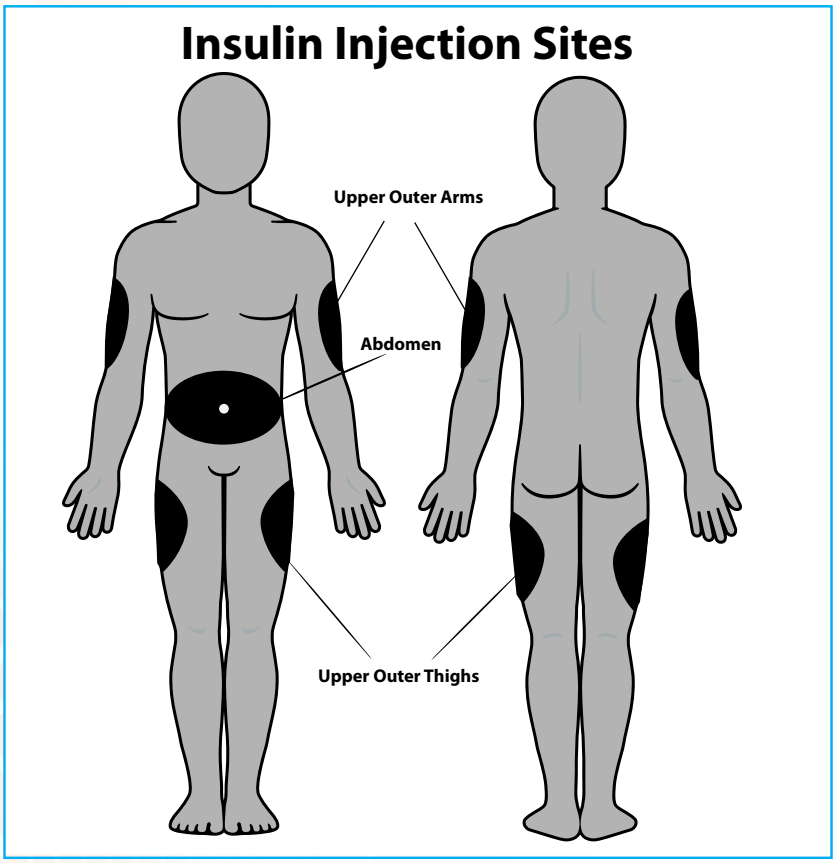
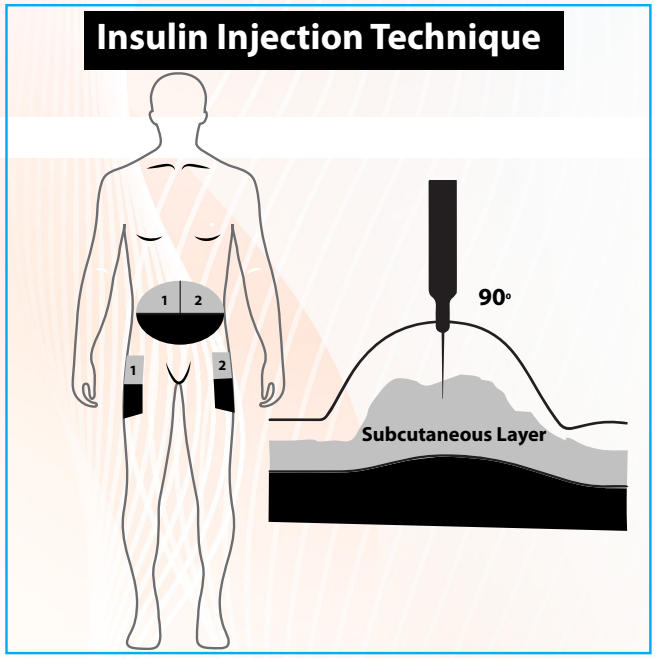
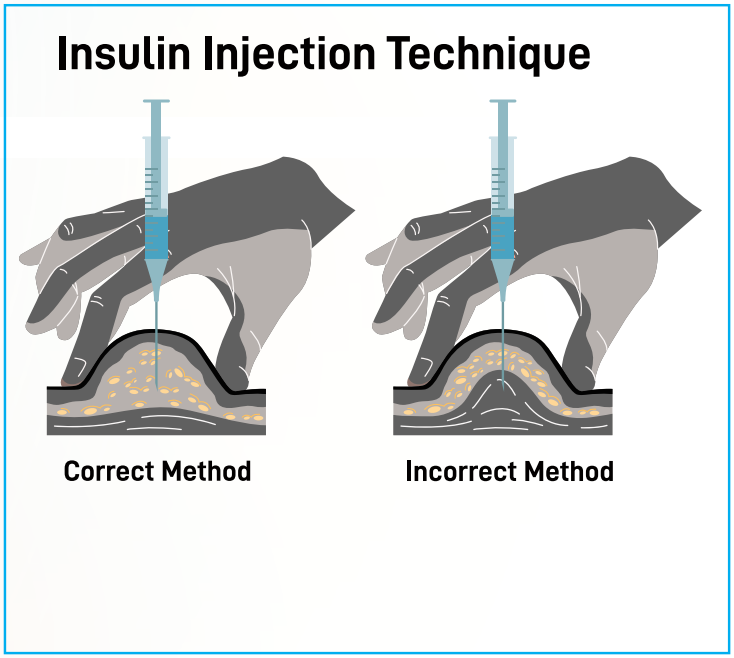


Figure 6. Recommended insulin injection technique





10.6.7 Side effects associated with insulin therapy and potential solutions

Insulin therapy, like any glucose-lowering therapy, is associated with some common side effects. These include:

1. Hypoglycaemia, which is the commonest and often occurs in cases of administration of inappropriately large insulin doses, low oral intake (either in critical illness or food insecurity), absence of SMBG, and presence of specific comorbidities such as renal dysfunction. This can be avoided by patient education (diet and insulin dose modification), regular SMBG, and the use of appropriate insulin regimens (analogue insulins preferably).
2. Weight gain is also common since insulin is a potent anabolic hormone. This can be avoided by regular physical activity and insulin dose adjustments.
3. Injection site complications such as injection site infections, abscesses, scaring, lipohypertrophy, and lipoatrophy are also common. These can be avoided by proper personal hygiene, insulin storage, and injection techniques (such as rotating injection sites and using the insulin syringes and needles for only one day).
4. Pain on insulin administration occurs especially with wrong injection techniques (diagonal, as opposed to perpendicular, administration of insulin), use of insulin syringes with a long needle length (>6 mm), and recycling of insulin syringes and prefilled insulin pen needles (>1 day of use). This can be avoided by regular patient education about optimal injection techniques and the appropriate use of insulin delivery devices.

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CHAPTER 11. CARDIOVASCULAR DISEASE RISK PROFILING AND MANAGEMENT

SUMMARY OF RECOMMENDATIONS

- Comprehensive screening of cardiovascular (CV) risk factors should be performed in people with type 2 diabetes at the time of diagnosis and then annually **(Level of evidence: A).**
- A multifactorial approach to optimally manage the existing CV risk factors, such as hyperglycaemia, hypertension, hyperlipidaemia, obesity, and albuminuria, is recommended in clinical practice **(Level of evidence: A).**
- Individuals with diabetes and hypertension should receive blood pressure (BP)-lowering therapy with individualised treatment targets. A BP goal <130/80 mmHg attained without complications is recommended **(Level of evidence: A).**
- Management of hypertension involves lifestyle modification (weight loss, an optimal diet, smoking cessation, and increased physical activity) and oral pharmacological therapy **(Level of evidence: A).**
- In the case of use of monotherapy (BP levels <150/90 mmHg), angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARBs) are recommended as the first-line BP-lowering therapy **(Level of evidence: A).**
- Combination BP-lowering therapy is recommended in individuals with diabetes and BP ≥150/90 mmHg **(Level of evidence: A).**
- The preferred combination of BP-lowering therapy in Black Africans with hypertension is ACEI or ARBs and calcium channel blocker combination **(Level of evidence: B).**
- Management of hyperlipidaemia involves lifestyle modification (weight loss, an optimal diet, and increased physical activity) and oral pharmacological lipid-lowering therapy **(Level of evidence: A).**
- Lipid profile assessment should be performed at the time of diagnosis or initial clinical encounter, 4-12 weeks after the initiation of therapy, and then annually **(Level of evidence: A).**
- For individuals aged 40-75 years with a high CV risk profile (≥1 CV risk factor), high-intensity statin therapy should be initiated to treat low-dense lipoprotein cholesterol level to the recommended target of <1.8 mmol/l (70 mg/dl) as primary prophylaxis against atherosclerotic cardiovascular disease (ASCVD) **(Level of evidence: A).**
- High-intensity statin therapy should also be initiated in individuals with type 2 diabetes and established ASCVD **(Level of evidence: A).**
- There is no compelling evidence to recommend routine statin therapy in individuals with type 2 diabetes and a low CV risk **(Level of evidence: C).**
- Low-dose oral antiplatelet therapy (cardiac aspirin or clopidogrel 75-150 mg per day) is indicated in individuals with type 2 diabetes and a history of ASCVD as secondary prophylaxis **(Level of evidence: A).**
- The use of low-dose oral antiplatelet therapy in the primary prophylaxis of ASCVD is not recommended due to a lack of compelling evidence of its effect in reducing all-cause or CV mortality **(Level of evidence: A).**

11.1 Introduction

Cardiovascular (CV) risk factors such as hypertension, overweight or obesity, dyslipidaemia, and albuminuria are common in patients with type 2 diabetes and increase the risk of atherosclerotic cardiovascular diseases (ASCVD) such as coronary heart disease, cerebrovascular disease, peripheral arterial disease, heart failure (regardless of ejection fraction), and atrial fibrillation (1, 2). A substantial proportion of patients with established ASCVD may have undiagnosed diabetes and prediabetes (3, 4).

Compelling evidence from clinical trials shows that combined optimal control of these CV risk factors has beneficial effects of reducing the burden of microvascular and macrovascular diabetes complications and CV-related mortality (5, 6). For this chapter of the guideline, we will discuss the multifactorial approach for controlling CV risk factors following the mnemonic – ABCD, i.e. A- Assessment of risk of ASCVD, A1c or glycaemic control, and Antiplatelet therapy, B- Blood pressure (BP) control, C- Cholesterol control and Cessation of smoking, and D- Diet and weight management (7). Approaches for diet and weight management and optimal management of hyperglycaemia have been comprehensively discussed in Chapters 5, 8, and 9 of this guideline. For this Chapter, we will mainly discuss the risk assessment for ASCVD, optimal management and control of BP and cholesterol levels, and the use of oral antiplatelet therapy in primary and secondary prevention of ASCVD.

11.2 Screening for cardiovascular risk factors in individuals with type 2 diabetes

Strategies for preventing and managing ASCVD and heart failure recommend comprehensive screening of CV risk factors in all individuals with type 2 diabetes at diagnosis or initial visit and then annually (8). The CV risk factors highly prevalent in individuals with type 2 diabetes include overweight or obesity, hypertension, atherogenic dyslipidaemia, albuminuria, smoking, family history of premature coronary heart disease, hyperuricaemia, and chronic kidney disease (1). The screening approaches for these CV risk factors have been discussed in Chapter 7.

11.3 Approaches for controlling blood pressure in individuals with type 2 diabetes

Hypertension is defined as an office systolic and diastolic BP ≥130 and ≥80 mmHg by the American Diabetes Association, American College of Cardiology, and American Heart Association (8, 9). The European Society of Hypertension, International Society of Hypertension, and European Society of Cardiology define hypertension as an office systolic and diastolic BP ≥140 and ≥90 mmHg (10, 11). Hypertension is a relatively common comorbidity in individuals with type 2 diabetes and increases the risk of microvascular and macrovascular diabetes complications (1). It is highly prevalent in adult Ugandans with type 2 diabetes and is often diagnosed late and suboptimally managed (12-14).

As part of the diabetes care package, measurement of BP should be routine at each clinic visit using a standardised approach. The patient is supposed to rest for a minimum of 5 minutes before the BP is measured on both arms using an appropriate cuff. Multiple abnormal BP readings, including home blood pressure measurements (HBPM) and readings or ambulatory blood pressure measurements (ABPM) taken over 24 hours, should be used as a basis for diagnosing hypertension. Both ABPM and HBPM typically provide BP estimates that are based on multiple measurements and provide a better method to predict long-term CVD outcomes than office BP (15, 16). Home-based self-monitoring of BP is more feasible than ABPM and should be encouraged in all individuals diagnosed with hypertension to help assess the effectiveness of BP-lowering therapy and to confirm white-coat hypertension (8).

11.3.1 Optimal targets for blood pressure

Just like glycaemic targets as discussed in Chapter 8, BP targets should also be individualised in certain patient populations such as the elderly, patients with orthostatic hypotension, and cognitive dysfunction. This is because complications associated with intensive BP control, such as hypotension, syncope, and acute kidney injury, occur with increased frequency in these patient groups (8).

Most professional societies, such as the American Diabetes Association, International Diabetes Federation, International Society of Hypertension, European Society of Hypertension, and European Society of Cardiology,

recommend optimal BP targets of <130/80 mmHg in all individuals with type 2 diabetes and hypertension (8, 10, 11, 17). Evidence from several clinical trials has shown that optimal reduction of BP reduces the risks of microvascular diabetes complications and CV-related events (18, 19).

11.3.2 Strategies for managing hypertension in individuals with type 2 diabetes

11.3.2.1 Lifestyle interventions

All individuals with type 2 diabetes and hypertension should be advised to use lifestyle interventions as an add-on to oral BP-lowering therapy as strategies for managing hypertension. Lifestyle interventions play a pivotal role in lowering BP and reducing overweight or obesity. These interventions, which have been discussed in detail in Chapter 5, include increased physical activity, cessation of smoking, and the use of a Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diet. (8, 11, 17).

11.3.2.2 Oral pharmacological approaches

All individuals with type 2 diabetes and hypertension should be initiated on BP-lowering drug classes with proven benefits of reducing CV events. The selection of the optimal BP-lowering therapies should also be individualised following a comprehensive patient profiling as discussed in Chapter 7. Factors such as the age of the patient and prevalent comorbidities or complications such as renal dysfunction, ASCVD, and heart failure (especially heart failure with reduced ejection fraction and mildly reduced ejection fraction) should be highly considered (8, 11).

All individuals with type 2 diabetes and hypertension (with or without established coronary heart disease and renal dysfunction) should be initiated on angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) as first-line BP-lowering oral agents. In individuals with a BP <150/90 mmHg, monotherapy with ACEI or ARBs such as captopril, ramipril, perindopril, losartan, and telmisartan is recommended. However, in individuals with BP ≥150/90 mmHg, BP-lowering combination therapy is recommended to achieve optimal BP control (8, 11).

The add-on therapy(ies) will also depend on the prevalent comorbidities. Generally, a fixed-dose single-pill combination of two or more blood pressure-lowering drugs is recommended instead of monotherapy, mainly to improve adherence and achieve early and optimal BP control (16, 20).

11.3.2.3 The ideal blood pressure-lowering combination therapy in Black Africans

The ideal oral BP-lowering combination therapy in Black Africans should be selected based on an in-depth understanding of the underlying pathophysiologic mechanisms of hypertension in this population. Compared with White populations of European ancestry, hypertension in Black Africans is mainly characterised by high salt sensitivity, reduced sympathetic activity, low plasma renin and nitric oxide levels, and high creatinine kinase levels (21-23). In a study by Mayito et al assessing the influence of angiotensin II and sympathetic activation in adult Ugandans with hypertension, serum angiotensin II, metanephrine, and normetanephrine were measured in 162 adult participants. High angiotensin II, metanephrine, and normetanephrine levels were noted in only 7%, 12%, and 3% of the participants, respectively (21). This confirmed earlier findings of low renin and sympathetic activation status in Black Africans with hypertension. These phenotypic differences between Black Africans and White populations of European ancestry explain why, if used as monotherapy, Black Africans respond better to calcium channel blockers (CCB) such as nifedipine, amlodipine, S-amlodipine, cilnidipine, and thiazide diuretics such as hydrochlorothiazide and indapamide observed in Black Africans compared with ARBs or ACEI and beta-blockers such as bisoprolol, carvedilol, nebivolol, and metoprolol (22, 24).

Because CCB and thiazide diuretic monotherapy are equally efficacious in

Black Africans with hypertension, the CREOLE (Comparison of Three Combination Therapies in Lowering Blood Pressure in Black Africans) trial evaluated what would be the most appropriate BP-lowering combination therapy in Black Africans. A total of 728 Black Africans recruited from six sub-Saharan African countries (Uganda, Nigeria, South Africa, Kenya, Cameroon, and Mozambique) were randomised to a CCB and ACEI arm (amlodipine and perindopril), CCB and thiazide diuretic arm (perindopril and hydrochlorothiazide), and CCB and thiazide diuretic arm (amlodipine and hydrochlorothiazide), and the effect of ambulatory BP-lowering was assessed across the three arms. Only 6% of the participants had co-existing diabetes (25).

After a 6-month follow-up period, compared with those on the perindopril-hydrochlorothiazide combination, the participants on amlodipine-hydrochlorothiazide and perindopril-amlodipine combinations had lower 24-hour ambulatory systolic BP. The between-group difference in the change of ambulatory systolic BP from baseline was −3.14 mm Hg; 95% confidence interval [CI], −5.90 to −0.38; P = 0.03; and −3.00 mm Hg; 95% CI, −5.8 to −0.20; P = 0.04, respectively. (25).

Similar to the CREOLE study, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial of 11,506 patients with hypertension and at high risk of CV events (about 60% having co-existing type 2 diabetes) demonstrated better lowering of the BP and fewer CV events such as CV-related mortality, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization with the benazepril-amlodipine (ACEI and CCB) combination compared with the benazepril–hydrochlorothiazide (ACEI and thiazide diuretic) combination in this study population (hazard ratio- 0.80, 95% confidence interval [CI] 0.72 - 0.90, p<0.001) (26). About 84% of the participants were White, with only 12% being of Black race (26).

The dual use of ACEI and ARBs in the management of hypertension is not recommended. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study, 25,620 participants (85% with ASCVD, 69% with hypertension, and 38% with type 2 diabetes) were randomised to receive 10 mg of ramipril per day, 80 mg of telmisartan per day, and both drugs (combination therapy), and followed up for a median period of 56 months. Compared with ramipril, the use of combination therapy was not associated with lower rates of CV-related mortality, myocardial infarction, stroke, or hospitalization for heart failure as a composite (relative risk- 0.99; 95% CI 0.92-1.07). The combination therapy arm was also associated with increased drug discontinuation due to increased hypotensive symptoms, syncope, diarrhea, and renal impairment when compared with the ramipril arm (27).

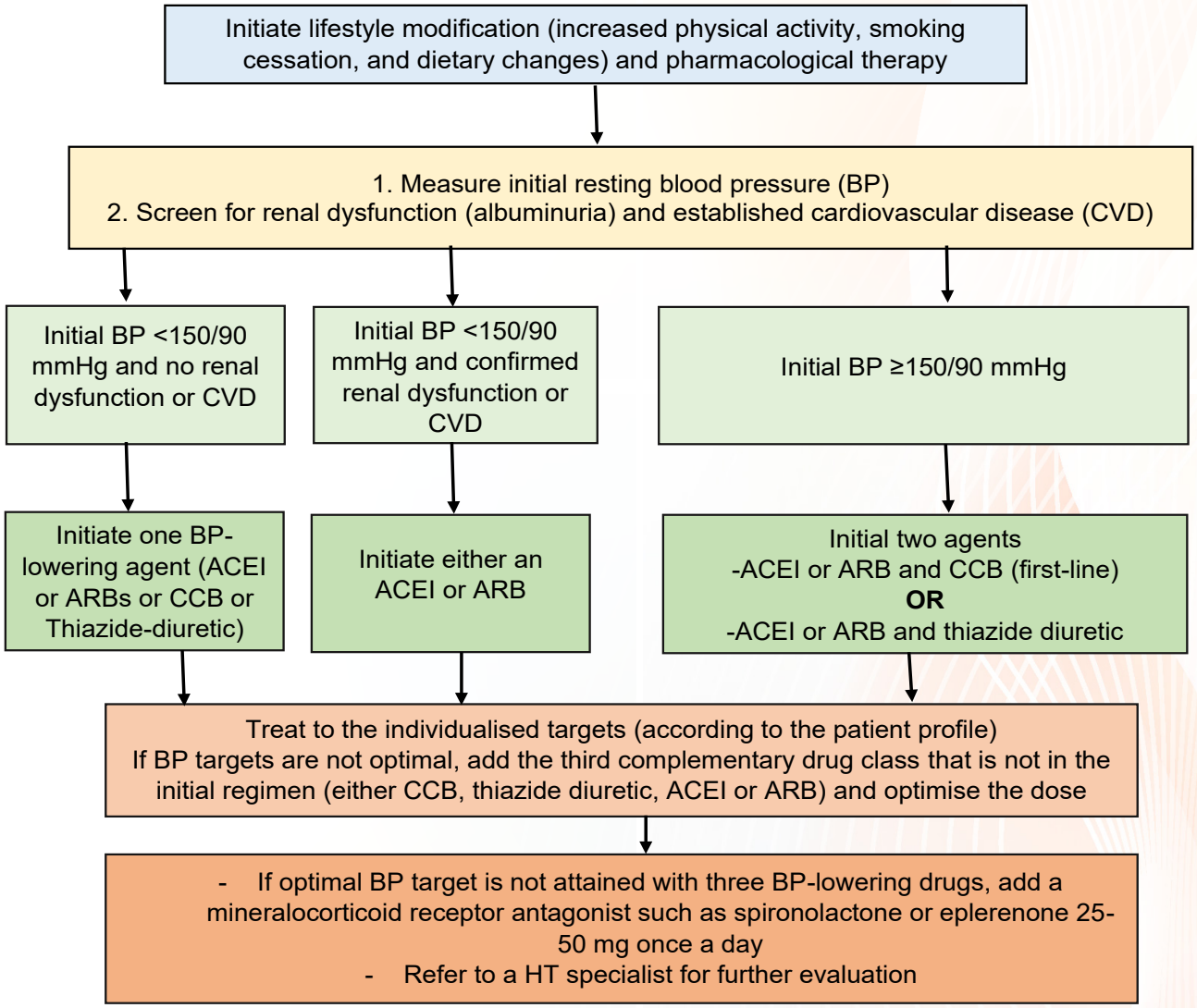
The understanding of the underlying pathophysiology of hypertension in Black Africans and evidence from the CREOLE study is compelling enough to recommend the use of a CCB and ACEI or ARB combination therapy as the first-line oral BP-lowering combination therapy in adult Africans with type 2 diabetes and BP ≥150/90 mmHg.

In cases of suboptimal control of BP, a mineralocorticoid receptor antagonist (MRA) such as eplerenone or spironolactone 25-50 mg once a day should be considered if blood pressure is still not controlled by the three-class combination (ARB/ACEI, thiazide diuretic, and CCB). However, using the ACEI/ARB-CCB-MRA combination carries a potential risk of acute kidney injury and hyperkalemia. This underscores the need for regular assessment of the patient's renal function and serum electrolyte levels (8).

Beta-blocker therapy as an add-on BP-lowering therapy is only indicated in patients with heart failure with reduced ejection fraction, atrial fibrillation, post-myocardial infarction, stable and unstable angina, and hyperthyroidism (8, 28).

Figure 1 below summarises the algorithmic approach to managing hypertension in individuals with type 2 diabetes.

Figure 1. Management of hypertension in individuals with type 2 diabetes



ACEI – Angiotensin converting enzyme inhibitor, ARB – Angiotensin II receptor blocker, CCB – Calcium channel blocker

11.6 Strategies for lipid management in individuals with type 2 diabetes

Atherogenic dyslipidaemia is characterised by increased serum levels of fasting and postprandial triglycerides (TGL), low-density lipoprotein cholesterol (LDLC), small-dense LDLC, apolipoprotein B, and low high-density lipoprotein cholesterol (HDLC) levels and is a common feature in individuals with type 2 diabetes (29, 30). Dyslipidaemia is highly prevalent in adult Ugandans with type 2 diabetes and is often suboptimally managed (31, 32). Because of its high prevalence, lipid profile screening (total cholesterol [TC], HDLC, LDLC, and TGL) at the time of diagnosis or initial contact, 4-12 weeks after the initiation of therapy, and annually should be routinely encouraged in all individuals with type 2 diabetes (8).

Lipid profile testing can be performed either in a fasting or non-fasting (random) state. Currently, most professional societies recommend non-fasting or random lipid profile testing as opposed to fasting lipid profile testing. This is because of its practicability, doesn't interfere with a patient's routine, and is time-saving. The utility of non-fasting or random lipid profile testing has also been demonstrated in large randomised clinical trials on statin therapy (33, 34).

11.6.1 Optimal lipid targets

Lipid targets should be individualised based

mainly on an individual's gender, CV risk stratification, and the presence of ASCVD. Lipid management in individuals with type 2 diabetes should be intensified to attain a target TC, TGL, and HDLC level of <5.0 mmol/l (200 mg/dl), 1.7 mmol/l (150 mg/dl), and >1.0 mmol/l (40 mg/dl) or >1.3 mmol/l (50 mg/dl) in males or females, respectively (8, 11). In individuals with and without established ASCVD or high CV risk, a target LDLC level of <1.8 mmol/l (70 mg/dl) and <2.6 mmol/l (100 mg/dl) is recommended, respectively (8, 11).

11.6.2 Approaches for lipid management in individuals with type 2 diabetes

Optimal lipid management in individuals with type 2 diabetes involves both lifestyle and oral pharmacological management. Lifestyle interventions such as increased physical activity and dietary modification are important in weight loss in overweight or obese people. Optimal glycaemic control also helps in the control of lipid levels, especially triglyceride levels (8, 11).

Among the lipid-lowering agents, statins such as atorvastatin, rosuvastatin, simvastatin, and pravastatin remain the first-line oral therapy to reduce LDLC levels (8, 11). This is due to their proven efficacy in preventing CV events and mortality in people with and without coronary heart disease (35-37). Statins act through a competitive and reversible inhibition of β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase, which is a rate-limiting step in cholesterol biosynthesis. The reduction in the cholesterol production within the hepatocytes results in the upregulation of LDLC receptor expression and an increase in the uptake of LDLC and LDLC precursors from the systemic circulation, in addition to inhibition of hepatic synthesis of apolipoprotein B and triglyceride-rich lipoproteins (30, 38).

LDL-C being the primary target of lipid-lowering therapies, high- and moderate-intensity statins reduce the LDLC levels by 40-60% (39). Because of this therapeutic effect, statin therapy should be initiated in all people with type 2 diabetes and an abnormal lipid profile test. The lipid profile should be reassessed after 4-12 weeks to assess drug response, guide dose adjustment, and then repeated annually (8, 11).

11.6.2.1 Statin therapy in primary and secondary prevention of cardiovascular diseases

For individuals aged 40-75 years with a high CV risk profile (≥1 CV risk factor), high-intensity statin therapy should be initiated to treat the LDLC level to the recommended target of <1.8 mmol/l (70 mg/dl) as primary prophylaxis against ASCVD (8, 11). High-intensity statin therapy should also be initiated in individuals with type 2 diabetes and established ASCVD (8, 11). Due to the lack of substantial evidence, no clear recommendations can be given for individuals with type 2 diabetes at low CV risk (11).

Examples of high-intensity statin doses are atorvastatin 40-80 mg and rosuvastatin 20-40 mg. Moderate-intensity statin doses are atorvastatin 10-20 mg and rosuvastatin 5-10 mg.

11.6.2.2 Side effects associated with statin therapy

Statins are relatively safe and well tolerated by most patients. Commonly reported adverse events include myalgias, myopathy, drug-induced hepatitis, and rhabdomyolysis. These are relatively rare. This statin intolerance is a class effect of statins. The severe forms of statin-induced myopathy and rhabdomyolysis are usually precipitated by co-administration with fibrates and the inhibitors and inducers of hepatic microsomal enzymes (cytochrome P450) such as cyclosporine A, azole antifungals, niacin, protease inhibitors, macrolide antibiotics, calcium channel blockers, and warfarin. The presence of comorbidities such as renal dysfunction and hypothyroidism can also precipitate these adverse events (40, 41).

11.6.2.3 Management of statin intolerance

In cases of statin intolerance, healthcare professionals should rule out other extraneous factors that may increase the risk of myopathy, rhabdomyolysis, or acute hepatitis. It is important to switch therapy from a mild lipophilic statin such as simvastatin, fluvastatin, pitavastatin, lovastatin, and atorvastatin to a high lipophilic statin such as rosuvastatin and pravastatin. The statin dosing can be changed from daily dosing

to alternate day or twice weekly dosing, in addition to using a lower dose of a more potent statin. A switch from a statin to non-statin lipid-lowering drugs such as an intestinal cholesterol absorption inhibitor (ezetimibe), a bile acid sequestrant (colesevelam), or bempedoic acid in combination with ezetimibe can be considered (42, 43).

11.6.2.4 Non-statin lipid-lowering drugs

In the Ugandan context and from clinical observation, fibric acid derivatives or fibrates such as fenofibrate are the second most commonly used oral lipid-lowering agents after statins and are mainly indicated in the management of severe hypertriglyceridaemia (serum triglycerides ≥5 mmol/l or 500 mg/dl) (8, 11). They are also associated with a moderate decrease in LDLC levels and an increase in HDLC levels. Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily called peroxisome proliferator-activated receptors (PPARs), resulting in a reduction in hepatic apoC-III production and an increase in lipoprotein lipase-mediated lipolysis. Additionally, they stimulate cellular fatty acid uptake, conversion to acyl-CoA derivatives, and catabolism by the beta-oxidation pathways, which, combined with a reduction in fatty acid and triglyceride synthesis, results in a decrease in very LDLC (VLDLC) production (44).

The management of severe hypertriglyceridaemia is important because it reduces the risk of the onset of acute pancreatitis and CV events. In addition to fibrates, fish oils such as Omega-3 fatty acids, obesity management through lifestyle intervention, and optimal glycaemic control can also be used in the management of severe hypertriglyceridaemia. In cases of mild to moderate increase in serum triglyceride levels, moderate- to high-intensity statin therapy can be used plus lifestyle modification because they lower serum triglyceride levels by 10-30% (45, 46).

Ezetimibe is another non-statin lipid-lowering drug that is available in Uganda. It possesses potent LDLC-lowering effects and acts by inhibiting cholesterol absorption in the ileum by targeting a sterol transporter called Niemann-Pick C1-Like 1 (NPC1L1; SLC65A2), which is localized at the brush border cells of the small intestine (47, 48).

The use of ezetimibe and a statin is recommended in individuals with diabetes and a recent acute coronary syndrome when the optimal LDLC target (<1.4 mmol/l or 55 mg/dl) is not attained with statin monotherapy (11). This recommendation is based on the findings of the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study that reported a significant 6% reduction in major adverse cardiovascular events (composite of CV death, non-fatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization ≥30 days after randomization, or non-fatal stroke) in patients post-acute coronary syndrome receiving simvastatin and ezetimibe combination therapy (hazard ratio or HR 0.94; 95% CI 0.89–0.99, p=0.016) (49). On subgroup analysis, this protective benefit was noted to be greater in individuals with diabetes (HR 0.85; 95% CI 0.78–0.94; p<0.001) (50).

11.7 Oral antiplatelet therapy in individuals with type 2 diabetes

At a cellular level, type 2 diabetes, especially in the setting of insulin resistance, is associated with a pro-inflammatory and coagulant state, endothelial dysfunction with reduced vascular nitric oxide, and a hypofibrinolytic state. These result in platelet activation and thrombin generation, and eventually atherosclerosis and thrombosis (51, 52). Because of this, oral antiplatelet and anticoagulant therapy play an important role in diabetes care.

Oral antiplatelet therapy is effective in reducing CV morbidity and mortality in high-risk individuals with a previous history of myocardial infarction and/or stroke in several studies (53). Because of this beneficial effect, low-dose oral antiplatelet therapy (cardiac aspirin or clopidogrel 75-150 mg per day) is indicated in individuals with type 2 diabetes and a history of ASCVD as secondary prophylaxis (8, 11). Regarding primary prophylaxis of ASCVD, there is a lack of compelling evidence of its effect in reducing all-cause or CV mortality (54, 55). Because of this, its use in the primary prophylaxis of ASCVD is not recommended (8, 11).

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CHAPTER 12. MANAGEMENT OF ACUTE DIABETES COMPLICATIONS

SUMMARY OF RECOMMENDATIONS

- Hypoglycaemia is confirmed by documentation of Whipple's triad (the presence of signs and symptoms of hypoglycaemia, confirmed low blood glucose concentration, and resolution of the signs and symptoms after correcting the low blood glucose concentration) **(Level of evidence: A).**
- Assessment of hypoglycaemia risk in individuals with diabetes should be performed at every clinical visit in routine care, and individuals at a high risk of hypoglycaemia should have individualised, less stringent glycaemic targets and be initiated on glucose-lowering drugs with a low associated risk of hypoglycaemia **(Level of evidence: A).**
- Episodes of hypoglycaemia should be promptly and swiftly treated with fast-acting carbohydrates, preferably pure glucose powder **(Level of evidence: A).**
- Hyperosmolar hyperglycaemic state (HHS) is characterised by severe dehydration, marked hypovolemia, elevated serum osmolarity, and hyperglycaemia, without significant ketonemia and acidosis **(Level of evidence: A).**
- The management of HHS aims to normalise the serum osmolarity and glycaemia, correct the fluid deficit and electrolyte imbalances, and prevent arterial or venous thromboembolism and other complications **(Level of evidence: B).**
- Intravenous fluid therapy using crystalloids is the initial step of management of HHS **(Level of evidence: A).**
- In the management of HHS, potassium replacement should be dependent on the measured serum potassium levels **(Level of evidence: A).**
- Insulin therapy should be administered as a fixed-rate insulin infusion or intravenous bolus administration of short-acting insulin, and preferably started after adequate fluid replacement **(Level of evidence: B).**
- Diabetic ketoacidosis (DKA) is characterised by a triad of hyperglycaemia (blood glucose >11.0 mmol/l or 200 mg/dl), significant ketonemia or ketonuria (serum ketone concentrations >3.0 mmol/l or >2+ ketones on urine dipsticks), and acidosis (serum bicarbonate concentration of <15 mmol/l and/or venous pH <7.3) **(Level of evidence: A).**
- Euglycemic DKA, which is characterised by the presence of normal or near normal serum glucose, has been described, particularly in patients with poor oral intake, treatment with insulin before arrival in the emergency department, in pregnant women, and with sodium-glucose co-transporter 2 (SGLT2) inhibitors **(Level of evidence: B).**
- The management of DKA is aimed at restoring normal circulatory blood volume, preventing and/or correcting prevalent electrolyte imbalances, and correcting acidosis and hyperglycaemia **(Level of evidence: B).**
- Intravenous fluid administration, preferably with crystalloids, is the first-line step in managing DKA, followed by intravenous insulin therapy administered as a fixed infusion or bolus of short-acting or regular insulin with hourly blood glucose monitoring **(Level of evidence: B).**
- Potassium replacement therapy in the management of DKA should be performed based on the serum potassium concentrations and co-existing comorbidities (notably renal dysfunction) **(Level of evidence: A)**.
- Intravenous phosphate replacement therapy is indicated only in cases of low serum phosphate concentrations (<0.3 mmol/l or <1.0 mg/dl) and the presence of respiratory and skeletal muscle weakness with anaemia **(Level of evidence: C).**
- Treatment with intravenous bicarbonate is not routinely recommended in the management of DKA **(Level of evidence: C).**

12.1 Introduction

For this section of the guideline, we will discuss the three acute diabetes complications commonly encountered in clinical practice. These are hypoglycaemia, diabetic ketoacidosis (DKA), and hyperosmolar hyperglycaemic state (HHS). Both DKA and HHS constitute the hyperglycaemic crises.

12.1.1 Hypoglycaemia: definition and physiological response to a hypoglycaemic episode

Hypoglycaemia is a common acute complication in the management of individuals with type 1 and type 2 diabetes (1, 2). Hypoglycaemia is confirmed by the presence of signs and symptoms of hypoglycaemia, low measured blood glucose concentration, and resolution of the signs and symptoms after the correction of the low blood glucose concentration. This is called Whipple's triad (3).

Hypoglycaemia is defined based on three levels. Level 1 hypoglycaemia is defined as a measured blood glucose concentration of <3.9 mmol/l (<70 mg/dl), but ≥ 3.0 mmol/l (≥54 mg/dl). At this level, there is activation of neuroendocrine mechanisms in response to the reduced blood glucose concentrations in individuals without diabetes. Level 2 hypoglycaemia is a measured blood glucose concentration of <3.0 mmol/l (<54 mg/dl). This level is associated with an increased risk of neurocognitive dysfunction and cardiovascular-related mortality. Level 3 hypoglycaemia is a severe life-threatening event characterised by altered mental and physical status requiring assistance (1, 2, 4).

Signs and symptoms of hypoglycaemia are either neuroglycopenic (due to the brain's deprivation of glucose) or neurogenic (due to the activation of the sympathoadrenal system). The neuroglycopenic signs and symptoms include behavioural changes, fatigue, confusion, irritability, seizures, and loss of consciousness, while the neurogenic signs and symptoms include palpitations, tremors, anxiety, profuse sweating, hunger, and paraesthesia (1-4).

Physiologically, glucose counter-regulatory mechanisms in healthy individuals are sufficient in preventing or rapidly correcting hypoglycaemic episodes. These include 1) a reduction in the endogenous secretion of insulin by the pancreatic beta-cells once the blood glucose concentrations decline below the normal physiological range; 2) An increase in glucagon and epinephrine secretion by the pancreatic alpha-cells and adrenal medulla, respectively; 3) A surge in cortisol and growth hormone secretion in cases of prolonged hypoglycaemia. If these defenses fail to correct the hypoglycaemic episode, the blood glucose levels continue to decline (3).

In most individuals with type 1 and type 2 diabetes, the above neurohumoral counter-regulatory responses to hypoglycaemia are impaired. Hypoglycaemia unawareness is a common feature, especially in the elderly and individuals with long-standing diabetes. Because of this, a measured blood glucose concentration of <3.9 mmol/l is clinically significant, regardless of existing signs and symptoms (4).

12.1.2 Hypoglycaemia risk assessment: Identification of high-risk individuals

The assessment of hypoglycaemia risk in individuals with diabetes should be performed at every clinical visit in routine care. This should include several aspects such as the frequency of the hypoglycaemic episode (in a day, week, or month), the timing of the hypoglycaemic episode (daytime, nocturnal, pre- or post-meal), the severity of the hypoglycaemic episode, the potential causes of the hypoglycaemic episode, the signs and symptoms that were present, and how the hypoglycaemic episode was managed (4, 5).

In risk profiling, individuals with the characteristics below should be considered to be at a high risk of hypoglycaemia:

1. Individuals on glucose-lowering therapies associated with hypoglycaemia, such as insulin (especially human insulins) and sulfonylureas (especially glibenclamide).
2. Individuals with kidney and liver dysfunction.
3. Elderly individuals
4. Preschool-age children
5. Individuals with a history of severe hypoglycaemia.
6. Individuals with a history of cognitive impairment or intellectual disability

that impairs swift response to a hypoglycaemic episode.
7. Individuals with hypoglycaemia unawareness.
8. Individuals with long-standing type 1 and type 2 diabetes.
9. Individuals with irregular eating schedules.
10. Individuals with co-existing untreated pituitary, adrenal, and thyroid insufficiency (especially individuals with type 1 diabetes and co-existing autoimmune polyglandular syndromes).
11. Individuals with psychiatric disorders.
12. Individuals with insulinoma.

Therefore, in these individuals, an individualised approach in the selection of their glucose-lowering therapies and glycaemic targets should be considered at the initial clinical visit to reduce the frequency and severity of the hypoglycaemic episodes (4, 5). This individualised approach has already been discussed in detail in Chapters 8,9, and 10 of this guideline. Drugs associated with a low risk of hypoglycaemia, such as dipeptidyl peptidase IV (DPP-IV) inhibitors, sodium-glucose cotransporters-2 (SGLT2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RA), thiazolidinediones, and analogue insulins, are preferred in individuals at a high risk of hypoglycaemia. Sulfonylureas (except for gliclazide, which has a low risk of hypoglycaemia) and human insulins are associated with a higher risk of hypoglycaemia and should be used with caution (5-8).

12.1.3 Management of hypoglycaemia

An episode of hypoglycaemia should be promptly managed by consuming any readily available fast-acting carbohydrate. If available, pure glucose powder is the preferred oral treatment. Intravenous glucose infusions, such as 50% or 5% dextrose solutions, can be used. Subcutaneous administration of glucagon is recommended in individuals who are unable to take it orally (4, 5). However, this drug is not readily available in Uganda.

12.1.4 Prevention of hypoglycaemia

Structured patient education offered at each clinic visit is pivotal in preventing hypoglycaemic episodes in individuals with diabetes. Healthcare professionals should teach patients what hypoglycaemia is, how to recognise it, situations that can provoke a hypoglycaemic episode such as fasting, physical activity, and skipping or delaying meals, and how to manage and avoid a hypoglycaemic episode (such as ingestion of a fast-acting carbohydrate, bedtime snacking, and dose adjustment). Consistent self-monitoring of blood glucose should be emphasised in individuals at high risk of hypoglycaemia (4, 5).

Healthcare professionals should also remember potential drug-drug interactions that can precipitate hypoglycaemic episodes, such as insulin and sulfonylurea interactions with fluoroquinolones, macrolides, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole (4).

HYPERGLYCAEMIC CRISES

12.2.1 Diabetic ketoacidosis: definition and precipitating factors

Diabetic ketoacidosis (DKA) is the commonest hyperglycaemic emergency observed in individuals with type 1 and type 2 diabetes in clinical practice. It develops due to an absolute or relative insulin deficiency with a concomitant increase in the circulating concentrations of the counter-regulatory hormones such as glucagon and epinephrine. This results in the triad that characterises DKA, i.e. hyperglycaemia (blood glucose >11.0 mmol/l or 200 mg/dl), significant ketonemia or ketonuria (serum ketone concentrations >3.0 mmol/l or >2+ ketones on urine dipsticks), and acidosis (serum bicarbonate concentration of <15 mmol/l and/or venous pH <7.3) (9-12).

It is important to note that DKA also occurs in individuals with newly diagnosed or long-standing type 2 diabetes. In the Uganda Diabetes Phenotype (UDIP) study that characterised diabetes in adult Ugandans with newly diagnosed diabetes, serum or urine ketosis was reported in ~31% of the 500 participants with confirmed islet-autoantibody negative type 2 diabetes. The frequency of serum or urine ketosis was higher in participants with a non-obese phenotype (body mass index or BMI <25 kg/

m2) compared with those with an overweight or obese phenotype (BMI ≥25 kg/m2) (39.1% vs 25.5%, p=0.02, respectively) (13).
DKA has also been described to occur commonly in individuals with an atypical diabetes subtype called ketosis-prone diabetes (KPD). This diabetes subtype, which is discussed in detail in Chapter 2 of this guideline, is characterised by severe hyperglycaemia, ketosis, insulin independence after the correction of the initial acute hyperglycaemic episode, and diabetes remission in most patients (14, 15).
The commonly identified precipitating factors for DKA include infections (mainly respiratory, urinary, and skin infections), intercurrent illnesses, poor adherence, dosing, and non-compliance to glucose-lowering therapies, pancreatitis (mainly due to alcohol ingestion or gallstones), and cardio or cerebrovascular events such as myocardial infarction and stroke (9-12). A distinct form of DKA called euglycaemic DKA has also been described in chronic alcoholic consumption, pregnancy, and individuals with type 2 diabetes on SGLT2 inhibitors and concomitant use of insulin therapy. This type of DKA is characterised by the presence of ketosis and acidosis in the presence of normal or near-normal blood glucose levels (blood glucose levels <11.0 mmol/l or 200 mg/dl) (16-18).

12.2.2 Pathophysiology of diabetic ketoacidosis

Absolute or relative insulin deficiency is associated with an increase in the circulating concentrations of counter-regulatory hormones such as glucagon, cortisol, growth hormone, and catecholamines. These lead to increased hepatic glucose production (glycogenolysis and gluconeogenesis), impaired peripheral uptake and utilisation of glucose, and increased protein catabolism from muscle. Additionally, the hormone-sensitive lipase in the adipose tissue is activated, resulting in an increase in lipolysis of the endogenous triglycerides and the release of large quantities of free fatty acids (FFA) and glycerol into the circulation. The FFA undergoes oxidation in the liver to three main ketone bodies, i.e., acetone, acetoacetate, and beta-hydroxybutyrate, with eventual ketosis and acidosis. The latter results in a reduction in serum bicarbonate concentrations and a high anion gap metabolic acidosis (9, 10).
Metabolically, DKA, similar to hyperosmolar hyperglycaemic state (HHS), is characterised by osmotic diuresis due to severe hyperglycaemia and ketoacidosis, leading to severe hypovolemia and a further increase in the circulating concentrations of the counter-regulatory hormones and worsening of acute kidney injury. Electrolyte imbalances, mainly hyperkalemia (due to insulin deficiency and volume losses with increased aldosterone secretion) and a pro-inflammatory and coagulation state (increased levels of pro-inflammatory cytokines and markers of thrombosis) are also characteristic of DKA (9, 10).

12.2.3 Presentation and initial workup of diabetic ketoacidosis

Unlike HHS, DKA presents acutely with a short history of the presence of the classical symptoms of hyperglycaemia, such as polyuria, polydipsia, marked weight loss, weakness, and nonspecific gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea. Clinically, patients present with features of profound volume depletion (hypotension-systolic blood pressure <100 mmHg, tachycardia-heart rate >100 beats/minute, and dry mucous membranes), altered mental state, and the classical Kussmaul's breathing (deep and labored breathing) due to metabolic acidosis (9-12).
The initial workup of a patient presenting with DKA should include focused tests aimed at identifying any underlying precipitating factor. These include blood glucose and ketone measurement (to confirm the diagnosis of DKA), urinalysis (to confirm urine ketosis and screen for urinary tract infection as a trigger), renal function tests (serum urea and creatinine concentrations with an estimated glomerular filtration rate), serum electrolytes (sodium, potassium, and phosphate [if available]), a complete blood count, a pregnancy test (in females if amenorrhoeic), a chest X-ray, and electrocardiography (if indicated to screen for a respiratory tract infection or cardiac

condition, respectively, as precipitating factors).

12.2.4 Management of diabetic ketoacidosis

Broadly, the goals of the management of DKA include the restoration of normal circulatory blood volume, the prevention and/or correction of prevalent electrolyte imbalances, the correction of acidosis and hyperglycaemia, and addressing the underlying cause (9-12).

12.2.4.1 Intravenous fluid therapy

Intravenous fluid administration is the first line of management of DKA. It aims to restore the intravascular volume and peripheral tissue perfusion, in addition to reducing blood glucose, metabolic acidosis, and the pro-inflammatory state. This further improves the peripheral insulin sensitivity (9-12).

Crystalloids are preferred to colloids as the fluids of choice (19). On average, a patient presenting with DKA has a fluid deficit of ~100 ml/kg body weight. The general guidance is to replace 50% of the fluid deficit in the first 12 hours after presentation and the remaining over the next 12-16 hours. However, the rate of fluid replacement can be adjusted in the presence of renal or cardiac comorbidities and features of fluid overload. The ideal i.v fluid to use in the initial fluid replacement is 0.9% sodium chloride solution (normal saline), and about 1 litre should be administered within the first hour. After the initial hour, 250-500 ml of i.v normal saline per hour can be administered in adults without the presence of renal or cardiac comorbidities and features of fluid overload (9-12).

Because blood glucose levels reduce faster before the resolution of ketoacidosis, a 5-10% glucose (dextrose) infusion should be introduced once the blood glucose concentrations are <14 mmol/l (250 mg/dl) to prevent hypoglycaemia and disequilibrium syndrome (cerebral oedema). This also allows the continuous use of insulin until ketonemia resolves. As explained above in the section on HHS, severe hyperglycaemia is associated with a reduction in serum sodium concentrations. This underscores the need to correct the serum sodium concentration according to the circulating blood glucose concentrations. In patients with DKA and corrected hypernatremia, 0.45% sodium chloride solution is preferred as the fluid of choice (9-12).

12.2.4.2 Insulin therapy

Individuals presenting with DKA should be managed with i.v insulin (administered using an infusion or bolus) until the DKA resolves and the patient can eat and drink normally. At this stage, the route of insulin administration can be switched from i.v.. to subcutaneous. Continuous i.v infusion or boluses of short-acting or regular insulin administered at a rate of 0.1 units/kg/hour are recommended, and capillary blood glucose concentrations should be monitored on an hourly basis. Insulin therapy should be started after adequate rehydration (preferably after the initial litre of fluids) and correction of any hypokaelemia. It helps reduce blood glucose concentrations, suppress ketogenesis, and correct electrolyte abnormalities (mainly hyperkalemia) (9-12).

Once the blood glucose concentrations reduce to <14 mmol/l (250 mg/dl), a 5-10% glucose (dextrose) infusion can be used to replace the 0.9% or 0.45% sodium chloride solution, and the rate of insulin infusion or bolus administration reduced to 0.05 units/kg/hour. This prevents the onset of hypoglycaemia and dysequilibrium syndrome (cerebral oedema) (9-12).

Once biochemical resolution of DKA is achieved (blood glucose concentrations <14 mmol/l or 250 mg/dl, pH >7.3, serum bicarbonate and ketone levels are >18 mmol/l and <1 mmol/l, respectively) and a patient can eat and drink, subcutaneous insulin therapy can be started using premixed or basal-bolus insulin. In hospitalised patients, a basal-bolus insulin regimen (three prandial or pre-meal short-acting or rapid-acting insulin and basal long-acting insulin) is preferred to the premixed insulin regimen because it is associated with lower rates of in-hospital hypoglycaemia. The appropriate dosing of each insulin type should be based on a total daily insulin dose requirement of 0.5 units/kg/day (9-12). The approach of insulin dosing in individuals with type

2 diabetes has been explained in detail in Chapter 10 of this guideline.

12.2.4.3 Potassium replacement therapy

Individuals with DKA often present with potassium abnormalities that develop due to gastrointestinal loss (vomiting and diarrhea) and insulin therapy (stimulates extracellular to intracellular potassium influx). These abnormalities in potassium concentrations are associated with paralytic ileus, marked muscle weakness, cardiac arrhythmia, and increased cardiovascular-related mortality (20).

Potassium replacement therapy should be based on serum potassium concentrations and co-existing comorbidities (notably renal dysfunction). Potassium chloride solution is the treatment of choice and should be administered as below:

- Potassium levels ≥5.5 mmol/l: No supplemental potassium is needed.
- Potassium levels 4.0-5.5 mmol/l: 20 mmol/l of i.v. Potassium chloride in each litre of replacement fluid.
- Potassium levels 3.5-4.0 mmol/l: 40 mmol/l of i.v. Potassium chloride in each litre of replacement fluid.
- Potassium levels <3.5 mmol/l: 40 mmol/l of i.v. Potassium chloride in each litre of replacement fluid, and do not initiate insulin therapy until serum potassium levels have normalised.

It is advised that patients on i.v potassium replacement therapy should undergo continuous cardiac monitoring and the serum potassium concentrations measured daily to guide replacement therapy (9-12).

12.2.4.4 Phosphate replacement therapy

Individuals with DKA usually have total body phosphate deficits at presentation or during therapy. However, routine phosphate replacement is not encouraged. However, in cases of low serum phosphate concentrations (<0.3 mmol/l or <1.0 mg/dl) and the patient has respiratory and skeletal muscle weakness with anaemia, 20-30 mmol/l of i.v. Phosphate replacement therapy is indicated. Hypophosphataemia is associated with complications such as rhabdomyolysis, respiratory failure, renal failure, arrhythmias, and haemolytic anaemia (9-12).

12.2.4.5 Bicarbonate replacement therapy

Treatment with intravenous bicarbonate is not routinely recommended in the management of DKA. It has been shown to increase the risk of hypokalaemia, slow the resolution of ketosis, cause paradoxical increases in cerebral acidaemia due to an increase in tissue partial pressure of carbon dioxide, and increase the risk of cerebral injury (9-12). Usually, adequate fluid replacement and initiation of insulin therapy are sufficient to correct the acidosis.

12.2.5 Complications associated with diabetic ketoacidosis

Individuals with DKA may present or develop several complications. The commonly encountered complications in clinical practice include electrolyte imbalances (hypernatremia, hypokaelemia, and hyperkaelemia), hypoglycaemia (due to aggressive correction of hyperglycaemia), dysequilibrium syndrome or cerebral oedema (also due to aggressive correction of hyperglycaemia and should be urgently managed using i.v mannitol), acute kidney injury, arterial or venous thromboembolism (due to the hypercoagulable state), and gastrointestinal bleeding (Cushing's or stress ulcers). Some of the rare complications include cardiac arrhythmias due to electrolyte derangements, intestinal necrosis, pulmonary oedema with respiratory failure, pneumomediastinum (thought to be due to protracted vomiting and hyperventilation), multiple organ dysfunction syndrome (hypoxic hepatitis and pancreatitis), rhabdomyolysis, and death if diagnosed late or poorly managed (9, 10).

12.3.1 Hyperosmolar hyperglycaemic state: definition, presentation, and precipitating factors

Previously referred to as hyperosmolar non-ketotic (HONK) coma, HHS is one of the acute diabetes complications or hyperglycaemic

crises commonly encountered in middle-aged and elderly individuals with type 2 diabetes. HHS is characterised by features of severe dehydration, marked hypovolemia (hypotension and tachycardia), osmolarity (≥320 mOsmo/L), and hyperglycaemia (≥30 mmol/l or ≥540 mg/dl), without significant ketonemia (serum ketone concentrations ≤3.0 mmol/l) and acidosis (pH ≥7.3 and serum bicarbonate concentrations ≥15 mmol/l) (10, 12, 21).

The serum osmolarity of an individual can be estimated using the formula below:

Calculated serum osmolarity (mOsmo/L) = (2 x serum sodium concentration in mmol/l) + blood glucose concentration in mmol/l + blood urea concentration in mmol/l (22).

The onset of the signs and symptoms of HHS (severe dehydration and hypovolemia) is slower than what is observed in individuals presenting with DKA. These signs and symptoms develop mainly due to the effects of severe hyperglycaemia and consequent osmotic diuresis and electrolyte abnormalities. Individuals with HHS may also present with mild ketosis and acidosis because the prevailing circulating insulin concentrations are adequate to prevent significant ketosis and acidosis (10, 21).

Some of the precipitating factors for HHS include infections (notably respiratory and urinary tract infections), omission of glucose-lowering drugs, cardiovascular events such as myocardial infarction, pancreatitis, and drugs such as corticosteroids and typical antipsychotics (10, 21).

It is important to note that a significant overlap between DKA and HHS has been reported in more than one-third of patients (23).

12.3.2 Management of hyperosmolar hyperglycaemic state

The general goals of the management of HHS are normalising the serum osmolarity, correcting the fluid deficit and electrolyte imbalances, gradual normalization of the blood glucose concentrations, and prevention of arterial or venous thromboembolism and other complications such as cerebral oedema (10, 12, 21).

12.3.2.1 Fluid replacement therapy

The typical water loss in an individual presenting with HHS is 100-220 ml/kg. Fluid replacement therapy aims to replace ~50% of the estimated fluid loss within the first 12 hours and the remainder over the next 12 hours. However, the rate of fluid replacement will be limited by co-existing comorbidities such as heart and renal dysfunction and an individual's body weight (10, 21). Crystalloids such as 0.9% or 0.45% sodium chloride or normal saline and Ringer's lactate solution are generally preferred to colloids such as albumin and hydroxyethyl starch fluids in intravenous (iv) fluid replacement therapy (12, 19).

Generally, healthcare professionals should aim to replace at least 1 litre of iv fluids over the first hour, followed by two to three litres of iv fluids in the next six hours, and then at least six litres of iv fluids in the next 12 hours (10, 21). Because the serum sodium concentration reduces by 1.6 mmol/l for every 5.6 mmol/l (100 mg/dl) increase in the blood glucose concentration above the normal range due to the water shifts from the intracellular to the extracellular compartment, the serum sodium concentration has to be corrected for the measured or prevailing blood glucose concentration using the formula below (24).

Corrected serum sodium concentration (mmol/l) = Measured serum sodium concentration in mmol/l + 1.6 (measured blood glucose concentration in mmol/l or mg/dl – 5.6 mmol/l [or 100 mg/dl]) / 5.6 mmol/l or 100 mg/dl.

When choosing which crystalloid should be used, a healthcare professional should refer to the patient's computed corrected serum sodium concentration. Particularly, in individuals presenting with HHS and hypernatremia, 0.45% sodium chloride solution is preferred to 0.9% sodium chloride solution as the fluid of choice. Adequate fluid replacement helps in the reduction of blood glucose concentrations and osmolarity (10, 21).

Assessment of the hydration status in individuals presenting with HHS is key, especially in the elderly, comatose, those with cardiorespiratory conditions, and the young (10, 21).

12.3.2.2 Potassium replacement

In individuals with HHS, hypokalemia usually develops due to increased osmotic diuresis and consequent hypertonicity from hyperglycaemia, resulting in increased intracellular potassium loss. Hypokalemia is further aggravated by hypovolemia due to vomiting and diarrhea (which activates the adrenocortical release of aldosterone) and insulin therapy (which causes intracellular potassium influx) (10, 20, 21).

Potassium replacement is directly dependent on the serum potassium levels at presentation and during therapy, as illustrated below (10, 12, 21):

- Potassium levels ≥5.5 mmol/l: No supplemental potassium is needed.
- Potassium levels 4.0-5.5 mmol/l: 20 mmol/l of potassium chloride in each litre of replacement fluid.
- Potassium levels 3.5-4.0 mmol/l: 40 mmol/l of potassium chloride in each litre of replacement fluid.
- Potassium levels <3.5 mmol/l: 40 mmol/l of potassium chloride in each litre of replacement fluid, and do not initiate insulin therapy until serum potassium levels have normalised.

Potassium replacement should be performed with caution in individuals with renal failure because it has a very narrow therapeutic window in this patient population.

12.3.2.3 Insulin therapy

Insulin therapy should preferably be started after adequate fluid replacement and/or when the blood glucose levels have stopped declining because fluid replacement alone can result in a reduction in the blood glucose concentrations.

A fixed-rate insulin infusion or i.v. bolus administration of short-acting or regular insulin of 0.05 units/kg/hour can be administered, and the capillary blood glucose concentrations monitored every hour. The blood glucose concentrations should ideally reduce by <5 mmol/l per hour (90 mg/dl per hour) and not decline below 10-15 mmol/l (180-270 mg/dl) during the first 24 hours of management. In case the blood glucose concentrations fall below 14 mmol/l (250 mg/dl), a 5% or 10% glucose or dextrose infusion with insulin should be started. This helps avert the complication of hypoglycaemia (10, 12, 21).

Individuals at a high risk of developing hypoglycaemia, such as the elderly, those with renal and/or liver dysfunction, and diabetic neuropathy, should be closely monitored to avoid episodes of insulin-induced hypoglycaemia.

12.3.2.4 Initiation of intravenous antibiotics

A detailed history, examination, and laboratory workup (infection screening) are recommended in all individuals presenting with HHS to confirm if an infection is a precipitant and to identify its focus. The i.v antibiotic to be initiated should be dependent on the infection identified and the local antibiotic susceptibility patterns or prescribing guidelines (10, 12, 21).

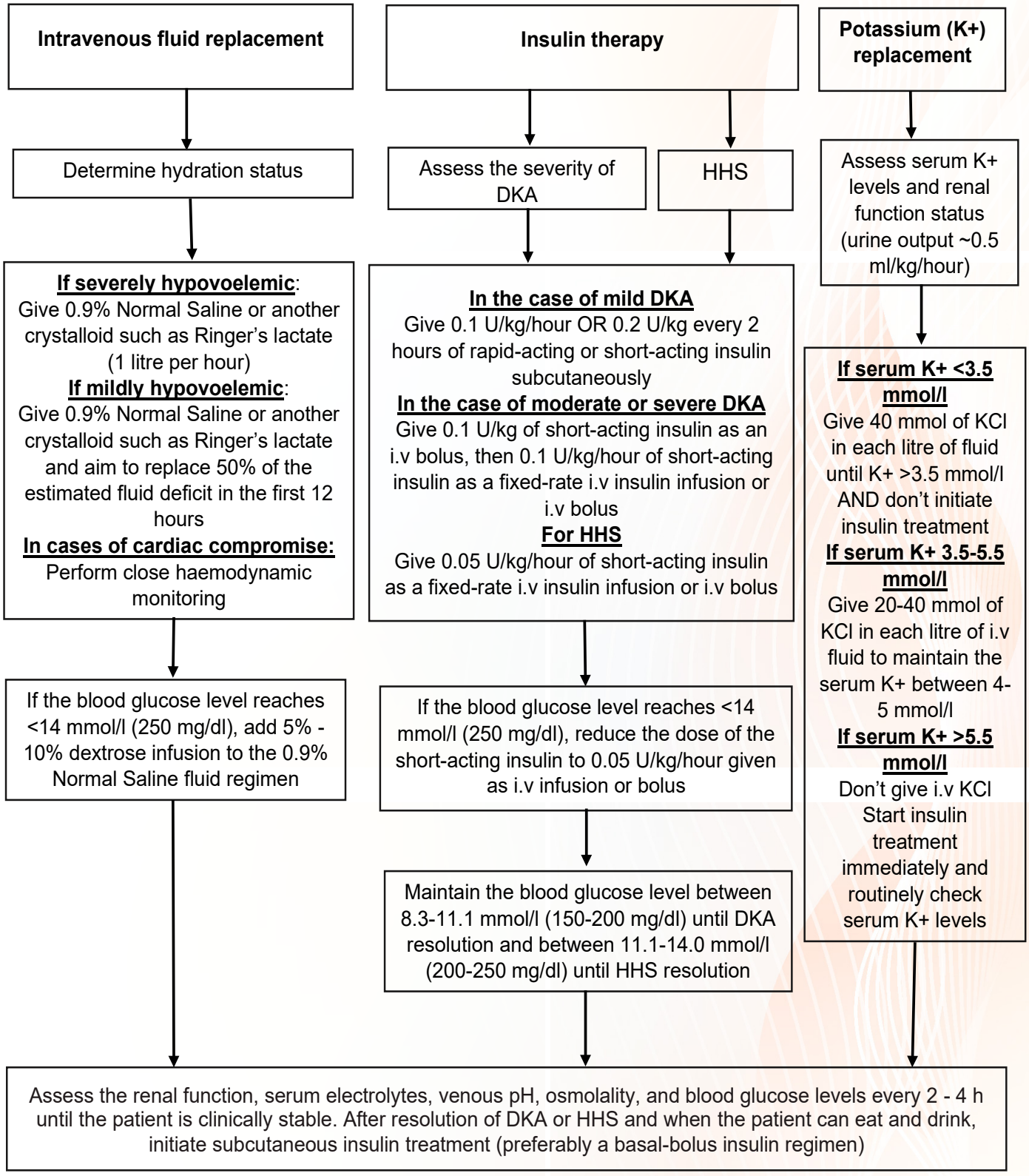
12.3.2.5 Initiation of anticoagulation

Individuals presenting with HHS are at an increased risk of arterial and venous thromboembolism. In the absence of any contraindication, it is recommended to provide prophylactic anticoagulation using low molecular weight heparin such as enoxaparin at the dose of 1 mg/kg/day for the full duration of the admission (10, 12, 21). In the presence of contraindications to anticoagulation, non-pharmacological measures such as the use of appropriate compressive stockings can be used.

12.3.3 Resolution of hyperosmolar hyperglycaemic state

Once all these management approaches have been instituted, the healthcare professional should assess to confirm the resolution of HHS. The criteria for resolution of HHS is 1) A return to premorbid normal clinical and cognitive status; 2) calculated or measured serum osmolarity <300 mOsmo/L (with a normal urine output of >0.5 ml/kg/hour); and 3) Measured blood glucose <15 mmol/l (270 mg/dl) (10, 12, 21).

Figure 1. A summary of the approach to the treatment for diabetic ketoacidosis and hyperosmolar hyperglycaemic state



Adapted from Umpierrez GE et al. Diabetes Care 2024; 47:1257–1275

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CHAPTER 13. AN OVERVIEW OF THE CHRONIC DIABETES COMPLICATIONS

SUMMARY OF RECOMMENDATIONS

Diabetic kidney disease

- Screening for diabetic kidney disease (DKD) should be performed in every individual with diabetes at the time of diagnosis or initial clinical visit and then annually **(Level of evidence: A).**
- Achieving and maintaining an optimal glycated haemoglobin of <7% (53 mmol/mol) and a blood pressure target of <130/80 mmHg is important in the primary prevention of DKD **(Level of evidence: A).**
- The cornerstone of pharmacological management of DKD involves the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors (SGLT2i), nonsteroidal mineralocorticoid receptor antagonists (MRA), and glucagon-like peptide 1 receptor agonists (GLP-1 RA), in addition to lifestyle modification **(Level of evidence: A).**

Diabetic retinopathy

- Diabetic retinopathy (DR) is the leading cause of visual loss in middle-aged individuals, and it is classified into nonproliferative DR (NDR) and proliferative DR (PDR) **(Level of evidence: A).**
- Screening for DR should be performed at the time of diagnosis or initial clinical visit in every individual with type 2 diabetes and within five years after the onset of diabetes in individuals with type 1 diabetes. In the absence of DR, the screening can be repeated every two years. In the presence of DR, the screening should be repeated at least annually **(Level of evidence: A).**
- Multifactorial intervention with optimal control of blood pressure, glycaemia, and lipids is essential in the management of DR because it has been shown to limit the progression of DR and the frequency of retinal photocoagulation procedures (Level of evidence: A).

Diabetic peripheral neuropathy

- Diabetic peripheral neuropathy is a diagnosis of exclusion characterised by loss of sensory function, intense pain, paraesthesia, and numbness that initially starts distally in the lower limbs and spreads to involve the hands **(Level of evidence: A).**
- Every individual with diabetes should be screened for diabetic peripheral neuropathy at diagnosis of type 2 diabetes and within five years after the diagnosis of type 1 diabetes, and then repeated at least annually **(Level of evidence: A).**
- Optimal glycaemic, blood pressure, and lipid control is essential in preventing and/or delaying the onset and progression of diabetic peripheral neuropathy **(Level of evidence: A).**
- The pharmacological therapies recommended in the management of diabetic peripheral neuropathy include gabapentin, pregabalin, duloxetine, carbamazepine, and antioxidants such as alpha-lipoic acid **(Level of evidence: B).**

Diabetes-related foot disease

- Diabetes-related foot disease (DFD) is defined as a disease of the foot of an individual with current or previously diagnosed diabetes that includes ≥1 of the following: peripheral neuropathy, peripheral arterial disease (PAD), infection, ulcer(s), neuro-osteoarthropathy, gangrene, or amputation **(Level of evidence: A).**
- Screening for DFD should be performed at the time of diagnosis and then annually in every individual with diabetes and more frequently in individuals at risk of DFD **(Level of evidence: A).**

- The prevention of DFD involves the identification of at-risk individuals, regular and structured education about foot care, and proper foot care **(Level of evidence: A).**
- Diabetes-related foot infections (DFI) of mild severity should be promptly managed using oral empirical antibiotic regimens for one to two weeks **(Level of evidence: B).**
- Moderate to severe DFI should be managed with intravenous empirical antibiotic regimens for two to four weeks **(Level of evidence: C).**

Peripheral arterial disease

- Peripheral arterial disease (PAD) is an obstructive atherosclerotic vascular disease of the arteries from the aorta to the foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities **(Level of evidence: A).**
- Screening for PAD is recommended at the time of diagnosis or initial clinical visit and then annually in every individual with type 2 diabetes aged >50 years **(Level of evidence: A).**
- An optimal glycaemic (HbA1c <8% or 64 mmol/mol), blood pressure (<140/90 mmHg), and lipid (LDLC <1.8 mmol/l [<70 mg/dl] or <1.4 mmol/l [<55 mg/dl] in case of a very-high cardiovascular disease risk using moderate- or high-intensity statin therapy) target is advised in individuals with PAD and diabetes **(Level of evidence: A).**
- Pharmacological management of individuals with PAD and diabetes involves the use of single low-dose antiplatelet therapy (clopidogrel is preferred to cardiac aspirin) **(Level of evidence: A).**
- Combination therapy of aspirin (75–100 mg once daily) and low-dose rivaroxaban (2.5 mg twice daily) can be considered for individuals with PAD and low bleeding risk **(Level of evidence: B).**
- Every individual with PAD should be initiated on SGLT2i or glucagon-like peptide-1 receptor agonist as the first-line glucose-lowering agents due to their proven cardiovascular protective benefits **(Level of evidence: A).**

13.1 Introduction

Chronic diabetes complications are disorders that develop due to hyperglycaemia (arising from insulin deficiency or resistance) and disorders of other metabolic pathways, such as disorders of lipid metabolism, and are associated with significant morbidity and mortality in individuals with type 1 and type 2 diabetes. Traditionally, chronic diabetes complications are classified into microvascular and macrovascular diabetes complications (1, 2).

For this Chapter of the guideline, we will discuss diabetic kidney disease, diabetic retinopathy, and diabetic peripheral neuropathy as microvascular diabetes complications, and diabetes-related foot disease and peripheral arterial disease as macrovascular diabetes complications. We will emphasise the practical approaches of targeted screening, management, and prevention of each complication to guide healthcare professionals in routine clinical practice.

13.2 Diabetic kidney disease

Diabetic kidney disease (DKD) is a diagnosis of exclusion and is relatively common in individuals with type 1 and type 2 diabetes. Studies conducted in Uganda on adults with type 1 and type 2 diabetes have reported prevalence ranging from 22.9% to 47.4% (3-5). This wide variation in the prevalence of DKD may be explained by the differences in the study populations (participants with newly diagnosed diabetes versus known diabetes), study settings (public versus private healthcare facilities), and study diagnostic approaches for DKD (microalbuminuria vs. macroalbuminuria). In these locally conducted studies, co-existing hypertension (3), family history of diabetes

(4), and pregnancy (5) were associated with an increased risk of developing DKD, while increased body mass index (3) and physical activity (5) were associated with lower odds of developing DKD.

13.2.1 Screening for diabetic kidney disease

Diabetic kidney disease should be assessed in all individuals with diabetes at the time of diagnosis or initial clinical encounter and then annually by measuring the serum creatinine concentrations (for calculation of the estimated glomerular filtration rate or e-GFR) and urine albumin: creatinine ratio (UACR) on a random spot urine sample by immunoassay or a dipstick specific for microalbuminuria (6-8). The e-GFR is usually calculated using the 2021 chronic kidney disease epidemiology (CKD-EPI) formula, which incorporates the serum creatinine and/or cystatin C concentrations. Using serum creatinine and cystatin C concentrations in the formula increases its diagnostic accuracy (9). However, the serum cystatin C test is not currently available in Uganda.

A normal UACR should be <30 mg/g (<3 mg/mmol). Levels between 30-300 mg/g (3-30 mg/mmol) and >300 mg/g (>30 mg/mmol) suggest the presence of microalbuminuria and macroalbuminuria, respectively. However, because UACR measurement is affected by many factors such as fever, exercise, infections, menses, and marked hypertension, it is advised to perform two to three additional tests within three to six months to confirm any abnormality in renal function (6, 7, 10).

Chronic kidney disease (CKD), which is defined as abnormalities of kidney structure or function and is present for a minimum of 3 months, is classified based on cause, e-GFR category (G1–G5), and albuminuria category (A1–A3), as shown in Figure 1 below (7).

Figure 1. Grading of kidney disease

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

CKD is graded as low-risk, moderately increased risk, high risk, and very high risk according to the level of albuminuria and e-GFR (7). It is important to grade all patients diagnosed with CKD because these grades have management and prognosis implications.
Table 1 below summarises the four grades of CKD.

Table 1. Categories of chronic kidney disease

CATEGORY OF CKD	DEFINITION
Low-risk	e-GFR >60 mL/min/1.73 m^2 with normal or mildly increased albuminuria (UACR <30 mg/g or <3 mg/mmol)
Moderately-increased risk	e-GFR 45-59 mL/min/1.73 m^2 with normal to mild albuminuria (UACR <30 mg/g or <3 mg/mmol) **OR** e-GFR >60 mL/min/1.73 m^2 with moderately increased albuminuria (UACR of 30-300 mg/g or 3-30 mg/mmol)
High-risk	e-GFR 30-44 mL/min/1.73 m^2 with mild albuminuria **OR** e-GFR 45 – 59 mL/min/1.73 m^2 with moderate albuminuria **OR** e-GFR >90 mL/min/1.73 m^2 with severely increased albuminuria
Very high-risk	e-GFR <30 mL/min/1.73 m^2 with normal to mild albuminuria **OR** e-GFR is 30-44 mL/min/1.73 m^2 with moderate albuminuria **OR** e-GFR is 45-<60 with severe albuminuria

In healthcare facilities where the measurement of UACR cannot be performed, dipstick proteinuria may serve as a surrogate marker for UACR (11). A persistent e-GFR <60 mL/min/1.73 m2 and/or a UACR >30 mg/g (>3 mg/mmol) is considered abnormal and suggestive of DKD in the absence of other primary causes of kidney disease (7).
In addition to the measurement of serum creatinine concentration and UACR, periodic assessment of serum potassium concentrations should be performed in patients on diuretics (because of the risk of hypokalemia) and angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), and nonsteroidal mineralocorticoid receptor antagonists (MRA) (because of the risk of hyperkalemia) (6, 7).

13.2.2 Prevention of diabetic kidney disease

The only proven primary prevention for CKD in individuals with diabetes is achieving and maintaining optimal glycated haemoglobin (HbA1c) and blood pressure (BP) targets of <7% (53 mmol/mol) and <130/80 mmHg, respectively (7, 12, 13). There is no evidence to support the routine use of ACEI or ARBs to prevent the development of DKD in individuals living with diabetes without co-existing hypertension and/or albuminuria (6, 7).

13.2.3 Management of diabetic kidney disease

The management of DKD aims to slow its progression and prevent related complications. Optimal blood glucose and pressure control significantly reduce the risk of developing microalbuminuria, macroalbuminuria, and/or overt nephropathy in individuals with type 1 or type 2 diabetes. The glycaemic and blood pressure targets in individuals with DKD should be individualised based on the age, severity of CKD, presence of macrovascular complications or other comorbidities, life expectancy, and risk of hypoglycemia (7).

13.2.3.1 Glycaemic control in individuals with DKD

Metformin can also be used safely in individuals with DKD and e-GFR ≥30 ml/min/1.73 m2. Other glucose-lowering therapies can be added to metformin depending on an individual's age, body mass index, co-existing comorbidities, duration of diabetes, and hypoglycemic risk (7).

Below an e-GFR of 60ml/min/1.73m2, dose adjustments of most glucose-lowering drugs may be required. Additionally, assessment of glycaemic control using HbA1c may not be clinically rational because of several factors such as uraemia, haemodialysis, and iron deficiency that affect red blood cell turnover and longevity, resulting in spurious HbA1c results (14). Table 2 below summarises the dose adjustments of the glucose-lowering therapies in individuals with chronic kidney disease.

		Renal impairment – CKD stage					
Drug	Class of drug	1 (eGFR >90)	2 (eGFR 60–90)	3a (eGFR 45–59)	3b (eGFR 44–30)	4 (eGFR 29–15)	5 (eGFR <15)
Metformin	Biguanide				Reduce dose to 500 BD*	eGFR may underestimate in obesity; potential role for 500 mg	
Gliclazide	Sulphonylurea	CBG	CBG	CBG	Dose reduction advised CBG	Off licence, high risk of hypoglycaemia CBG	
Repaglinide	Meglitinide	CBG	CBG	CBG	CBG	Dose reduction advised CBG	Dose reduction advised CBG
Sitagliptin	DPP-4i			<50 mL/min reduce dose to 50 mg	Reduce dose to 50 mg	Reduce dose to 25 mg	Reduce dose to 25 mg
Saxagliptin	DPP-4i			<50 mL/min reduce dose to 2.5 mg	Reduce dose to 2.5 mg	Reduce dose to 2.5 mg	
Linagliptin	DPP-4i						
Pioglitazone**	Thiazolinedione						
Lixisenatide	GLP-1 agonist			Caution in CrCl$ <50 mL/min			
Exenatide	GLP-1 agonist			Caution in CrCl$<50 mL/min	Conservative dosing		
Exenatide MR	GLP-1 agonist			Stop if CrCl$<50 mL/min			
Liraglutide	GLP-1 agonist					Dose reduction might be needed	***off licence, few small studies suggest no harm
Semagutide	GLP-1 agonist						
Dulaglutide (Trulicity)	GLP-1 agonist						
Dapagliflozin	SGLT-2i						
Canagliflozin	SGLT-2i				Reduce dose to 100 mg	&	
Empagliflozin	SGLT-2i			Reduce dose to 10 mg		%	
Insulin					Dose reduction may be needed	Dose reduction should be needed	

* Sick day guidance

** Monitor for fluid retention, contraindicated in heart failure, macular oedema

$ CrCl- creatinine clearance as an estimate of glomerular filtration rate, usually calculated using Cockroft-

*** Use of Liraglutide for eGFR<15 ml/min is off licence as there is insufficient evidence of substantial grade, but some studies suggest no harm, which is in keeping with its liver

CKD: chronic kidney disease, DPP-4i: dipeptidyl peptidase 4 inhibitors, eGFR: estimated glomerular filtration rate, GLP-1: glucagon-like peptide 1, SGLT-2i: sodium/glucose cotransporter-2 inhibitors.
The new eGFR cut-off for the SGLT2 inhibitors dapagliflozin and empagliflozin is 20 ml/min/1.73 m2 as per the 2024 Kidney Disease Improving Global Outcomes (KDIGO) guidelines.
Colour codes: Green- use without caution, Orange- dose adjustment required, Red- avoid its use.
This table is adapted from Chowdhury TA, et al. Management of diabetes in people with advanced chronic kidney disease. Diabet Med. 2024:e15402.

13.2.3.2 Management of hypertension in individuals with DKD

The ACEI such as enalapril, ramipril, and captopril or ARBs such as losartan, telmisartan, and valsartan are the mainstay for the management of individuals with CKD with albuminuria and hypertension-diabetes comorbidity. Because hypertension is a significant predictor of the onset and progression of CKD, ACEI or ARBs have been reported to reduce the risk of progression of CKD (6, 7, 15). The combination of ACEI and ARBs is not recommended due to the increased risk of hyperkalemia. Additionally, all individuals with DKD should also be initiated on moderate- or high-intensity statin therapy depending on the prevalent cardiovascular risk status (7).

13.2.3.3. Delaying progression and managing complications of diabetic kidney disease

For glucose-lowering therapies, individuals with DKD should be initiated on sodium-glucose cotransporter 2 inhibitors (SGLT2i) such as dapagliflozin, empagliflozin, and canagliflozin or glucagon-like peptide 1 receptor agonists (GLP-1 RA) such as semaglutide due to their proven renal protective benefits (reduction of risk of CKD progression and acute kidney injury) (16-20). These classes of glucose-lowering drugs are recommended for individuals with type 2 diabetes, CKD, and an e-GFR ≥20 mL/min/1.73 m2 (6, 7).

Recent evidence from clinical trials has also shown that the nonsteroidal MRA called finerenone plays a significant role in reducing the progression of DKD and cardiovascular events (major adverse cardiovascular events and hospitalisation for heart failure) in individuals with advanced DKD (21-24), hence indicated in the management of DKD. Finerenone is currently available in Uganda as generics.

In summary, from the evidence discussed above, the principles of management of DKD involve the use of ACEIs or ARBs, SGLT2i, GLP-1 RA, and finerenone, in addition to lifestyle modification (a healthy diet, increased physical activity, cessation of smoking, and weight loss), optimal glucose, blood pressure (preferably using ACEIs or ARBs in combination with a calcium channel blocker), and lipid (moderate- or high-intensity statin therapy) control (6, 7).

13.2.4 When to refer a patient with diabetic kidney disease to a nephrologist

Early referral of a patient with DKD should be considered in these situations: i) atypical presentation (urinary sediment abnormalities, accelerated proteinuria or absence of retinopathy); ii) if the e-GFR falls below 30mL/min/1.73m2 or when albuminuria exceeds 300mg/g; iii) acute decrease in e-GFR (>25% decrease versus baseline); iv) rapid loss of e-GFR (e-GFR slope faster than −5mL/min/1.73m2/year); v) refractory hypertension; vi) serum potassium concentrations >5.5 or <3.5mmol/l; vii) presence of renal anaemia (haemoglobin <10.5g/dL) in patients with CKD and optimal iron availability (defined as a transferrin saturation index >20% and serum ferritin >100ng/mL) (25).

13.3 Diabetic retinopathy

Diabetic retinopathy (DR) or diabetic eye disease is a common diabetes complication and the leading cause of visual loss in middle-aged and elderly people with diabetes (26). Studies conducted on adult Ugandans with diabetes have reported the prevalence of diabetic retinopathy ranging from 9.6% to 84.0%, reflecting varying prevalence, probably due to differences in diagnostic approaches (self-reported history versus direct fundoscopy) (27-31).

Clinically, DR is classified into two stages, i.e. nonproliferative DR (NPDR) and proliferative DR (PDR). The former represents the early stage of the condition and is characterised mainly by the presence of microaneurysms, retinal dots, and blot haemorrhages, and hard exudates or cotton wool spots seen on fundoscopy and may be largely asymptomatic. The latter is the advanced stage of DR characterised by the presence of neovascularisation, vitreous or pre-retinal haemorrhage, retinal detachment, and diabetic macular oedema (which is the commonest cause of vision loss) (26).

The commonly recognised risk factors of DR in individuals with diabetes include long

duration of diabetes, suboptimal glycaemic, blood pressure, and lipid control, puberty, pregnancy, and co-existing diabetes complications such as diabetic nephropathy and neuropathy (26, 32).

13.3. 1 Screening of diabetic retinopathy

All individuals with type 2 diabetes should have a comprehensive eye examination by an ophthalmologist or ophthalmic clinical officer at the time of diagnosis of diabetes or initial clinical visit and within five years after the onset of diabetes in individuals with type 1 diabetes.

The screening for DR can be performed using visual acuity assessment and indirect ophthalmoscopy using a dilated slit lamp examination or direct ophthalmoscopy using fundus photography. In the absence of any features suggestive of DR, the eye examinations can be repeated every two years. However, in case any feature suggestive of DR is identified, the screening should be repeated depending on the severity of the DR (annual screening for mild to moderate NPDR, 3-6 monthly screening for severe NPDR, and <3 monthly screening for PDR) (32).

Additionally, because pregnancy is a recognised risk factor for the onset and progression of DR, women with type 1 and type 2 diabetes planning to become pregnant or who have become pregnant should be counselled to have baseline screening for DR (32).

13.3.2 Management of diabetic retinopathy

Intensive glycaemic management is important in diabetes care because it has been shown to prevent and/or delay the onset and progression of DR, reduce the need for future eye surgeries, and reduce the risk of visual impairment or loss (33-35). Additionally, multifactorial optimal blood pressure, glycaemia, and lipid control by healthcare professionals is very important in the management of DR because it has been shown to limit the progression of DR and the frequency of retinal photocoagulation procedures (36).

Specialised treatment for DR should be performed by an experienced ophthalmologist. This includes pan-retinal laser photocoagulation therapy (for individuals with PDR and severe forms of NDR), intra-vitreous injection of anti-vascular endothelial growth factor (anti-VEGF) for individuals with diabetic macular oedema, and intravitreal injections of corticosteroid for individuals with persistent diabetic macular oedema and/or focal/grid laser. Individuals presenting with sudden severe vision loss and those diagnosed with diabetic macular oedema, moderate or severe NDR (that precedes PDR), and PDR should be urgently referred to an experienced ophthalmologist to initiate specialist management (26, 32, 37).

13.4 Diabetic peripheral neuropathy

Diabetic peripheral neuropathy is a diagnosis of exclusion characterised by loss of sensory function, intense pain, paraesthesia, and numbness that initially starts distally in the lower limbs and spreads to involve the hands in a classical glove and stocking distribution. Other diabetes-related neuropathies that can occur include autonomic neuropathy (such as cardiac arrhythmias, postural hypotension, gastrointestinal dysmotility, erectile dysfunction, reduced vaginal lubrication with dyspaurenia, reduced sweating, and bladder dysfunction with lower urinary tract symptoms) and motor neuropathy (such as muscle weakness and atrophy) (38, 39).

Several studies conducted on adult Ugandans with diabetes have reported the prevalence of diabetic peripheral and autonomic neuropathy to range between 29.4% and 65.8% (40-43), suggesting a relatively high prevalence in our local adult population with diabetes.

13.4.1 Screening of diabetic peripheral neuropathy

All individuals with diabetes should be screened for diabetic peripheral neuropathy at diagnosis of type 2 diabetes and within five years after the diagnosis of type 1 diabetes and then repeated at least annually (32, 44). The assessment should involve a focused medical history and neurological examination. The symptoms suggestive of diabetic peripheral neuropathy include pain (described either as burning, cold, tingling, stabbing, or shooting), paraesthesia (tingling,

pricking, or ant-like sensations), dysesthesia (unpleasant abnormal sensation), sensory ataxia (ataxic gait), and numbness. On neurological examination, there is loss of sensation to a pinprick (tested using a 10 g monofilament), temperature (mostly cold), vibration, and proprioception (tested using a 128 HZ tuning fork), with loss or reduced ankle reflexes (tested using a patella hammer) (32, 44).

Healthcare professionals should also remember the differential diagnoses of diabetic peripheral neuropathy in individuals with diabetes such as alcoholic neuropathy, medication-induced chemotherapy such as chemotherapy-related neuropathy, co-existing vitamin B12 deficiency (especially in individuals with type 2 diabetes and on long-term metformin therapy), hypothyroidism, multiple myeloma, renal dysfunction (uremic neuropathy), autoimmune and connective tissue disorders, and neuropathy due to other medical comorbidities such as HIV (32, 44).

13.4.2 Prevention and management of diabetic peripheral neuropathy

Large multicentre clinical trials have shown that optimal glycaemic, blood pressure, and lipid control prevent and/or delay the onset and progression of diabetic peripheral neuropathy (34-36).

The oral pharmacological therapies recommended in the management of diabetic peripheral neuropathy include gabapentinoids such as gabapentin and pregabalin, serotonin-norepinephrine reuptake inhibitors such as duloxetine, sodium channel blockers such as carbamazepine and valproic acid, weak opioids such as tramadol, and antioxidants such as alpha-lipoic acid (32, 44, 45).

13.5 Diabetes-related foot disease

Diabetes-related foot disease (DFD) is defined as a disease of the foot of an individual with current or previously diagnosed diabetes that includes ≥1 of the following: peripheral neuropathy, peripheral arterial disease (PAD), infection, ulcer(s), neuro-osteoarthropathy, gangrene, or amputation (46). DFD is a common complication in individuals with diabetes (especially type 2 diabetes) and is associated with reduced quality of life and poses a significant financial strain on patients, immediate family, and healthcare systems to manage (47). The condition has been well described in adult Ugandans with diabetes. Most of the patients with DFD in Uganda present with severe disease (Wagner classification 3-5) and combined clinical features of distal sensorineuropathy and peripheral ischaemia (48-50).

Distal sensorineuropathy is often associated with loss of protective sensation (to pain, temperature, and position), foot deformities (clawed feet and Charcot arthropathy), and limited joint movement. This results in abnormal biochemical loading of the foot with increased mechanical stress, callus formation, and eventual skin ulceration (47). The clinical factors that increase the risk of developing DFD include poor glycaemic control, smoking, the presence of peripheral neuropathy, diabetic retinopathy, nephropathy, PAD, foot deformities, pre-ulcerative corns or calluses, prior ulceration, and amputation (47).

13.5.1 Screening for diabetes-related foot disease

Screening for DFD using a focused history (history of ulceration, amputation, intermittent claudication, and medical comorbidities such as diabetic retinopathy and nephropathy) and clinical examination of the feet to identify the above-discussed risk factors should be performed at the time of diagnosis and then annually in every individual with diabetes and more frequently in individuals at risk of DFD (47).

Table 3 below summarises the frequency of screening for DFD depending on ulcer risk and characteristics as recommended by the International Working Group on the Diabetic Foot (IWGDF).

A detailed clinical examination of the feet involves the assessment of the skin integrity (colour, temperature, presence of ulcers, calluses, and infection), evaluation for loss of protective sensation, position, and vibration sense using a 10 g monofilament and a 128 HZ tuning fork, respectively, assessment for foot deformities, and palpation of the feet pulses (dorsalis pedis and posterior tibial arteries). It is also important to check the footwear of patients to make sure that it is well-fitting and appropriate (47).

Table 3. The International Working Group on the Diabetic Foot 2023 risk stratification system and corresponding frequency of foot screening

Category	Ulcer risk	Characteristics	Frequency
0	Very low	No LOPS and no signs of PAD	Once a year
1	Low	LOPS or PAD	Once every 6–12 months
2	Moderate	LOPS + PAD or LOPS + foot deformity or PAD + foot deformity	Once every 3–6 months
3	High	LOPS or PAD, and one or more of the following: - history of a foot ulcer - a lower-extremity amputation (minor or major) - end-stage renal disease	Once every 1–3 months

LOPS, Loss of Protective Sensation; PAD, Peripheral Artery Disease

13.5.2 Prevention of diabetes-related foot disease

Broadly, the prevention of DFD involves these five key components: 1) Identification of individuals at risk of DFD as discussed above; 2) Regular self- and healthcare professional-provided inspection and examination of the feet of every individual with diabetes, especially those at risk of DFD; 3) Provision of regular and structured education about proper feet care to the patients, their immediate families, and healthcare professionals; 4) Encouraging routine wearing of appropriate footwear; 5) Optimal management of all risk factors of feet ulceration.

Regular and structured education about foot care should emphasise daily washing and examination of the feet, early recognition and proper care of pre-ulcerative lesions such as calluses, regular use of vaseline or lotion or any emollient to avoid having dry skin, walking with socks and well-fitting shoes, keeping toenails short and trimming them well, and avoiding high heel shoes (>4cm) (32, 47).

13.5.3 Management of diabetes-related foot infections

Diabetes-related foot infections (DFI), such as infected ulcers, cellulitis, local abscesses, and osteomyelitis, should be treated promptly. The IWGDF/Infectious Diseases Society of America (IDSA) has made several recommendations for the management of individuals with moderate or severe DFI (51). These include:

1. Urgent evaluation and surgical intervention to remove all necrotic tissue.
2. Assessment for PAD using any locally available radiological modalities such as angiography and arterial ultrasound Doppler scan. Start with a duplex lower limb arterial ultrasound Doppler scan, since it is usually readily available, followed by a computed tomography (CT) angiography of the lower limbs. Healthcare professionals need to assess a patient's eGFR before performing the CT angiography of the lower limbs to prevent aggravating acute kidney injury in patients with advanced CKD.
3. Urgent initiation of empiric, parenteral, and broad-based antibiotics to cover both gram-positive and negative bacteria and obligate anaerobes.
4. Adjustment of the parenteral antibiotic regimen based on clinical response and culture and sensitivity results when available.
5. For soft tissue DFI, antibiotic therapy should be one to two weeks in duration and longer duration in cases of slowly resolving infections, severe PAD, or post-amputation (≥3 weeks).

The initiated parenteral antibiotics should be based on the local antibiotic susceptibility pattern with the ability to efficiently cover the likely causative pathogens (51). Data on the microbial characterisation of DFI and the profile of antibiotic susceptibility in adult

Ugandans with diabetes is limited (48, 49). In one systematic review that collated the findings of two studies investigating the microbial profile of DFI in adult Ugandans with diabetes, >120 bacterial isolates were reported. These included World Health Organization-ascribed priority pathogens such as *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species (ESKAPE)*. Gram-negative bacteria constituted 75% of the total isolates, with the rest being gram-positives. Additionally, ~14% of the isolates were extended-spectrum beta-lactamase (ESBL) producers, and ~5% were methicillin-resistant Staphylococcus aureus (MRSA). Most bacteria showed susceptibility to imipenem, vancomycin, and clindamycin and different levels of resistance to cotrimoxazole, ceftriaxone, cefepime, ampicillin, and ceftazidime (52).

13.5.3.1 Proposed Empirical Antibiotic Therapy for Diabetes-Related Foot Infections

Oral or parenteral broad-spectrum antibiotics can be used until the culture and susceptibility results are available. For DFI of mild severity, the following empirical antibiotic regimens are recommended for use for one to two weeks: oral cloxacillin and cephalexin, or oral amoxicillin-clavulanate or oral fluoroquinolones such as levofloxacin and moxifloxacin (in case of beta-lactam allergy or recent exposure to antibiotics) or oral linezolid in cases of high-risk MRSA. In cases of DFI of moderate to severe severity, use intravenous (i.v) amoxicillin-clavulanate or a 2nd or 3rd generation i.v cephalosporin such as cefuroxime, cefotaxime, and ceftriaxone, or i.v piperacillin-tazobactam and ceftazidime, or i.v carbapenems such as meropenem. In cases of possible MRSA-associated DFI, consider adding or substituting with vancomycin or linezolid. The total duration of oral or i.v therapy should be 2-4 weeks (51).

13.5.4 Pressure offloading and ulcer protection in the management of diabetes-related foot diseases

Pressure offloading is a key component in the management of diabetic foot ulcers that develop due to repeated mechanical stress. Pressure offloading can be provided using an offloading device such as a total contact cast, a removable walker, or specially designed footwear (47). Currently, podiatric services are not well-developed in most tertiary hospitals in Uganda. However, specially designed footwear (shoes and sandals) with offloading properties is available in the private market.

13.6 Peripheral arterial disease

Peripheral arterial disease (PAD) is another common macrovascular diabetes complication in individuals with type 2 diabetes and often precedes the onset of DFD and most cardiovascular events. It is defined as an obstructive atherosclerotic vascular disease of the arteries from the aorta to the foot with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities (53).

Two studies conducted on adult Ugandans with diabetes receiving outpatient diabetes care from two tertiary hospitals in Southwestern (54) and Central Uganda (55) have reported a prevalence of PAD of 24% and 39%, respectively. The identified independent predictors of PAD in these two local studies were the presence of a history of intermittent claudication, microalbuminuria, female sex, and the use of glibenclamide (a sulfonylurea) (54, 55).

13.6.1 Screening for peripheral arterial disease

Screening for PAD using history and clinical examination is recommended in every individual with type 2 diabetes and >50 years of age at the time of diagnosis or initial clinical visit, and then annually. The noninvasive testing of PAD can be repeated after five years if normal at the initial assessment (32, 53). A detailed history should include evaluating for risk factors of PAD, such as chronic smoking history, and assessing for a history of leg fatigue, intermittent claudication, and rest pain. It is important to know that the classical symptoms of PAD, such as intermittent claudication and rest pain, may be absent in some individuals with diabetes due to diabetes-related sensorineuropathy. The clinical examination should involve the

assessment for signs of ischaemia such as hyperpigmentation of the skin of the feet, loss of hair, changes in the temperature (coldness of the feet), and feeble or absent foot pulses. If PAD is suspected, the patient can be referred for noninvasive assessment using either arterial Doppler ultrasound scanning or CT angiography of the lower limbs. An ankle-brachial index of <0.90 and <0.50 suggests the presence of PAD and critical stenosis, respectively. The latter increases the likelihood of major amputation (32, 53).

13.6.2 Management of peripheral arterial disease

The management of PAD involves medical and surgical intervention (revascularization procedures). The latter form of management is not widely available in Uganda.

For this Chapter, we will only discuss the pharmacological medical management of PAD because the recommended oral therapies are readily available in most clinical settings in Uganda.

In the management of individuals with PAD and diabetes, achieving the optimal glycaemic (HbA1c <8% or 64 mmol/mol), blood pressure (<140/90 mmHg), and lipid (LDLC <1.8 mmol/l [<70 mg/dl] or <1.4 mmol/l [<55 mg/dl] in case of a very-high cardiovascular disease risk using moderate- or high-intensity statin therapy) therapeutic targets is advised (32, 53). Individuals with PAD and diabetes should also be initiated on single antiplatelet therapy with clopidogrel (dose of 75 mg) recommended as the first choice in preference to cardiac aspirin. Combination therapy of aspirin (75–100 mg once daily) and low-dose rivaroxaban (2.5 mg twice daily) should be considered for individuals without a high bleeding risk. Regarding the management of hyperglycaemia, SGLT2i or GLP-1 RA should be initiated as the first-line glucose-lowering agents in every individual with diabetes and PAD due to their proven cardiovascular protective benefits (32, 53).

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CHAPTER 14. IN-HOSPITAL MANAGEMENT OF HYPERGLYCAEMIA

SUMMARY OF RECOMMENDATIONS

- In-hospital hyperglycaemia is defined as blood glucose levels >7.8 mmol/l (>140 mg/dl) in a hospitalised individual. An admission glycated haemoglobin level ≥6.5% (48 mmol/mol) confirms the presence of diabetes preceding hospitalisation **(Level of evidence: B).**
- Both diabetes and stress (reactionary) hyperglycaemia are associated with adverse clinical outcomes such as prolonged hospital stays, increased incidence of in-hospital complications, rehospitalisation, and mortality **(Level of evidence: B).**
- Several studies have shown that, compared with conventional glucose control (targeting a blood glucose level of ≤10.0 mmol/l or 180 mg/dl), intensive glucose control (targeting a blood glucose level of 4.5-6.0 mmol/l or 81-108 mg/dl) is associated with adverse clinical outcomes such as increased in-hospital mortality and hypoglycaemic episodes in critically ill hospitalised patients **(Level of evidence: A).**
- Glucose-lowering therapy (either insulin and non-insulin therapies) should only be initiated to manage persistent hyperglycaemia of ≥10 mmol/l (≥180 mg/dl) and treat to a glycaemic target of 7.8-10.0 mmol/l (140-180 mg/dl) in all critically ill medical and surgical hospitalised patients **(Level of evidence: A).**
- In noncritically ill individuals with in-hospital hyperglycaemia (newly diagnosed or with stress hyperglycaemia), treat to a glycaemic target of 5.6-10.0 mmol/l (100-180 mg/dl) **(Level of evidence: B).**
- Continuous intravenous fixed-dose insulin infusion therapy is the preferred method of management of hyperglycaemia for critically ill patients in the intensive care unit **(Level of evidence: A).**
- In noncritically ill individuals with in-hospital hyperglycaemia, insulin administered subcutaneously is the preferred therapy **(Level of evidence: B).**
- In the absence of some contraindications, specific non-insulin glucose-lowering therapies such as dipeptidyl peptidase IV inhibitors, metformin, and sodium-glucose cotransporter-2 inhibitors can also be used in specific patient populations as add-on glucose-lowering therapies **(Level of evidence: A).**
- The use of the sliding scale in the management of in-hospital hyperglycaemia should be generally discouraged because it is associated with several complications, such as poor in-hospital glycaemic control, recurrent episodes of hypoglycaemia, and glycaemic variability, which increase the risk of in-hospital cardiovascular events and mortality **(Level of evidence: A).**
- The basal or basal-bolus approach of insulin administration is the preferred mode of insulin administration to premixed insulin administration in hospitalised individuals with type 2 diabetes **(Level of evidence: A).**

14.0 Introduction

Individuals with overt diabetes (pre-existing diabetes and undiagnosed diabetes) and stress or reactionary hyperglycaemia (hyperglycaemia that develops during hospitalisation but reverts to normoglycaemia post-hospital discharge) account for a significant proportion of critically and non-critically ill hospitalised patients (1, 2).

Both overt diabetes and stress hyperglycaemia are associated with adverse clinical outcomes such as prolonged hospital stays, increased incidence of in-hospital complications, rehospitalisation, mortality, and increased health costs (3-6). In Uganda, individuals with diabetes account for a significant proportion of adult patients admitted to the medical wards in tertiary hospitals (7, 8). Studies conducted on critically ill hospitalised adults and children in Uganda have also reported similar findings of adverse clinical outcomes, such as increased mortality associated with hyperglycaemia (9, 10), further underscoring the need for timely identification and optimal management of hyperglycaemia in critical care settings.

14.1 Standard definition of in-hospital hyperglycaemia

In-hospital hyperglycaemia is defined as blood glucose levels >7.8 mmol/l (>140 mg/dl) in a hospitalised or admitted individual. An admission glycated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol) suggests overt diabetes preceding hospitalisation (1, 2, 5).

Because of the adverse clinical outcomes associated with in-hospital hyperglycaemia, standard practices aimed at assessing and diagnosing hyperglycaemia in all admitted medical and surgical patients should be encouraged in clinical settings. The assessment should involve clear documentation of the type of diabetes that the individual is diagnosed with (type 1 diabetes, type 2 diabetes, gestational diabetes, secondary diabetes, etc.). The different subtypes of diabetes have been discussed comprehensively in Chapter 2 of this guideline. In addition, an HbA1c level should be measured in all individuals with diabetes and stress hyperglycaemia admitted to the hospital (2).

14.2 Glycaemic targets and monitoring for hospitalised patients

Several clinical trials have been undertaken to date to inform how to optimally manage hyperglycaemia in critically and non-critically ill hospitalised patients (11-13). However, the large landmark multicentre clinical trial called the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial provided the most compelling evidence of in-hospital management of hyperglycaemia in critically ill patients (13). The NICE-SUGAR clinical trial evaluated the effects of intensive glucose control (target blood glucose level of 4.5-6.0 mmol/l or 81-108 mg/dl) versus conventional glucose control (target blood glucose level of ≤10.0 mmol/l or 180 mg/dl) in 6,104 critically ill medical and surgical patients admitted in an intensive care unit (ICU). Compared with conventional glucose control, intensive glucose control was associated with a 14% increase in in-hospital mortality (27.5% vs. 24.9%, odds ratio [OR] for intensive glucose control - 1.14, 95% CI 1.02-1.28, p=0.02). This finding may be explained by the increased frequency of hypoglycaemia in the intensive glucose control arm (13).

Other systematic reviews and meta-analyses also reported the findings of increased in-hospital mortality and hypoglycaemia associated with intensive glucose control in critically ill hospitalised patients (14, 15). These findings provided compelling evidence that intensive glucose control in critically ill hospitalised individuals should be discouraged. Additionally, glucose-lowering therapy (insulin and non-insulin therapies should be only initiated to manage persistent hyperglycaemia of ≥10 mmol/l (≥180 mg/dl) and treat to

a glycaemic target of 7.8-10.0 mmol/l (140-180 mg/dl) in all critically ill medical and surgical hospitalised patients (1, 2). However, in noncritically ill individuals with in-hospital hyperglycaemia (newly diagnosed or with stress hyperglycaemia), treat to a glycaemic target of 5.6-10.0 mmol/l (100-180 mg/dl) (1, 2, 5). Concerning in-hospital glucose monitoring, individuals with diabetes who are feeding orally, point-of-care blood glucose monitoring should be performed before each meal. In individuals unable to feed orally, blood glucose monitoring should be performed every 4-6 hours, depending on the clinical setting and availability of resources (1, 2, 5).

14.3 Pharmacological management of in-hospital hyperglycaemia

14.3.1 Use of insulin therapy in the management of hyperglycaemia in critically ill patients

Continuous intravenous (i.v) fixed-dose insulin infusion therapy is the preferred method of management of hyperglycaemia for critically ill patients in the ICU. Individuals with mild and uncomplicated diabetic ketoacidosis can be managed using subcutaneous rapid-acting or short-acting (regular) insulin administered every 1-2 hours (1, 2).

14.3.2 Use of insulin therapy in the management of hyperglycaemia in non-critically ill patients

In non-critically ill individuals with in-hospital hyperglycaemia, insulin administered subcutaneously is the preferred therapy. Some specific non-insulin glucose-lowering therapies, such as dipeptidyl peptidase IV (DPP-IV) inhibitors, metformin, and sodium-glucose cotransporter-2 inhibitors (SGLT2i), can also be used in specific patient populations as add-on therapies (1, 2, 5).

Subcutaneous rapid-acting or short-acting insulin administered before each meal should be used in individuals able to eat. In those unable to feed orally and are on continuous enteral or parenteral nutrition, subcutaneous rapid-acting or short-acting insulin can be administered every 4-6 hours to prevent episodes of hyperglycaemia. In some non-critically ill hospitalised individuals with inadequate or restricted oral intake or in the peri-operative period, basal insulin (at a dose of 0.1-0.2 units/kg/day given once or twice daily) or a basal-bolus insulin regimen may be preferred (1, 2).

The dosing of insulin in the case of using a basal insulin alone or a basal-bolus insulin approach has been discussed in detail in Chapter 10 of this guideline. The healthcare professional should consider a total daily insulin dose (TDD) to be 0.3-0.5 units/kg/day. About 40-50% of the TDD should be assigned to the basal insulin and 50-60% to the rapid-acting or short-acting prandial insulin, which is administered before each meal. Lower doses of the TDD should be used in individuals at risk of developing hypoglycaemia, such as the elderly, individuals with renal dysfunction, and poor oral intake (1, 2, 5).

As discussed in Chapter 10 of this guideline, the use of the sliding scale in administering subcutaneous insulin remains commonly practiced in healthcare facilities in Uganda. Its use should be generally discouraged in the management of in-hospital hyperglycaemia (1). This is because it is associated with several complications such as poor in-hospital glycaemic control, recurrent episodes of hypoglycaemia, and glycaemic variability, which increase the risk of in-hospital cardiovascular events and mortality (16). Additionally, findings from systematic reviews and meta-analyses of randomised clinical trials have consistently shown that, compared with the sliding scale approach of insulin administration, the basal-bolus approach of insulin administration provides better glycaemic control and is associated with fewer in-hospital complications in individuals hospitalised with type 2 diabetes (17, 18). Premixed insulin therapy (especially human insulin) is not recommended in the management

of in-hospital hyperglycaemia because it is associated with high rates of hypoglycaemia (1, 2, 5).

14.3.3 Use of noninsulin therapies in the management of hyperglycaemia in hospitalised ill patients

Data from recent clinical trials suggest that some non-insulin therapies can be used in the management of hyperglycaemia in hospitalised individuals with type 2 diabetes.

14.3.3.1 Metformin

Metformin can be safely used in most hospitalised patients with type 2 diabetes. However, it should be avoided in patients at risk of developing lactic acidosis, such as patients with sepsis, hypoxia, and impaired renal (estimated glomerular filtration rate or e-GFR <30 ml/min/1.73 m2) and liver function. Its dose has to be reduced if the e-GFR IS 30-45 ml/min/1.73 m2 (5).

14.3.3.2 Sulfonylureas and thiazolidinediones

Sulfonylureas such as glibenclamide and glimepiride should be avoided in the management of in-hospital hyperglycaemia due to their associated increased risk of hypoglycaemia, especially in the elderly, patients on concomitant insulin therapy, and in the presence of renal dysfunction. Thiazolidinediones such as pioglitazone should also be avoided because they are associated with increased fluid retention and heart failure (5, 19).

14.3.3.3 Dipeptidyl peptidase IV inhibitors

Clinical trials have shown that DPP-IV inhibitors are relatively well-tolerated and effective in controlling glycaemic levels. Because they are associated with a low risk of hypoglycaemia, they can be used in the management of in-hospital hyperglycaemia (20-22).

14.3.3.4 Sodium-glucose cotransporter-2 inhibitors

These are the first-line oral glucose-lowering therapies in patients with type 2 diabetes with renal dysfunction and heart failure, regardless of the ejection fraction (23, 24). Recent evidence from large clinical trials has shown that SGLT2i can be initiated early in hospitalised patients with acute heart failure. The drugs are well-tolerated and are associated with reduced in-hospital mortality and lower rates of acute kidney injury (25-27).

14.4 Management of glucocorticoid-induced hyperglycaemia

Hyperglycaemia is a common finding in hospitalised patients receiving supraphysiological doses of glucocorticoids (1). This is usually part of the pharmacological management of immunological and rheumatological conditions such as rheumatoid arthritis, systemic lupus erythematosus, polymyositis, haemato-oncological conditions such as lymphoma, leukemias, and immune thrombocytopenic purpura, and endocrine conditions such as adrenal insufficiency (28).
Glucocorticoid-induced hyperglycaemia is associated with a prolonged hospital stay, increased risk of infection, cardiovascular events, and in-hospital mortality (1, 5). It can be managed by using either 1) a Neutral Protamine Hagedorn (NPH)-based insulin regimen given once in the morning or twice daily at a dose of 0.1-0.3 units/kg/day; or 2) a basal-bolus insulin regimen (a single basal insulin dose given once or twice daily and short-acting or rapid-acting insulin given before each meal). The insulin doses can be adjusted according to the glucocorticoid dose used, the extent of oral intake, and the nutritional status of the individual undergoing treatment (1, 2, 5).

14.5 Peri-operative management of hyperglycaemia

The stress of surgery and anaesthesia (especially general anaesthesia) is associated with an increased release of counter-regulatory hormones such as cortisol, glucagon, and catecholamines. This results in an increase in the risk of stress or reactionary hyperglycaemia, which is associated with adverse clinical outcomes such as delayed wound healing, prolonged hospital stay, and in-hospital mortality (29).

Pre-operative anaesthetic reviews are recommended for all individuals with diabetes, especially those at high risk for coronary artery disease, individuals with autonomic neuropathy, and renal dysfunction (2, 29). The pre-operative HbA1c goal for elective surgical cases should be <8% (64 mmol/mol). The blood glucose target in the peri-operative period should be 5.6-10.0 mmol/l (100-180 mg/dl) within the first four hours of surgery (2, 29).

Concerning glucose-lowering therapies, metformin should be stopped on the day of surgery and restarted when a patient resumes a normal diet. All SGLT2i should be discontinued 3-4 days before surgery. Apart from DPP-IV inhibitors that can be taken continuously during the pre- and post-operative period, all other oral glucose-lowering drugs should be stopped on the morning of the surgery and restarted post-surgery when the patient is feeding normally. About 50-80% of the NPH or premixed insulin doses and 75-80% of the long-acting analogue insulin should be administered a day before the surgery and on the morning of the surgery (2).

The blood glucose levels have to be monitored at least every 2-4 hours if the patient is not feeding orally, and short-acting or rapid-acting insulin should be used to manage the hyperglycaemia (2, 29).

14.6 Referral of in-hospital patients with recently diagnosed or known diabetes for specialist review

The International Diabetes Federation recommends that healthcare professionals refer certain categories of patients with newly diagnosed or known diabetes, once reviewed in the hospital or an outpatient care setting, to a diabetologist for specialist management (30). These include:

1. Individuals with poor glycaemic control despite good self-reported adherence and compliance with medicines.
2. Individuals with diabetes and multiple comorbidities.
3. Individuals with diabetes on complex treatment regimens such as >3 glucose-lowering therapies (including basal insulin).
4. Individuals with diabetes and atypical presentations, such as early-onset diabetes with a strong family history of diabetes (may reflect monogenic diabetes).
5. Individuals with diabetes with early oral hypoglycaemic agent failure.
6. Individuals with diabetes and features suggestive of endocrinopathies such as Cushing's syndrome, thyrotoxicosis, and acromegaly.

In addition, individuals with diabetes and abnormal ophthalmologic screening findings, renal function status (e-GFR <30 ml/min/1.73 m2 or presence of unexplained severe proteinuria), and vascular examination findings (severe peripheral arterial disease) should be referred to an ophthalmologist, nephrologist, and vascular surgeon, respectively, for specialist management and follow-up care.

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CHAPTER 15: DIAGNOSIS AND MANAGEMENT OF TYPE 1 DIABETES IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS

SUMMARY OF RECOMMENDATIONS

- Autoimmune type 1 diabetes (T1D) is marked by the presence of ≥2 islet-cell autoantibodies (glutamic acid decarboxylase 65 autoantibodies [GADA], tyrosine phosphatase-like insulinoma antigen 2 [IA-2A], insulin autoantibodies [IAA], and beta-cell specific zinc transporter 8 autoantibodies [ZnT8A]) with or without absolute endogenous insulin deficiency **(Level of evidence: A).**
- The aetiology of T1D is multifactorial, with environmental factors such as early-life enterovirus infections thought to play a key role in the onset of islet-cell autoimmunity **(Level of evidence: B).**
- A comprehensive management plan that has a holistic, compassionate, and individualised approach should be established following the diagnosis of T1D **(Level of evidence: E).**
- A structured and individualised diabetes education plan is integral in the management of T1D **(Level of evidence: A).**
- Diabetes education should address key aspects of care such as the causes and management of T1D (emphasising the pivotal role of lifelong insulin therapy), insulin storage, optimal injection techniques, self-monitoring of blood glucose (SMBG), optimal treatment targets, healthy eating habits, and features and management of hyperglycaemia and hypoglycaemia **(Level of evidence: A).**
- A proper nutritional plan emphasising a balanced diet of proteins, carbohydrates, fat, dietary fibre, vitamins, and minerals should be encouraged in individuals with T1D **(Level of evidence: A).**
- Insulin therapy is the only recommended glucose-lowering therapy in individuals with T1D **(Level of evidence: A).**
- A basal-bolus approach of insulin administration consisting of three pre-meal short- or rapid-acting bolus insulin doses and one or two doses of basal (intermediate- or long-acting) insulin doses is recommended to closely mimic the body's normal physiologic secretion of insulin by the pancreatic beta-cells **(Level of evidence: A).**
- Individuals with T1D are advised to perform SMBG at least six times a day (pre-breakfast, pre-mid morning snack, pre-lunch, pre-mid-afternoon snack, pre-supper, and at bedtime) **(Level of evidence: B).**
- The recommended target random blood glucose, fasting blood glucose, and glycated haemoglobin levels are 4.0-10.0 mmol/l (70-180 mg/dl), 4.0-7.0 mmol/l (70-120 mg/dl), and <7% (53 mmol/mol), respectively **(Level of evidence: A).**
- The HbA1c test should be performed every three months **(Level of evidence: A).**
- Insulin dose adjustments and more frequent SMBG is advised in individuals with T1D during periods of acute illness **(Level of evidence: E).**
- Effective management of T1D at school is important in improving school performance and prevention of diabetes-related complications **(Level of evidence: E).**

15.0 Introduction

The Uganda Diabetes Association fully endorses the East African Diabetes Study Group (EADSG) (1) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (2) guidelines for the management of type 1 diabetes. This chapter aims to exclusively review type 1 diabetes in children, adolescents, and young adults. We will discuss the definition, pathogenesis, and diagnosis of type 1 diabetes, and how to establish a comprehensive management plan for type 1 diabetes. The comprehensive management plan includes diabetes self-management education, nutritional management, insulin therapy in type 1 diabetes, glycaemic targets, home self-monitoring of blood glucose levels, management of sick days, and management of type 1 diabetes in children, adolescents, and young adults in schools.

15.1 Definition, pathogenesis, and diagnosis of type 1 diabetes

Type 1 diabetes (T1D) is a chronic disease that develops due to the autoimmune destruction of the beta-cells in the islets of Langerhans, resulting in insulin deficiency (absolute or relative). This state of insulin deficiency results in hyperglycemia and subsequent diabetes complications (1, 3). It is the most common chronic endocrine condition in children. It is characterised by chronic immune-mediated pancreatic beta-cell damage which occurs at a variable rate (ranging from months to years before the manifestation of clinical symptoms) and is influenced by several factors such as age, genetic predisposition (HLA DR and DQ alleles), environment (especially early-life infections and nutritional deficiencies), and race (3).

The aetiology of T1D is multifactorial, occurring during early life (in-utero), infancy, childhood, or adulthood. A close interaction between genes and the environment has been noted to play a central role in the pathogenesis of T1D (4-6). Genetic factors such as expression of the human leukocyte antigen (HLA) class II genes DR4, DQ8, and DQ2, which are present in 90% of individuals with T1D and 40% of healthy controls, have been shown to increase the susceptibility to develop T1D. In addition to the HLA genes, genes such as cathepsin H (CTSH), INS, GLIS3, CCR5, and BAD have also been implicated in predisposition to T1D (5, 6). These genes trigger an autoimmune process directed towards specific autoantigens such as insulin B-chain peptide and other components of the beta cells of the pancreas, such as glutamic acid decarboxylase-65, the protein tyrosine phosphatase, and the transmembrane zinc transporter 8 (4-6).

Besides the genetic influence, environmental factors such as viral infections, pesticide exposure, and dietary factors such as early infant introduction to cow milk and vitamin D deficiency have all been associated with the onset of T1D. Enterovirus infections, such as coxsackie B viral infections and congenital rubella syndrome, have been associated with the onset of islet-cell autoimmunity (3-7).

The diagnosis of T1D is dependent on recognition and assessment of symptoms, signs, and confirmation by blood tests. Healthcare professionals and the community need to have a high index of suspicion to diagnose T1D early because the condition commonly presents in childhood and adolescence, and may mimic other childhood illnesses. The symptoms of T1D are initially subtle and may progressively worsen over a few weeks to months (1, 3). Below are some of the common symptoms of T1D in children, adolescents, and young adults:

1. Polyphagia (excessive hunger)
2. Polyuria (passing large volumes of urine)
3. Polydipsia (excessive drinking to the excessive thirst)
4. Polyphagia (increased hunger)
5. Progressive weight loss and/or poor weight gain
6. Enuresis (bedwetting) or nocturia.
7. Fatigue or lethargy
8. Recurrent infections such as vaginal candidiasis especially in prepubertal girls, balanitis in uncircumcised boys, oral thrush, skin infections
9. Poor vision

10. Poor school grades/decline in school performance with inattention

The severe symptoms of T1D may include:

1. Lethargy with or without loss of consciousness, fits, and coma.
2. Severe dehydration (commonly unresponsive to rehydration).
3. Vomiting
4. Abdominal discomfort with abdominal pain
5. Fast deep breathing (hyperventilation)
6. Presence of fruity (sweet) breath

In addition to the above clinical signs and symptoms, laboratory evidence of hyperglycaemia and islet-cell autoantibody positivity is required to confirm the diagnosis of T1D. In children, adolescents, or young adults who present without classical symptoms of T1D, a diagnosis of T1D should be based on at least two abnormal blood glucose tests (Random blood glucose [RBG] level ≥11.1 mmol/l or 200 mg/dl, and/or fasting blood glucose [FBG] level ≥7.1 mmol/l or 126 mg/dl, and/or glycated haemoglobin [HbA1c] ≥6.5 % or 48 mmol/mol). If only one of the tests is abnormal, it is advised to repeat it on a different day. In children, adolescents, or young adults who present with the classic symptoms of hyperglycaemia (i.e., polyuria, polydipsia, weight loss), a diagnosis of T1D can be made based on a single RBG test result of ≥11.1 mmol/L (200 mg/dL) (1, 3).

Healthcare practitioners should be encouraged to test blood glucose levels in acutely ill children presenting with disorders of breathing and circulation and reduced levels of consciousness to rule out acute presentation of T1D (1).

The presence of ≥2 islet-cell autoantibodies such as glutamic acid decarboxylase autoantibodies (GADA) GAD-65, insulin autoantibodies (IAA), tyrosine phosphatase islet antigen 2 autoantibodies (IA-2A), and zinc transporter 8 autoantibodies (ZnT8A) also confirm the presence of T1D and preclude further testing for other diabetes subtypes that commonly occur in children, adolescents, and young adults such as monogenic diabetes (1, 3, 8). In one hospital-based study conducted on 85 recently diagnosed children and adolescents with T1D receiving specialised outpatient diabetes care from 19 tertiary hospitals in Uganda, the prevalence of autoantibodies to GAD-65, ZnT8, and insulin was 4.9% (95% confidence interval [CI] 1.8-12.4), 18.3% (95% CI 11.2-28.3), and 76.8% (95% CI 66.3-84.3), respectively. In this study population, T1D was associated with HLA-DQB1*02 and HLA-DRB1*04 (HLA-DR3 and HLA-DR4) genotypes (9).

The prevalence of islet-cell autoantibody positivity in individuals with T1D greatly varies with ethnicity. Compared with White populations of European ancestry, a low prevalence of islet-cell autoantibody positivity has been reported in Black African populations (10, 11). This suggests that, contrary to its significance in the diagnosis of T1D in White populations, screening for islet-cell autoantibodies in Black individuals suspected to have T1D may be of limited value.

Because T1D is characterised by autoimmune destruction of the islet cells of the pancreas, absolute insulin deficiency is the hallmark of T1D in some individuals (3, 8). Measurement of fasting, random, or stimulated (post-glucagon, mixed meal tolerance test, or oral glucose load) serum C-peptide concentrations in the absence of acute metabolic decompensation is a prudent approach for assessing endogenous insulin secretion and classifying diabetes subtypes (1, 12, 13). Therefore, measurement of random or fasting C-peptide concentrations as part of diagnosing T1D should be encouraged in tertiary healthcare facilities in Uganda.

The presence of random (stimulated) and fasting serum C-peptide concentrations of <0.20 nmol/l (0.6 ng/ml) and <0.08 nmol/l (0.2 ng/ml) reflects absolute insulin deficiency and significantly correlates with T1D (12, 13). However, it is important to note that a relative proportion of individuals with T1D may have residual insulin production by the beta-cells (especially early in the course of the condition), hence normal circulating serum C-peptide concentrations (9, 10, 12). In one study that undertook phenotypic and genotypic

characterisation of 85 Ugandan children and adolescents with recently diagnosed T1D, 50% (95% CI 35.9-64.0) of the study participants had relatively normal fasting serum C-peptide concentrations of ≥0.20 nmol/l (0.6 ng/ml) (9).

15.2 Establishing a comprehensive management plan after diagnosing type 1 diabetes

After confirming the diagnosis of T1DM, a comprehensive management plan that embraces a compassionate approach and a holistic understanding of the child or adolescent and his or her immediate family and other caregivers is preferred. The initial contact of the healthcare professionals and the patient, plus the immediate family, is crucial because it lays the foundation for future engagements with the family and also builds trust and confidence. It is important to identify and engage the primary caretakers (including school teachers) as early as possible in the management process (1).

Healthcare professionals should endeavour to keep the discussion about T1D as simple and honest as possible in a language that the family members and other caregivers can comprehend. Below are some of the aspects of T1D that need to be addressed during the initial and subsequent medical visits (1):

1. Address all the beliefs, fears, and expectations of the patient, parents, relatives, and other caregivers.
2. Discuss the available treatments and therapeutic options. It is important to emphasise that insulin is the mainstay of treatment.
3. Provide education on insulin administration, transportation, and storage.
4. Provide education on how to recognise, manage, and avoid common emergencies such as hypoglycemia and hyperglycemia.
5. Provide basic dietary advice such as ensuring a balanced diet, food portions, limiting additional sugar, and food hygiene. Families should be encouraged to use the available and culturally acceptable foods.
6. Provide education on the importance of regular and lifelong medical follow-up since T1D is a chronic disease and can lead to serious complications if not properly managed.
7. Discuss the basics of self-management support as a main pillar in achieving optimal goals of care. Communicate the need to regularly monitor blood glucose levels using a glucometer and how to interpret the measured blood glucose levels.
8. Schedule future education sessions, initially weekly or fortnightly and subsequently monthly or as appropriate.
9. Agree on one or two goals to work on.
10. Provide patients and family members with a provisional patient-tailored management plan and review it periodically.
11. Discuss the cultural beliefs and practices, especially the belief that traditional medicines can cure diabetes.

15.3 Diabetes self-management and education in type 1 diabetes

Because of the complexity of the treatment of T1D as a condition, children, adolescents, and young adults with T1D plus their families and caregivers require continuous support and patient-centred diabetes education from a multi-disciplinary team of healthcare professionals to achieve optimal treatment outcomes (1, 14). This aids the patients, family, and caregivers to understand the condition in great detail and empowers them to make appropriate, informed decisions concerning the management of the condition.

The standard diabetes education programs should be person-centred and interactive to ensure the active involvement of the child, adolescent, and young adult in the management process (14). To achieve the desired treatment outcomes, these diabetes educational programs should aim to address several key areas such as:

1. Discuss what T1D is, the probable causes or triggers, its symptoms, and the mode of treatment (underscoring

the need for lifelong insulin replacement therapy).
2. How the different types of insulin work (onset and duration of action).
3. Appropriate techniques of administration and storage of insulin.
4. The optimal treatment targets and goals.
5. The need to regularly monitor blood glucose levels and how to interpret them.
6. A detailed nutritional management plan and carbohydrate counting.
7. The signs and symptoms of hyperglycaemia and hypoglycaemia, and how to manage and prevent those two complications.
8. The clinical benefit of regular and lifelong medical follow-up.

15.4 Nutritional management in type 1 diabetes

An appropriate nutritional management plan is integral in managing children, adolescents, and young adults with type 1 diabetes. It should be individualised, considering the cultural, ethnic, and family traditions, in addition to the cognitive and psychosocial circumstances of the child or adolescent and their immediate family (1, 15). A specialist dietician or nutritionist should be part of the multidisciplinary paediatric diabetes care team to provide essential nutrition education to individuals with diabetes, parents, caregivers, and family members. The dietician or nutritionist should advise on the composition and timing of the meals and snacks, considering the child's growth and development needs, lifestyle, and current insulin regimen (15).

As part of healthy eating habits, a balanced diet composed of protein, carbohydrates, fat, dietary fibre, vitamins, and minerals is recommended for children, adolescents, and young adults with type 1 diabetes. To ensure that everyone benefits from and maintains good eating habits, it is strongly advised that the entire family adjust their eating habits to match those of the family member who has just received a T1D diagnosis.

Individuals with T1D, their parents, immediate family members, and caregivers should be introduced to the term "glycaemic index" (GI) and provided with adequate information about the glycaemic indices of the different commonly consumed types of food locally (1). Glycaemic index evaluates the quality of carbohydrates by assessing how they alter the blood glucose levels. It is calculated as a ratio of the change in the blood glucose levels postprandially (glycaemic response) after consumption of a standard food portion containing 50 grams of available carbohydrates relative to the glycaemic response induced by 50 grams of a reference carbohydrate, typically glucose or white wheat bread (16). Foods with a high GI (GI≥70 on the glucose scale) are those carbohydrate-containing foods that undergo rapid digestion, absorption, and metabolism, hence causing a high postprandial glucose excursion. In contrast, the foods whose digestion, absorption, and metabolism are slow are categorised as low-GI foods (GI≤55 on the glucose scale) (16-18).

The consumption of high-GI foods should be discouraged. In case some are to be consumed, the frequency and quantity should be greatly regulated. Individuals with T1D are advised to have a mixed meal containing at least one low-GI food to regulate the postprandial glucose levels. Fresh fruits and vegetables should be included in the daily meals because of their nutritional value (source of micronutrients) and low GI (1).

A table summarising the GI of some of the commonly consumed foods in Uganda has been presented in Chapter 6 of the guideline.

15.5 Insulin therapy in type 1 diabetes

Because T1D is a progressive condition with absolute insulin deficiency developing later in the course of the condition for most individuals, insulin therapy initiated immediately following diagnosis is the mainstay of management of T1D (1, 19). To achieve optimal and sustained glycaemic control, children, adolescents, and young adults with T1D ideally require multiple daily insulin injections (MDI) or

basal-bolus insulin administration. This approach of insulin administration closely mimics the normal physiologic pattern of insulin secretion by the pancreatic beta-cells (continuous low-level basal insulin secretion and postprandial high-level insulin secretion). It is preferred to the twice-daily premixed insulin administration (1, 19). The MDI constitutes pre-meal rapid-, short-, or analogue insulin administration and long-acting insulin administration at bedtime or intermediate-acting insulin administered once or twice daily (1, 19).

Before the initiation of insulin therapy, individuals with T1D, their family members, and caregivers have to be educated on several important aspects related to insulin use. These include the different insulin types (mode, onset, and duration of action), optimal insulin injection techniques and storage, daily home self-monitoring of blood glucose, meal planning (emphasis on carbohydrate intake), additional blood glucose testing in case of illness, physical activities, and during stressful conditions such as examination periods, and quick recognition and management of common diabetes-related acute complications such as hypoglycaemia related to insulin dosing and administration.

The onset, peak, and duration of action of the different types of insulin, plus the recommended insulin storage and injection techniques, are summarised and discussed in Chapter 10 of this guideline on insulin therapy in the management of T2D. The appropriate insulin dose for a child, adolescent, or young adult with T1D is dependent on several factors such as age, weight, pubertal stage, duration of diabetes, nutritional patterns, exercise patterns, menstrual cycles, intercurrent illness, and results of blood glucose and HbA1c (19). The recommended total daily insulin doses (TDD) for prepubertal, pubertal children, and adolescents are 0.7 to 1.0 IU/kg/day, 1.0 IU/kg/day, and 2.0 IU/kg/day, respectively. The recommended doses may be varied up or down from patient to patient, depending on how they respond to insulin therapy. For individuals with T1D in a partial remission period or honeymoon period (characterised by an increase in beta-cell insulin secretion), the TDD is usually <0.5 IU/kg/day. After calculating the TDD, the prandial (pre-meal) insulin dose requirements are about 55-70% of the TDD, while the basal or long-acting insulin dose requirement is about 30-45% of the TDD (19). The insulin doses to be administered are dependent on the pre-meal measured blood glucose levels, the composition of the meal (especially the portion and type of carbohydrate to be ingested), and any planned physical activity.

15.6 Self-monitoring of blood glucose and glycaemic targets in type 1 diabetes

Regular and planned self-monitoring of blood glucose (SMBG) using a glucometer or continuous glucose monitoring (CGM) using CGM devices is key in the management of T1D to avert the onset and progression of acute and chronic diabetes complications.

An individual with T1DM should perform SMBG at least six times a day. The recommended target RBG and FBG levels are 4.0-10.0 mmol/l (70-180 mg/dl) and 4.0-7.0 mmol/l (70-120 mg/dl). The HbA1c test should be performed every three months. Generally, the recommended target HbA1c for young individuals with T1D is <7% (53 mmol/mol) without frequent hypoglycaemia and/or severe hypoglycaemia. However, the HbA1c targets should be individualised based on specific circumstances (1, 20).

15.7 Ambulatory diabetes care in children, adolescents, and young adults with type 1 diabetes

Ambulatory or outpatient diabetes care for individuals with T1D requires a multidisciplinary team to plan an individualised treatment plan and targets, and also ensure a high quality of life, normal growth and development, early detection of comorbidities, and prevention of acute and chronic diabetes complications.

Individuals with T1D should be reviewed in an outpatient clinic at least every three months. At each clinic visit, structured

diabetes education emphasising insulin as a life-saving treatment for T1D, insulin dose adjustment, SMBG, glycaemic targets, healthy eating habits, meal planning, and the management of acute diabetes complications should be provided to individuals with T1D, family members, and caregivers (21). In addition to the structured diabetes education, the following should also be performed at each clinic visit:

1. Assess self-management skills
2. Assess for any history of hypoglycaemia (frequency, severity, and how it was managed)
3. Review the blood glucose monitoring records and adjust insulin prescriptions accordingly
4. Resting blood pressure and anthropometric measurements (weight, height, and body mass index) and assessment of the pubertal status (weight loss and/or delayed puberty may be suggestive of suboptimal glycaemic control)
5. A comprehensive oral, thyroid, and feet examination to detect any comorbidities.
6. A psychosocial assessment by screening for depression, family conflict, risk-taking behaviours, or other psychosocial dysfunction.
7. Assessment for substance abuse by asking about the use or experimentation with tobacco products (smoking).

Regarding laboratory tests, testing for GADA, IA-2, IAA, and ZnT8A should be performed once at the time of diagnosis. The complete blood count, urea, and serum electrolytes should be performed at diagnosis and only repeated if there is a clinical indication during an outpatient visit. The HbA1c test should be performed initially at diagnosis and then repeated every three months. A fasting or random (preferably) lipid profile should be performed initially at diagnosis if >2 years of age. If the initial lipid profile is within the normal limit, initiate serial screening from the age of 11 years. If the results are normal, it can be repeated every three years (21).

Screening for diabetic kidney disease and neuropathy using urine albumin creatinine ratio measurement and neurologic foot examination, respectively, can be performed at puberty or ≥10 years, or after five years of diabetes duration. Screening for diabetic kidney disease and neuropathy should be repeated annually. Screening for diabetic retinopathy using dilated eye examination (digital fundal photography or slit-lamp examination) can be performed after 11 years of age, or the onset of puberty, or after 3-5 years of diabetes. It should be repeated every two years (21).

Screening for hypothyroidism due to autoimmune thyroiditis can be done at diagnosis after the patient is clinically stable and then repeated every 1-2 years. Screening for coeliac disease using the tissue transglutaminase auto-antibodies should be done at diagnosis and repeated within two years of the diagnosis, then every five years if the initial tests are within the normal limits (21).

15.8 Sick day management in children, adolescents, and young adults with type 1 diabetes

Children, adolescents, and young adults with T1D are also prone to acute illnesses and delayed recovery from infection, especially if the glycaemic control is suboptimal due to the related alteration in the immune function (22). Acute illnesses presenting with fever are associated with increased circulating concentrations of stress hormones such as cortisol, norepinephrine, and glucagon, which promote glycogenolysis, gluconeogenesis, and insulin resistance with eventual hyperglycaemia and diabetic ketoacidosis if the insulin doses are not adjusted (23). Acute illnesses associated with vomiting and diarrhea (such as gastroenteritis) may lower blood glucose, with the possibility of hypoglycemia rather than hyperglycemia. This is due to decreased food intake, poor intestinal absorption, and reduced gastric emptying (24, 25).

In acute illnesses, frequent blood glucose monitoring is recommended to guide insulin dose reductions. Stopping insulin treatment is not recommended. Hyperglycaemia, fever, excessive

glycosuria, and ketonuria collectively contribute to increased fluid losses. Because of this, increased oral intake of fluids is recommended (24). Sugar-free fluids are recommended if the blood glucose level is > 10 mmol/l, while sugar-containing fluids are recommended if the blood glucose level is <10 mmol/l (1).

To manage acute illness-related hyperglycaemia and prevent ketoacidosis and hospital admission, additional doses of short- or rapid-acting insulin are required. In cases of hyperglycaemia with minimal or without ketosis, it is recommended to give an additional 5-10% of TDD as short-acting insulin. Do not increase the insulin dose by more than 0.1 units/kg. This may be repeated every 2–4 hours based on the blood glucose results (1, 24). In case of a fever > 38°C or hyperglycaemia and marked ketonuria (moderate to high), it is recommended to give an additional 10-20% of TDD as short-acting insulin. Young individuals with T1D and a fever >39°C may require as much as 50% more of TDD. For children with T1D who are in the honeymoon period, increase the TDD up to 1 unit/kg/day. Monitor the blood glucose every 2-4 hours and serum or urine ketones 1-2 times per day (1, 24).

In cases of acute illness associated with hypoglycaemia, such as gastroenteritis, oral intake of sugar-rich fluids such as sugary fruit juices and oral rehydration solution is recommended. Close monitoring of the urine output and body weight is advised with continuous oral rehydration. Reduction of the TDD by 20-50% may be required. Additionally, the short- or rapid-acting pre-meal insulin can be excluded from the treatment regimen or its dose reduced by 1-2 units. The intermediate- and long-acting insulin doses should also be reduced to avoid episodes of hypoglycaemia (1, 24).

15.9 Management of children, adolescents, and young adults with type 1 diabetes at school

Effective management of T1D in the school environment is key for optimal school performance and prevention of acute and long-term diabetes complications. Given that children and adolescents spend a considerable amount of time at school, school personnel should be prepared to support students with diabetes mellitus to fully participate in academic and extracurricular activities. Key to effective T1D management is ensuring optimal blood glucose control by carefully balancing food intake, physical activity, insulin, and/or other medication, every day (1, 26).

For effective diabetes management, young individuals with T1D should be supported to do the following:

1. Regularly check their blood glucose levels
2. Plan for the disposal of sharp objects and materials that come in contact with blood
3. Recognize and treat hypoglycemia
4. Recognize and treat hyperglycemia
5. Administer insulin and/or other diabetes medication
6. Plan for school-wide disasters and emergencies
7. Follow an individualized meal plan
8. Promote regular physical activity
9. Maintain a healthy weight
10. Help to plan for special events, field trips, and extracurricular activities
11. Deal with emotional and social issues
12. Understand why diabetes self-management is important

For one to deliver effective T1D management in the school environment, the following needs to be in place: a school health team, a diabetes management plan, an education plan, training, and support for school health team members. Healthcare providers should be advocates for young individuals with T1D in the school setting. Working collaboratively with school personnel, healthcare providers should ensure that young individuals with T1D have the same educational and extracurricular activities as their peers in the communities (1, 26).

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CHAPTER 16: MANAGEMENT OF ACUTE AND CHRONIC COMPLICATIONS IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH TYPE 1 DIABETES

SUMMARY OF RECOMMENDATIONS
ACUTE DIABETES COMPLICATIONS

Hypoglycaemia

- Hypoglycaemia is characterised by the presence of signs and symptoms of hypoglycaemia, low measured blood glucose concentration (blood glucose level ≤3.9 mmol/l or 70 mg/dl), and resolution of the signs and symptoms after the correction of the low blood glucose concentration (Whipple's triad) **(Level of evidence: A).**
- Risk factors of hypoglycaemia include excess insulin doses, reduced food intake, increased physical activity or exercise, prior history of severe hypoglycaemia, long duration of diabetes, and comorbidities such as coeliac disease, Addison's disease, and hypothyroidism **(Level of evidence: B).**
- Monitoring for hypoglycaemia is a key component of diabetes care and education. Self-monitoring of blood glucose should be encouraged in young individuals with type 1 diabetes (T1D) to easily detect and manage hypoglycaemia **(Level of evidence: A).**
- Immediate management of a hypoglycaemic episode using any locally available form of sugar is advised. The risk factors of hypoglycaemia should also be addressed **(Level of evidence: A).**
- Future episodes of hypoglycaemia should be prevented in young individuals with T1D due to its associated long-term sequelae. Diabetes education to children, adolescents, and young adults with T1D, the family, caregivers, and the community is important in the prevention of hypoglycaemia **(Level of evidence: A).**

Diabetic ketoacidosis

- Diabetic ketoacidosis (DKA) is characterised by the triad of hyperglycaemia (blood glucose >11.0 mmol/l or 200 mg/dl), significant ketonemia or ketonuria (serum ketone concentrations >3.0 mmol/l or >2+ ketones on urine dipsticks), and acidosis (serum bicarbonate concentration of <15 mmol/l and/or venous pH <7.3) (Level of evidence: B).
- Management of DKA should involve urgent measurement of the blood glucose, blood or urine ketones, serum electrolytes, and blood gases (if available), and assessment of the level of consciousness **(Level of evidence: E).**
- The goals of therapy are to correct dehydration and acidosis, reverse ketosis, reduce blood glucose concentrations, monitor for acute complications, and identify and treat any precipitating factor **(Level of evidence: B).**
- Fluid replacement should be initiated before insulin therapy. Use one or more boluses of 0.9% normal saline infused over 20-30 minutes and replace the estimated fluid deficit using the appropriate crystalloid (not colloids) over 24-48 hours (Level of evidence: A).
- Initiate insulin therapy at least one hour after fluid replacement. Begin with 0.05-0.1 units/kg/hour (0.05 units/kg/hour in mild DKA) **(Level of evidence: B).**
- Potassium replacement should be dependent on the measured serum potassium concentrations. Generally, start with 40 mmol/l of potassium chloride or 3-4 mmol/kg/day (Level of evidence: B)
- The use of bicarbonate therapy is not recommended in the management of DKA (Level of evidence: C).
- Phosphate replacement therapy should be initiated immediately in cases of severe hypophosphatemia (<1 mg/dl or 0.32 mmol/l) with or without associated features (Level of evidence: C).
- Prevention of DKA should involve identification and management of the underlying cause **(Level of evidence: E).**

CHRONIC MICRO- AND MACROVASCULAR DIABETES COMPLICATIONS

- Individuals with TID can also develop chronic vascular-related complications, especially in adulthood **(Level of evidence: E).**
- Intensive diabetes education and achieving the optimal glycaemic targets are pivotal in preventing the onset and progression of chronic diabetes complications **(Level of evidence: A).**

Diabetic kidney disease

- Screening for diabetic kidney disease (DKD) should be performed at puberty or from age 11 years, whichever is earlier, with 2–5 years of diabetes duration, and repeated annually thereafter, by measuring the urine albumin-creatinine ratio (ACR) on an early-morning urine sample and serum creatinine to calculate the e-GFR (Level of evidence: B).
- Management of DKD should involve optimising blood glucose, blood pressure, and lipid control, and therapy using angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-2 receptor blockers (ARBs) **(Level of evidence: A).**

Diabetic neuropathy

- Screening for peripheral neuropathy should start at puberty or from 11 years with 2-5 years of diabetes duration and then be repeated annually, by performing a comprehensive foot examination and assessment of symptoms of neuropathic pain **(Level of evidence: B).**

Diabetic retinopathy

- Screening for diabetic retinopathy (DR) should start at puberty or from age 11 years with 2–5 years of diabetes duration, using fundal photography or indirect ophthalmoscopy using a dilated slit lamp examination **(Level of evidence: B).**
- The frequency of screening depends on the findings of the initial screening of DR (every three years for those without DR, every two years for those with optimal glycaemic control and mild nonproliferative DR [NPDR], and every three months for those with long-standing suboptimal glycaemic control and moderate to severe NPDR and proliferative DR) **(Level of evidence: B).**

Hypertension

- Hypertension in children and adolescents (<13 years) is defined as blood pressure (BP) ≥ the 95th percentile for age, sex, and height. In older adolescents (age ≥13 years), it is defined as systolic BP ≥130 and/or DBP ≥80 mmHg. Hypertension should be diagnosed after measurement of ≥3 abnormal blood pressure readings **(Level of evidence: B).**
- The management of hypertension in young individuals with T1D should involve lifestyle interventions such as weight loss, increased physical activity, and dietary modifications. If unable to achieve optimal blood pressure targets with these interventions, initiate oral blood pressure-lowering therapy **(Level of evidence: E).**

Dyslipidaemia

- Screening for dyslipidaemia by performing a random lipid profile test is recommended soon after diagnosis (when glycemia is stabilized) in all young individuals with T1D from 11 years of age **(Level of evidence: E).**
- The optimal low-density lipoprotein cholesterol (LDL) level is <2.6 mmol/l (100 mg/dl) **(Level of evidence: E).**
- Aim to improve glycaemic control and initiate lifestyle interventions such as dietary changes and increased physical activity if the LDL levels are ≥2.6 mmol/l (100 mg/dl) **(Level of evidence: E).**
- Statin therapy should be considered in children aged >10 years if the lifestyle management interventions do not achieve the optimal LDL level **(Level of evidence: E)**

This chapter will discuss the commonly encountered acute and chronic vascular-related diabetes complications in children, adolescents, and young adults with type 1 diabetes (T1D), in addition to specific metabolic conditions associated with T1D.

16.1 Hypoglycaemia in children, adolescents, and young adults with type 1 diabetes

Hypoglycaemia, a common acute complication in individuals with T1D, has been extensively discussed in Chapter 12 of this guideline. It is characterised by the presence of Whipple's triad i.e., the presence of signs and symptoms of hypoglycaemia, low measured blood glucose concentration (blood glucose level ≤3.9 mmol/l or 70 mg/dl), and resolution of the signs and symptoms after the correction of the low blood glucose concentration (1). Hypoglycaemia in young individuals with T1D may present in different degrees of severity. Clinically important or serious hypoglycaemia occurs if the blood glucose level is <3.0mmol/L (54mg/dl). Neurogenic symptoms and cognitive dysfunction occur below this level. Severe hypoglycaemia is defined as an event associated with severe cognitive impairment (including coma and convulsions) requiring assistance by another person to administer carbohydrates, glucagon, or intravenous dextrose solution (2-4). Impaired awareness of hypoglycaemia is a condition in which the ability to detect hypoglycaemia is diminished or absent because of defective counter-regulatory hormone responses following recurrent episodes of hypoglycaemia (5). During hypoglycaemia episodes in healthy individuals without diabetes, endogenous insulin secretion is shut down, and counter-regulatory hormones (glucagon, epinephrine, and norepinephrine) are released in response. However, in people with diabetes, there is a progressive loss of glucagon response to insulin-induced hypoglycemia. This has been demonstrated as early as 12 months after diabetes onset and is lost in most people with T1D by 5years of disease (5, 6).

16.1.1 Risk factors and manifestation of hypoglycaemia in young individuals with T1D

Several risk factors increase the risk of hypoglycaemia in young individuals with T1D. These include precipitants such as excess insulin doses, reduced food intake, increased physical activity or exercise, and alcohol ingestion, impaired awareness of hypoglycaemia, prior history of severe hypoglycaemia, long duration of diabetes, and comorbidities such as coeliac disease, Addison's disease, and hypothyroidism (4, 7).

The manifestation of hypoglycaemia has also been discussed in Chapter 12 of the guideline. The signs and symptoms of hypoglycaemia are either neuroglycopenic (due to the brain's deprivation of glucose) or neurogenic (due to the activation of the sympathoadrenal system) (4, 7). Because episodes of hypoglycaemia may occur at night, it is important to be aware of some of the clues of nocturnal hypoglycaemia in children, adolescents, and young adults with T1D. These include the inability to sleep or restlessness, moaning, sweating profusely, waking up with a fast heart rate, memory loss, headache, sleepwalking, and having nightmares. For young individuals with T1D, always look out for nonspecific manifestations of hypoglycaemia such as difficulty concentrating, irritability, agitation, quietness, stubbornness, and tantrums (4).

16.1.2 Management of hypoglycaemia in children, adolescents, and young adults with type 1 diabetes

Diabetes education should focus on the recognition of precipitants and risk factors for hypoglycaemia, the ability to detect subtle symptoms, the importance of confirming low glucose levels by blood glucose monitoring, appropriate

hypoglycaemia treatment, and how to prevent future hypoglycaemic events.

The general rule for managing a hypoglycaemic episode is to give sugar in any available form immediately. These include sweets, glucose tablets or powder, sugar, honey (1 tablespoon), a glass (125 mls) of juice or soda (not diet soda) (4, 7). After this correction of hypoglycaemia, it takes 10-20 minutes for the blood glucose levels to rise. Therefore, the blood glucose level has to be tested 15 minutes following the correction. If it is still <3.9 mmol/l, give another carbohydrate. Once hypoglycaemia is reversed, the individual should have his or her usual meal or snack (4, 7).

In cases of severe hypoglycaemia, the treatment should be urgent. Its management involves the administration of intramuscular or subcutaneous glucagon if available (1 mg and 0.5 mg for individuals weighing >25 kg and <25 kg, respectively) or intravenous dextrose solution (3 ml/kg of 10% dextrose or 1 ml/kg of 50% dextrose). If the patient can eat, give oral rapid-acting foods such as glucose, sugar, or honey (4, 7).

16.1.3 Prevention of hypoglycaemic episodes

One of the key strategies for preventing future and recurrent episodes of hypoglycaemia is providing regular structured diabetes education to the patients, parents, caregivers, peers, and community. They should be provided with information about the early warning signs and symptoms of hypoglycaemia and how to urgently manage these hypoglycaemic episodes, the significance of regular SMBG (with additional blood glucose monitoring during physical activities and acute illness) and proper planning of meals (with daytime and bedtime snacks), the effects of physical exercise on blood glucose levels, and adjustment of glycaemic targets, insulin types, and doses (especially in children and individuals with hypoglycaemic unawareness) (4, 7).

16.2 Diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes

Diabetic ketoacidosis (DKA) is another common acute complication in young individuals with T1D. It develops due to an absolute or relative insulin deficiency with a concomitant increase in the circulating concentrations of the counter-regulatory hormones such as glucagon and epinephrine, resulting in the triad of hyperglycaemia (blood glucose >11.0 mmol/l or 200 mg/dl), significant ketonemia or ketonuria (serum ketone concentrations >3.0 mmol/l or >2+ ketones on urine dipsticks), and acidosis (serum bicarbonate concentration of <15 mmol/l and/or venous pH <7.3) (7-9).

16.2.1 Manifestation of diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes

The signs and symptoms of DKA, as discussed in Chapter 12 of this guideline, are similar in individuals with T1D and type 2 diabetes (T2D). It is important to know that most of the symptoms are nonspecific and may mimic several infections in our settings, such as malaria, pneumonia, and gastroenteritis. Therefore, healthcare professionals are advised to routinely perform fingerstick blood glucose measurements for children or adolescents presenting with unexplained reduced levels of consciousness, rapid breathing, abdominal pain, nausea, and vomiting without diarrhea (7, 9).

The physical examination of a child or adolescent with DKA should involve a thorough assessment for dehydration or volume depletion (to determine the severity), level of consciousness, and measurement of weight. The blood glucose and ketone levels should be measured either in the laboratory or using glucometers or ketone test strips. In the absence of glucometers, glucose,

and ketone strips, a urinalysis can also be performed to test for urine glucose and ketones. Other vital laboratory tests that should be performed include renal function tests (including extended serum electrolytes), a full blood count, arterial blood gases (if available), culture, and sensitivity tests for specific microbiological samples if an infection is suspected (7).
It is important to remember the differential diagnoses for DKA, such as gastroenteritis (in DKA, vomiting is present without diarrhea), surgical emergencies presenting with acute abdominal pain, such as acute appendicitis, and infections associated with metabolic acidosis, such as severe pneumonia and malaria (7).

16.2.3 Management of diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes

As highlighted in Chapter 12 of this guideline, the goals of the management of DKA in individuals with T1D and T2D should be the restoration of normal circulatory blood volume, the prevention and/or correction of prevalent electrolyte imbalances, the correction of acidosis and hyperglycaemia, monitoring for complications associated with DKA, and addressing the underlying cause. Broadly, the steps of management of DKA include fluid replacement (which is usually the initial intervention), insulin therapy, electrolyte replacement therapy, management of complications associated with DKA, and identification and management of the precipitating factors of DKA (7, 9, 10).

16.2.3.1 Fluid replacement in children, adolescents, and young adults with type 1 diabetes

The first step in the management of a critically ill or shocked patient is resuscitation, ensuring appropriate life support (airway, breathing, and circulation). A large-bore intravenous cannula has to be set up immediately to initiate fluid replacement therapy. Generally, crystalloids are preferred to colloids (7, 9). Children with DKA have a deficit in extracellular fluid (ECF) volume of about 7% of body weight. In cases of mild, moderate, and severe DKA, the estimates of ECF volume deficit are 5%, 7%, and 10% of body weight, respectively, in relation to the dehydration status (9).
As previously highlighted in Chapter 12, it is important to calculate the corrected serum sodium concentration to help assess the true relative deficits of sodium and water. Because hyperglycaemia is associated with osmotic movement of water into the extracellular space, this results in dilutional hyponatremia. This means that the measured serum sodium concentration is not a true reflection of serum sodium status in a state of hyperglycaemia. Several formulae for correcting serum sodium in cases of hyperglycaemia are available freely online (11, 12).
For children or adolescents who are volume-depleted but not in shock, fluid replacement should be initiated immediately using 0.9% normal saline infusion with 10-20 ml/kg infused over 20-30 minutes. In case of poor tissue perfusion and shock, the initial fluid bolus volume should be 20 ml/kg infused as fast as possible. The circulatory status should be assessed after each bolus of fluid (7, 9). For fluid deficit replacement or maintenance therapy, 0.45%-0.9% normal saline or Ringer's lactate infusion, depending on the serum sodium and potassium levels, is preferred. The healthcare professional should aim to replace the estimated fluid deficit (minus the initial fluid bolus amount) over 24-48 hours. Once the blood glucose levels reduce to 17 mmol/l (300 mg/dl), add 5%-10% dextrose infusion to the intravenous replacement fluids (7, 9).

16.2.3.2 Insulin therapy in children, adolescents, and young adults with type 1 diabetes

Initiation of insulin therapy is important

in restoring normal cellular metabolism, suppressing lipolysis and ketogenesis, and normalising blood glucose concentrations (13). Insulin therapy should be initiated after one hour of fluid therapy, after restoring optimal circulatory status. Initiate an intravenous insulin infusion of short-acting (soluble or regular) insulin at 0.05-0.1 units/kg/hour. The lower rate of insulin infusion of 0.05 units/kg/hour is preferred for children <5 years and mild DKA. In case intravenous cannulation is not possible due to severe dehydration, administer the insulin via the intramuscular route. Avoid the use of central venous catheters for insulin administration because it is associated with erratic insulin delivery (7, 9).

Insulin therapy at the above-recommended rates should be continued until the resolution of DKA (pH >7.30, serum bicarbonate >18 mmol/l, normal serum or urine ketones, and clinical improvement). This process usually takes longer than the normalisation of blood glucose concentrations (9). To avoid the sudden decrease in the blood glucose concentrations and the onset of hypoglycaemia, a 5% dextrose infusion should be added to the intravenous fluids once the blood glucose concentrations drop to approximately 14-17 mmol/l (250-300 mg/dl) (Add 50 mls of 50% dextrose to 450 mls of normal saline to make a 5% dextrose or 0.9% saline solution 7, 9).

In situations where continuous intravenous insulin administration is not possible and in children or adolescents with uncomplicated mild to moderate DKA (in the absence of peripheral tissue hypoperfusion), subcutaneous hourly or two-hourly rapid-acting insulin analogues (initiated at a dose of 0.1-0.15 units/kg every 2 hours) or subcutaneous four-hourly short-acting insulin (initiated at a dose of 0.8-1.0 units/kg/day in divided doses) can be used as an option to intravenous insulin administration. The doses can be adjusted based on changes in the blood glucose concentrations and acidosis status (9).

A change from intravenous to subcutaneous insulin therapy in individuals with DKA can be initiated once vomiting ceases and oral intake improves. Additionally, continuous intravenous insulin therapy may not be indicated if the blood glucose concentrations reduce, metabolic acidosis resolves (serum bicarbonate ≥18 mmol/l and venous pH >7.3), and serum electrolytes such as potassium are within the normal ranges. It is important to remember that urine ketone strips measure acetoacetate and acetone, which may be persistent in urine despite having normal serum beta-hydroxybutyrate levels. Therefore, regarding the resolution of ketosis, the absence of ketonuria should not be used as an endpoint for determining the resolution of DKA (7).

Subcutaneous short- or rapid-acting insulin can ideally be started before a meal, and the intermediate- and long-acting basal insulin maintained. To avoid rebound hyperglycaemia, rapid-acting insulins such as insulin aspart or lispro, and short-acting insulins such as soluble or regular insulin should be administered 15-30 minutes and 30-60 minutes before stopping the insulin infusion, respectively (7, 9).

16.2.3.3 Potassium replacement therapy in children, adolescents, and young adults with type 1 diabetes

Young individuals with DKA usually present with total body potassium deficits of 3-6 mmol/kg. The potassium loss in patients with DKA is due to several factors, such as the effects of insulin deficiency, acidosis, and volume depletion (due to vomiting) with secondary hyperaldosteronism. Insulin administration and correction of acidosis are associated with intracellular influx of potassium, hence reducing the serum potassium concentrations. Acute kidney injury associated with DKA results in hyperglycaemia (7, 9). Because of this, measurement of serum potassium concentrations and monitoring of urine

output are important before initiating potassium replacement therapy.

If the child or adolescent with DKA is hypokalaemic, initiate intravenous potassium replacement at the time of initial fluid replacement and before starting insulin therapy. If the initial serum potassium levels are <3.5 mmol/l, do not initiate insulin therapy. It is advised to give a bolus of potassium (not exceeding 0.5 mmol/kg/hour) alongside cardiac monitoring. If the child or adolescent with DKA is hyperkalaemic, do not initiate potassium replacement therapy until adequate urine output is recorded. Give only non-potassium-containing fluids and reassess serum potassium levels every hour. Initiate intravenous potassium infusion when the serum potassium levels are <5.5 mmol/l (7, 9).

Generally, potassium replacement should be initiated after the initial fluid replacement therapy and concurrently with insulin therapy. Initiate potassium replacement by adding potassium chloride to intravenous normal saline fluids at a total concentration of 40 mmol/l or 3-4 mmol/kg/day (i.e., 20 mmol per 500ml normal saline infusion). The amount and rate of potassium replacement should depend on the measured serum potassium concentrations. The maximum recommended rate of intravenous potassium replacement is usually 0.5 mmol/kg/h. The serum potassium concentrations should be monitored every 6 hours or more often after starting insulin therapy (7, 9).

In cases where intravenous potassium is unavailable, potassium may be replaced by giving the child or adolescent fresh fruit juice (watermelon, passion fruit) or bananas. If using oral rehydration solution, no additional potassium is required (7).

Cardiac monitoring with electrocardiography (ECG) is important when replacing potassium levels, especially in cases where immediate or regular serum potassium measurement is unavailable. Prolongation of the PR interval, T wave flattening and inversion, ST depression, prominent U waves, and apparent long QT interval (due to fusion of the T and U waves) on ECG indicates hypokalaemia while tall, peaked, symmetrical, T waves and shortening of the QT interval suggest hyperkalemia (7, 9).

16.2.3.4 Correction of acidosis and phosphate replacement therapy in children, adolescents, and young adults with type 1 diabetes

Fluid and insulin replacement are usually adequate to reverse acidosis in patients with DKA. Available evidence does not show any clinical benefit with the use of bicarbonate in the correction of acidosis in DKA. Bicarbonate therapy in DKA is associated with paradoxical central nervous system acidosis and can cause hypokalaemia due to rapid correction of acidosis. However, bicarbonate therapy can be used in children presenting with life-threatening hyperkalemia or severe acidosis (venous pH <6.9) with compromised cardiac function (9).

Phosphate depletion is common in patients with DKA due to the effects of osmotic diuresis, metabolic acidosis, fluid, and insulin replacement therapy. Severe hypophosphatemia may manifest as metabolic encephalopathy, seizures, impaired cardiac function, ventricular arrhythmia, proximal myopathy, ileus, haemolytic anaemia, and rhabdomyolysis. Phosphate replacement therapy should be initiated immediately in cases of severe hypophosphatemia (<1 mg/dl or 0.32 mmol/l) with or without associated features. Insulin therapy can be stopped or the rate of administration reduced until the serum phosphate concentrations normalise (9).

16.2.3.5 Monitoring of children, adolescents, and young adults with diabetic ketoacidosis

Individuals with DKA should be monitored closely. The table below summarises

Table 1. Parameters to monitor and the frequency of monitoring

PARAMETERS	MONITORING INTERVAL
A: CLINICAL CHARACTERISTICS	
Mental status	1 hour
Vital signs (temperature, pulse rate, respiratory rate, and blood pressure)	1 hour
Electrocardiography	Initially, and as indicated
Weight	Initially and daily
B: THERAPY	
Fluid intake and output (ml/hour)	4 hours
Insulin (units/hour)	1 hour
Potassium (mmol/l)	4 hours
Glucose (mmol/l)	4 hours
Bicarbonate and phosphate (mmol/l)	4 hours (if indicated)
C: LABARATORY PARAMETERS	
Glucose concentrations (bedside)	1 hour
Serum potassium and pH	2 hours
Serum sodium, chloride, and bicarbonate concentrations	4 hours
Serum phosphate and magnesium concentrations	4 hours
Serum urea and creatinine	4 hours

16.2.3.6 Complications of diabetic ketoacidosis

The complications of DKA have been discussed in Chapter 12 of this guideline. However, for this chapter, we will discuss cerebral oedema or dysequilibrium syndrome as one of the complications of DKA because it is associated with a high rate of mortality.

The onset of cerebral oedema and ensuing increased intracranial pressure is related to the severity of acidosis, rate and amount of rehydration, the severity of electrolyte imbalance and hyperglycaemia, and rate of reduction of the serum blood glucose concentrations (7, 9). Patients with cerebral oedema will present with altered mentation (restlessness, irritability, increased drowsiness, and convulsions), headache, hypertension, bradycardia, and irregular breathing pattern (Cushing's triad) (7, 9).

Its management should be initiated promptly by giving intravenous mannitol at a dose of 0.5-1 g/kg over 10-15 minutes or 3% hypertonic saline at a dose of 2.5-5 ml/kg over 10-15 minutes (9). It is important to note that once you suspect cerebral oedema, initiate the treatment immediately. Do not wait for a radiologic diagnosis.

16.3 Chronic microvascular and macrovascular diabetes complications in children, adolescents, and young adults with type 1 diabetes

Similar to adults with T2D, young

individuals with T1D can also develop chronic microvascular and macrovascular diabetes complications, leading to premature morbidity and mortality. These complications include diabetic neuropathy, diabetic retinopathy (DR), diabetic kidney disease (DKD), stroke, peripheral arterial disease (PAD), and cardiac disease (7, 14).

These complications are rarely clinically evident in childhood and adolescence. However, in cases when an individual was diagnosed with T1D at a young age or has had poor glycaemic control over a prolonged period, these complications can develop even in childhood and adolescence (7, 14). This clarifies the significance of early and maintained optimal glycaemic control in T1D care, as it plays a pivotal role in mitigating the onset and progression of chronic vascular-related diabetic complications (15, 16). This concept is called the legacy effect or metabolic memory (17). Additionally, growth failure and pubertal delay are some of the early indicators of poor glycemic control (18, 19) and may indicate the onset of chronic diabetes complications. Therefore, regular growth monitoring in children and adolescents is one of the important screening tools for chronic diabetes complications.

Other risk factors of chronic microvascular and macrovascular diabetes complications in young individuals with T1D include longer duration of diabetes, older age, puberty, smoking, dyslipidaemia, co-existing hypertension, obesity, and family history of cardiovascular disease (CVD) (20-24).

16.3.1 Diabetic kidney disease in children, adolescents, and young adults with type 1 diabetes

Diabetic kidney disease is one of the common microvascular diabetes complications in individuals with T1D, especially in the setting of long diabetes duration, suboptimal glycaemic control, dyslipidaemia, and hypertension (20, 23, 25). The grading of chronic kidney disease based on the degree of albuminuria and estimated glomerular filtration rate (eGFR) has been discussed in Chapter 13 of this guideline.

The screening for DKD should be performed at puberty or from age 11 years, whichever is earlier, with 2–5 years of diabetes duration, and repeated annually thereafter. The recommended screening approaches are the measurement of the urine albumin-creatinine ratio (ACR) on an early-morning urine sample and serum creatinine to calculate the e-GFR (7, 14, 26). An early-morning urine sample is preferred to minimise the effects of exercise, postural changes, and diurnal variations on albumin excretion. The ACR is also affected by other factors such as fever, infections, menstrual periods, and marked hypertension (14, 27).

If the ACR ≥3 mg/mmol (30 mg/g), albuminuria is present. This should be confirmed by repeating the test on 2 additional samples over 3-6 months. If 2 out of the 3 urine samples tested for albuminuria are positive (ACR ≥3 mg/mmol), it reflects persistent albuminuria. Individuals with ACR ≥30 mg/mmol or eGFR <90ml/min/1.73m2 at the 1st screening test should be referred to a nephrologist for further evaluation (14).

As part of the management plan, it is advised to optimise blood glucose, blood pressure, and lipid control. Individuals with albuminuria or DKD should be initiated on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-2 receptor blockers (ARBs). Due to the teratogenic effects of ACEI and ARBs, women of childbearing age should receive reproductive counselling and be advised about the use of reliable contraceptive methods (7, 14, 26).

16.3.2 Diabetic neuropathy in children, adolescents, and young adults with type 1 diabetes

Type 1 diabetes affects both the somatic and autonomic components of the nervous system. Peripheral neuropathy presents with paraesthesia, hyperaesthesia, numbness, and reduced reflexes. These features occur in a symmetric distal-to-proximal gradient described as a "glove and stocking" pattern. Autonomic neuropathy may present as altered gastric function (gastroparesis), bloating, decreased appetite, constipation, diarrhea, urinary retention, palpitations, erectile dysfunction, abnormal sweating, and abnormal pupillary responses (7, 14).

The screening for peripheral neuropathy in young people with T1D should start at puberty or from 11 years with 2-5 years of diabetes duration, and then be repeated annually. The screening should involve a comprehensive foot examination, including inspection, palpation of dorsalis pedis and posterior tibial pulses, determination of proprioception, vibration, and monofilament sensation, and assessment of symptoms of neuropathic pain (7, 14, 26).

16.3.3 Diabetic retinopathy in children, adolescents, and young adults with type 1 diabetes

Diabetic retinopathy is mainly caused by bleeding and new blood vessel formation in the retina. It is one of the most common causes of preventable blindness. The risk factors for the onset and progression of DR in young individuals with T1D include poor blood glucose control, increasing duration of diabetes, hypertension, pregnancy, dyslipidaemia, and albuminuria (28-30). Screening for diabetic retinopathy (DR) should start at puberty or from age 11 years with 2–5 years of diabetes duration. The screening should be performed by an ophthalmologist or ophthalmic clinical officer by direct ophthalmoscopy using fundal photography or indirect ophthalmoscopy using a dilated slit lamp examination. For young individuals with diabetes duration of <10 years, mild nonproliferative DR (NPDR, i.e., microaneurysms only), and optimal glycaemic targets, screening assessment is recommended every two years. The screening of DR can be performed every 3 years if no features of DR are observed on initial screening. More frequent screening performed every three months for 6-12 months is recommended for individuals with long-standing suboptimal glycaemic control and moderate to severe NPDR and proliferative DR (PDR) (7, 14, 26).

The screening should also assess for the presence of additional ocular disorders such as major refractive errors, glaucoma, and cataracts. Young individuals with vision-threatening DR (severe NPDR and diabetic macular oedema) should be urgently referred to an experienced ophthalmologist for specialist treatment. The recommended treatment options for such vision-threatening forms of DR include laser therapy and intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents (14).

16.3.4 Macrovascular diabetes complications in children, adolescents, and young adults with type 1 diabetes

Macrovascular diabetes complications may manifest as myocardial infarction, stroke, or peripheral arterial disease. However, they are uncommon in children and adolescents with diabetes, with onset mainly observed in adulthood. The key risk factors for macrovascular diabetes complications in young adults with T1D include poor glycemic control, obesity, hypertension, dyslipidaemia, DKD, long diabetes duration, hypoglycaemia, glycaemic variability, and lifestyle habits such as smoking, alcohol, sedentary lifestyle, and stress (31, 32).

16.3.4.1 Screening and management of hypertension in children, adolescents, and young adults with type 1 diabetes

Hypertension in children and adolescents (<13 years) is defined as blood pressure (BP) ≥ the 95th percentile for age, sex, and height. In older adolescents (age ≥13 years), it is defined as systolic BP ≥130 and/or DBP ≥80 mmHg. Elevated BP (previously known as pre-hypertension") is defined as BP ≥90th percentile for age, sex, and height, or from the age of 13 years as BP between 120 and 129/80 mmHg. Children and adolescents with elevated BP or hypertension should have an elevated BP confirmed on three separate days (7, 14).

In cases of an elevated BP in a child or adolescent, lifestyle modifications (moderate to vigorous physical activity and Dietary Approaches to Stop Hypertension or DASH diet) are recommended as the initial management approach. Oral pharmacological therapy using ACEI or ARBs in combination with a long-acting calcium channel blocker, or a thiazide diuretic is recommended. The goal of treatment is a BP consistently <90th percentile for age, sex, and height (7, 14).

16.3.4.2 Screening and management of dyslipidaemia in children, adolescents, and young adults with type 1 diabetes

Screening for dyslipidaemia should commence from 11 years of age in youth with T1D. In the presence of a family history of either hypercholesterolemia or early cardiovascular death, screening should start as early as 2 years. Screening involves performing a random lipid profile test and repeating it every three years if normal. In cases where the triglycerides (TGL) or low-density lipoprotein cholesterol (LDL) levels are abnormal, then a fasting lipid profile should be performed (7, 14).

The optimal LDL level is <2.6 mmol/l (100 mg/dl). In case the LDL level is ≥2.6 mmol/l (100 mg/dl), lifestyle management interventions include improving glycaemic control, dietary changes (reducing intake of saturated fats), and increased physical activity. Statin therapy should be considered in children aged >10 years if the lifestyle management interventions do not achieve the optimal LDL level (7, 14).

16.4 Additional commonly encountered complications in children, adolescents, and young adults with type 1 diabetes

Type 1 diabetes is associated with several metabolic conditions that do not directly arise due to diabetes or poor glycemic control but due to related autoimmune processes similar to what is observed in T1D (7, 14, 26, 33). These include:

1. Autoimmune thyroid dysfunction causing either hyperthyroidism or hypothyroidism
2. Coeliac disease (characterised by intolerance to gluten-containing foods and micronutrient deficiencies)
3. Addison's disease (primary adrenal insufficiency)
4. Osteopenia (arising from calcium and vitamin D deficiency)
5. Necrobiosis lipoidica diabeticorum (defined as itchy or painful hardened skin patches on the anterior aspects of the lower limbs)
6. Lipohypertrophy and lipoatrophy at insulin injection sites
7. Pernicious anaemia (vitamin B12 deficiency)
8. Autoimmune hepatitis
9. Dermatomyositis

The approach and frequency of screening of some of the above conditions has been discussed in Chapter 7 of this guideline. Generally, depending on the clinical setting, the targeted screening of some of these conditions is recommended at the time of diagnosis of T1D or when the specific symptoms develop (7, 14, 26, 33).

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CHAPTER 17. MANAGEMENT OF HYPERGLYCAEMIA IN PREGNANCY

SUMMARY OF RECOMMENDATIONS

- Hyperglycaemia in pregnancy (HIP) constitutes pre-gestational diabetes (diabetes existing before the pregnancy), overt diabetes in pregnancy/DIP, and gestational diabetes mellitus (GDM). The latter is carbohydrate intolerance of variable severity with onset or first recognition during pregnancy, diagnosed in the second or third trimester, that was not overt diabetes before conception.
- The majority of cases of HIP are due to GDM (~90%), while the rest are due to DIP and overt type 1 or 2 DM unmasked by pregnancy.
- Screening for HIP should be performed using the "one-step" approach as recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), World Health Organisation (WHO), and International Federation of Gynaecology and Obstetrics (FIGO) **(Level of evidence: A).**
- The "one-step" approach involves performing a 75-gram oral glucose tolerance test (OGTT) at any gestation age of pregnancy with measurement of the fasting blood glucose (FBG) level initially and then the 1-hour and 2-hour blood glucose levels after ingestion of glucose solution at any time during pregnancy as recommended by WHO **(Level of evidence: A).**
- Universal early screening for HIP by FBG, random blood glucose (RBG), or glycated haemoglobin (HbA1c) measurement at first antenatal contact to detect undiagnosed cases is recommended if OGTT is not possible **(Level of evidence: B).**
- Women with FBG ≥7.0 mmol/l (126 mg/dl), random plasma glucose ≥ 11.1 mmol/l (200 mg/ dl) in the presence of diabetes symptoms, and/or HbA1c ≥6.5% (48 mmol/mol) have confirmed pre-gestational diabetes and DIP **(Level of evidence: A).**
- At any gestation age, GDM is diagnosed based on FBG levels 5.1-6.9 mmol/l (92-125 mg/ dl), a 1-hour post-load blood glucose level ≥10.0 mmol/l (180 mg/dl), and a 2-hour post-load blood glucose level 8.5-11 mmol/l (153-199 mg/dl) **(Level of evidence: A).**
- Early diagnosis and management of GDM using lifestyle modification and pharmacological agents reduces the risk of foetal and neonatal adverse outcomes (Level of evidence: A).
- For women diagnosed with GDM, lifestyle behavioural modification using an optimal diet and increased physical activity is the first-line approach to managing GDM **(Level of evidence: A).**
- Insulin is the recommended first-line pharmacological agent in managing GDM in women who are unable to attain optimal glycaemic control with lifestyle behavioural modification **(Level of evidence: A).**
- A basal-bolus approach is the preferred mode of insulin administration. Although analogue insulin is preferred to human insulin due to its rapid onset of action and better safety profile, human insulin is much cheaper and may be more affordable in low-resource settings **(Level of evidence: B).**
- Treatment targets should be FBG of 4.0-5.5 mmol/L and 2-hour post-prandial blood glucose of <6.7 mmol/L (<120 mg/dL) or HbA1c of <6.0-6.5%.
- Metformin can be used as the second-line pharmacological agent in managing GDM in women who cannot use or decline insulin therapy **(Level of evidence: B).**
- Women who are initiated on metformin should be counselled about its effect of crossing the placenta and its long-term cardiometabolic impact on the offspring (it's associated with increased adiposity in early childhood) **(Level of evidence: B).**
- Sulfonylureas should not be used in managing GDM because they are associated with an increased risk of neonatal hypoglycaemia, macrosomia, and adiposity. Safety data regarding their use in pregnancy is also limited **(Level of evidence: A).**

- Women diagnosed with GDM should be tested 6-12 weeks post-delivery and thereafter should be tested every 1-3 years for up to 7-10 years for type 1 diabetes and lifelong for diabetes type 2 diabetes **(Level of evidence: B).**
- Women with pre-gestational diabetes should receive preconception counselling emphasising the benefits of optimal glycaemic control (HbA1c <6.5% or 48 mmol/mol before conception). They should also be counselled about the risk of new-onset or worsening diabetic retinopathy in pregnancy, hence the need for periodic screening **(Level of evidence: B).**
- Preconception optimal glycemic control is associated with a reduction of congenital anomalies by 70% **(Level of evidence: A).**
- Preconception care should also include folic acid (FA) supplementation advice. A higher dose of FA is recommended for obese women with type 2 DM **(Level of evidence: B).**
- Management of pre-gestational diabetes involves both lifestyle intervention and pharmacological management **(Level of evidence: A).**
- Insulin therapy is the preferred approach for managing pre-gestational diabetes **(Level of evidence: A).**
- Metformin can be used as a second-line agent or an add-on to insulin in the management of pre-gestational diabetes, especially in obese women and women with polycystic ovarian syndrome **(Level of evidence: A).**
- Other glucose-lowering therapies such as dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, and glucagon-like peptide 1 agonists are not recommended in the management of pre-gestational diabetes due to lack of evidence about their safety when used in pregnancy **(Level of evidence: E).**

17.0 Introduction: Burden and outcomes of hyperglycaemia in pregnancy

The term hyperglycaemia in pregnancy (HIP) broadly encompasses all degrees of hyperglycaemia in pregnancy. These include pre-existing or pre-gestational diabetes (diabetes known to exist before the index pregnancy, as well as diabetes diagnosed in the first trimester of pregnancy), overt diabetes in pregnancy (DIP) which appears for the first time after the first trimester in an asymptomatic woman and may resolve following delivery in some women, and gestational diabetes mellitus (GDM). Gestational diabetes constitutes the majority of cases of HIP (~90%) and is the milder form of HIP (1-4).

Globally, there is a steady increase in the prevalence of HIP and associated short- and long-term maternal and neonatal complications (5). In one systematic review and meta-analysis of 33 studies with 31,821 women and 2,146 cases of GDM investigating the burden, risk factors, and maternal and foetal outcomes of GDM in 12 sub-Saharan African countries, the pooled prevalence of GDM was 9.0% (95% CI 7.0–12.0%). Family history of type 2 diabetes, previous history of GDM, macrosomia, stillbirth, abortion, increased body mass index (BMI), age >25years, and pre-existing hypertension were the risk factors for GDM in this systematic review and meta-analysis (6).

Several hospital-based studies conducted in Uganda have reported the prevalence of HIP to range between 4.5% and 31.9% (7-13). This wide variation in the prevalence could be explained by the differences in the study settings (rural versus urban settings and private versus public hospitals), the number of study participants, and differences in the definition of HIP. A higher prevalence of HIP has been mainly reported in studies

conducted in urban tertiary hospitals (8-11). Age >25 years, increased BMI, multiparity (>3 pregnancies), pre-existing hypertension, current and previous history of macrosomia, and family history of type 2 diabetes in the first-degree relatives were reported to independently predict GDM in adult Ugandan women in some of these studies (7-13).

There is adequate documented evidence demonstrating that HIP is associated with several adverse maternal, foetal, and neonatal outcomes such as an increased risk of primary caesarian section, preterm delivery, low one-minute APGAR score, macrosomia, respiratory distress syndrome, neonatal jaundice, admission to neonatal intensive care unit (NICU), and neonatal hypoglycemia (5, 14, 15). Studies conducted in Uganda have reported GDM to be associated with an increased risk of birth canal injuries, macrosomia and large-for-gestation age babies, stillbirth, shoulder dystocia, caesarian delivery, neonatal hypoglycaemia, and intensive care unit admissions (16-19). In one of these studies, these HIP-related adverse outcomes were noted to occur more in women diagnosed with pre-gestational diabetes compared with those with GDM (17).

17.1 Physiological changes in glucose metabolism in pregnancy

Pregnancy is associated with marked changes in glucose metabolism. Initially, the fasting blood glucose (FBG) levels reduce due to the dilutional effects following the increase in maternal blood volume and an increase in foetal glucose utilisation. This decline in FBG levels is compensated by an increase in maternal hepatic gluconeogenesis and free fatty acid levels (3, 20). Additionally, compared with the pre-pregnancy state, pregnancy is associated with higher postprandial glucose levels due to reduced maternal postprandial glucose utilisation and pancreatic beta-cell insulin secretion (20). Pregnancy is also associated with a phase of accelerated starvation, which is thought to be due to a rapid maternal adaptation to fat metabolism, sparing the less expendable sources of energy such as glucose and amino acids for the foetus. This effect is due to the relative insulin deficiency and is augmented by the counterregulatory placental hormones (21, 22).

During pregnancy, there is a uniform 50–60% decrease in insulin sensitivity with advancing gestation in both normal glucose tolerance and gestational diabetes. Usually, in the first trimester, insulin resistance is low until the second trimester (3, 20). However, as the pregnancy progresses with the formation of the placenta, there is an increase in the circulating concentrations of human placental lactogen, placentally-derived human growth hormone, and other hormones such as progesterone, cortisol, and prolactin. The rise in the circulating levels of these hormones results in an eventual decline in insulin sensitivity in the peripheral tissues such as the skeletal muscles and adipose tissue, especially in the second and third trimesters of pregnancy (3, 20, 23).

Additionally, the pro-inflammatory state associated with pregnancy and the increased circulating concentrations of cytokines such as tumour necrosis factor-alpha and adipose tissue-derived hormones such as leptin further aggravate the insulin-resistant state (3, 20, 23). These physiological changes are associated with the changes in glucose metabolism observed in pregnancy and explain the development of HIP.

17.2 Screening and diagnosis of hyperglycaemia in pregnancy

Figure 1 below summarises who, when, and how to screen and diagnose HIP.

The screening of HIP is mainly based on the one-step approach using a 75-gram 2-hour oral glucose tolerance test (OGTT)

as recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the World Health Organisation (WHO). It involves performing an OGTT using 75 grams of anhydrous glucose at any gestation age or 24-28 weeks of gestation with measurement of the FBG level when a woman has had at least eight hours and then measurement of blood glucose levels one and two hours later after ingestion of a 75-gram glucose solution (one- and two-hour post-load glucose levels) (1, 2, 4, 24-27).

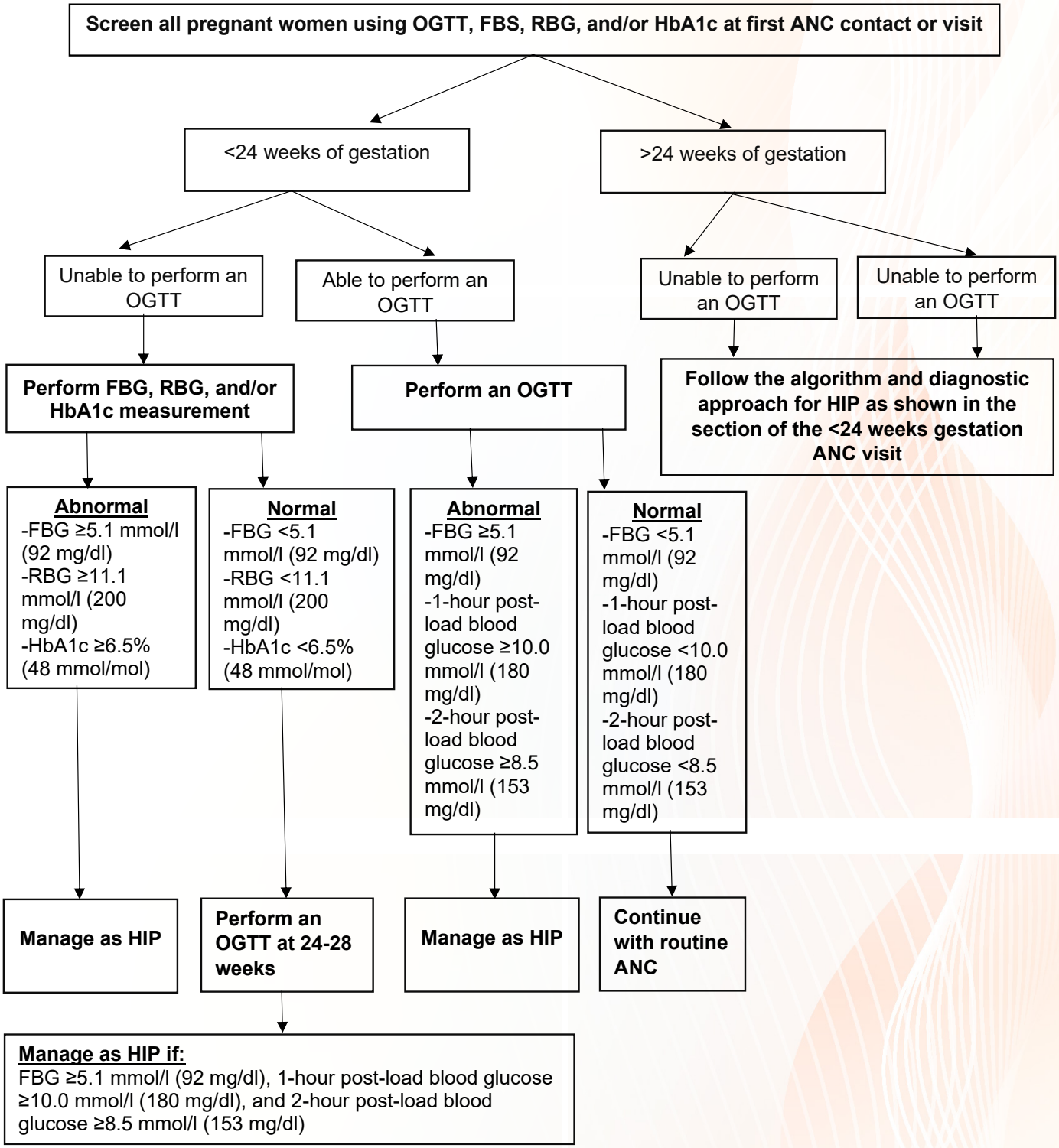
In case a pregnant woman is not known to have diabetes mellitus before pregnancy, universal early screening at the first antenatal contact for undiagnosed pre-gestational diabetes by measuring either FBG, random blood glucose (RBG) or glycated haemoglobin (HbA1c) is recommended as opposed to selective screening of only those with risk factors. Women with FBG ≥7.0 mmol/L (126 mg/dL) and HbA1c ≥6.5% (48 mmol/mol) have confirmed pre-gestational or pre-existing diabetes. The FBG levels ≥5.1 mmol/L (92 mg/dL) but <7.0 mmol/L (126 mg/dL) confirm the presence of GDM. If the FBG level <5.1 mmol/L (92 mg/dL), it is advised to screen for GDM again at 24-28 weeks of gestation using the one-step approach as discussed above (1, 2, 26). At 24-28 weeks of gestation, GDM is diagnosed based on FBG levels are 5.1-6.9 mmol/L (92-125 mg/dL, a 1-hour post-load blood glucose level ≥10.0 mmol/L (180 mg/dL), and a 2-hour post-load blood glucose level of 8.5-11 mmol/L (153-199 mg/dL) (1-3, 24-27).

Based on current evidence, universal screening for GDM using the one-step approach is superior to the selective risk-based approach, which misses over 30% of GDM patients (28). A 2021 systematic review concluded that universal screening is more likely to be cost-effective than screening targeting the high-risk population (29). Furthermore, in one study by Nakabuye et al conducted on 251 pregnant women at 24 weeks of gestation attending antenatal care at an urban tertiary hospital in Kampala, Uganda, about 24% of the women diagnosed with HIP did not have any of the commonly known risk factors (10). Therefore, for Uganda, a universal screening approach using FBG, RBG, or HbA1c measurement in the first trimester and a 75-gram OGTT between 24-28 weeks is clinically rational because of the reported high prevalence of GDM, especially in urban centres.

Deranged FBG, post-load 1-hour, and 2-hour blood glucose levels directly influence maternal, foetal, and neonatal outcomes. In one prospective study conducted on 3,852 pregnant women at 24-28 weeks of gestation attending antenatal care from five urban and peri-urban hospitals in Uganda, women who had both elevated FBG and post-load glucose levels had a 1.74-fold (relative risk [RR] 1.74, 95% confidence interval [CI] 1.12-2.68), and 2.1-fold increase (RR 2.07, 95% CI 1.23-3.47) in the risk of having macrosomic babies and neonatal ICU admission, respectively. A single elevated FBG level was associated with a 1.4-fold increase (RR 1.36, 95% CI 1.05-1.76) in the risk of caesarian delivery. A single elevated post-load blood glucose level was not associated with any adverse maternal and foetal outcomes (19).

Similar findings of adverse maternal and foetal outcomes in the presence of combined abnormal fasting and post-load blood glucose levels have been reported by several studies (30-32). The clinical implication of such findings is that the one-step screening of HIP must include the measurement of the fasting, 1-hour post-load, and 2-hour post-load blood glucose levels for appropriate subtyping of the HIP.

Figure 1. Approach for screening and diagnosing hyperglycaemia in pregnancy



ANC: Antenatal care, FBG: Fasting blood glucose, HbA1c: Glycated haemoglobin, HIP: Hyperglycaemia in pregnancy, OGTT: Oral glucose tolerance test, RBG: Random blood glucose

17.3 Management of gestational diabetes mellitus

A Cochrane review of eight clinical trials and 1,418 participants showed that compared with routine antenatal care, the management of mild GDM using lifestyle and pharmacological agents was associated with a reduction in the composite outcome of perinatal morbidity (death, shoulder dystocia, bone fractures, and nerve palsy), macrosomia, large-for-gestation age babies, and pre-eclampsia. However, pharmacological agents were associated with an increased risk of neonatal hypoglycaemia (related to insulin therapy) and ICU admission (33).

Evidence also recommends early initiation of management of GDM to reduce the risk of adverse foetal and neonatal outcomes (34, 35). In one clinical trial, a total of 802 women between 4-19 weeks and 6 days of gestation with a risk factor of hyperglycaemia and a diagnosis of GDM were randomised to an immediate-treatment arm (before 20 weeks of gestation) and deferred or no treatment arm (after 24 weeks of gestation). Early management of GDM was associated with fewer adverse neonatal outcome events (24.9% vs. 30.5%, with an adjusted risk difference, −5.6% points; 95% confidence interval −10.1 to −1.2). No differences in maternal pregnancy-related hypertension and mean neonatal lean body mass were observed between both arms (34).

The findings of these studies support the early and aggressive management of GDM in Uganda to reduce the frequency of specific adverse maternal and foetal outcomes.

17.3.1 Lifestyle behavioural modification

Compelling evidence shows that lifestyle behavioural modification (proper dietary intake and increased physical activity) initiated early in pregnancy (first or early second trimester) reduces the risk of GDM in pregnant women (36, 37). For women diagnosed with GDM, lifestyle behavioural modification is the first-line approach to managing GDM. A balanced diet of complex high-fibre carbohydrates, protein, unsaturated fat, and increased physical activity, especially after meals (30 minutes of moderate-intensity physical activity at least five days a week or a minimum of 150 minutes per week) is recommended (2, 25).

17.3.2 Pharmacological management of gestational diabetes mellitus

Insulin is recommended as the first-line agent for managing GDM in women who are unable to attain optimal glycaemic control with lifestyle behavioural modification measures (2, 3, 25). The starting insulin dose is 0.7-1.0 units/kg/day. A basal-bolus approach of insulin therapy, as discussed in Chapter 10 of this guideline, is the preferred approach. Analogue insulin types such as rapid-acting insulin lispro and aspart and long-acting basal insulins such as insulin glargine and detemir are preferred to the human insulin types due to their rapid onset of action and better safety profile (25). However, in cases of high cost and unavailability of analogue insulins, human insulins such as short-acting insulin and intermediate-acting (Neutral Protamine Hagedorn or NPH) insulin can be used.

For women who cannot use, access, or decline insulin therapy, metformin can be used as the second-line mode of management of GDM, especially if it can optimally control blood glucose levels. However, women being initiated on metformin should be counselled about its effect of crossing the placenta and its long-term cardiometabolic impact on the offspring (2, 25). Some randomised clinical trials have demonstrated comparable efficacy of metformin and insulin in managing GDM. Compared with insulin therapy, metformin is associated with less maternal weight gain, neonatal hypoglycaemia, and hypertensive emergencies. However, it may be associated with an increase in the risk of

preterm birth (38).
Regarding the long-term cardiometabolic effects on offspring, one prospective study conducted in Australia assessed the effect of metformin and insulin on body composition and metabolic outcomes after 7-9 years of follow-up of >200 children born to women with GDM and managed with metformin (±insulin) or insulin alone. Children born to women whose GDM was managed using metformin had higher markers of adiposity (weight, arm, and waist circumference, waist: height ratio, BMI, and triceps skinfold) at nine years of age compared with those whose mothers were managed with insulin alone. The metabolic parameters (lipid profile, insulin resistance, FBG, HbA1c, leptin, and adiponectin concentrations) were, however, similar in children born to women managed with metformin and insulin (39).
Sulfonylureas cross the placenta and are associated with an increased risk of neonatal hypoglycaemia, macrosomia, and adiposity (increased neonatal abdominal circumference) when compared with insulin or metformin (40, 41). There is also a lack of long-term safety data associated with their use. Because of these clinical reasons, the use of sulfonylureas is not recommended in the management of GDM (2, 25).

17.4 Glycaemic targets

Women with GDM should be managed to achieve these glycaemic targets: FBG <5.3 mmol/l (95 mg/dl), and either one-hour postprandial blood glucose level <7.8 mmol/l (140 mg/dl) or two-hour postprandial blood glucose level <6.7 mmol/l (120 mg/dl) (2, 3, 25, 42).

17.5 Foetal surveillance and timing of delivery of women diagnosed with gestational diabetes mellitus

Increased frequency of foetal assessment is recommended in women with GDM that are poorly controlled and/or in the presence of additional risk factors such as low for gestational age (LGA), polyhydramnios, and comorbidities or high-risk conditions (hypertension, obesity, late maternal age, in-utero growth restriction, previous stillbirth). Foetal well-being assessment includes measurement of foetal growth (estimated foetal weight percentile growth) and biophysical profile with foetal doppler velocimetry studies to assess the umbilical blood flow in cases of excessive or poor foetal growth or presence of comorbidities such as pre-eclampsia. All women with GDM should have a first-trimester ultrasound scan done at 11 -14 weeks of gestation for foetal viability, number of foetuses, pregnancy dating, screening for aneuploidies, and identification of major congenital anomalies (43, 44).
For women with GDM who are well-controlled on diet, plan for delivery between 39 weeks and <41 weeks of gestation. For those well controlled on medication, deliver between 39+0 – 39+6 weeks of gestation. The mode of delivery has to be individualised for women who are poorly controlled on diet and medicines because there is a lack of clinical evidence to guide the decision of when to plan the delivery. Earlier delivery between 36+0 – 38+6 weeks' gestation should be considered based on glycemic control and the presence of other comorbid conditions such as preeclampsia, poor glycemic control, and a history of in-utero foetal death. The choice of mode of delivery should be based on obstetric considerations, and induction of labour is a feasible option (25).

17.6 Complications associated with gestational diabetes mellitus

As highlighted above, poorly managed and/or undiagnosed GDM is associated with several short- and long-term maternal, foetal, and neonatal complications (3). Table 1 below summarises the commonly recognised maternal, foetal, and neonatal complications.

Table 1. Maternal and neonatal complications of gestational diabetes mellitus

Complications	Maternal	Neonatal
Short-term	-Preeclampsia -Gestational hypertension -Polyhydramnios -Urinary tract/vaginal infections -Instrumental delivery -Caesarean delivery -Traumatic labour or perineal tears -Postpartum haemorrhage	-Stillbirth -Neonatal death -Preterm birth -Congenital malformations -Macrosomia -Birth trauma -Shoulder dystocia -Bone fracture -Brachial plexus injury -Hypoglycaemia -Hyperbilirubinemia -Respiratory distress syndrome
Long-term	-Recurrence of gestational diabetes -Type 2 diabetes (occasionally, type 1 diabetes) -Hypertension -Ischaemic heart disease -Metabolic dysfunction-associated steatotic liver disease -Dyslipidaemia -Chronic kidney disease	-Metabolic syndrome -Hyperinsulinemia -Childhood obesity -Excess abdominal adiposity -Higher blood pressure -Possible earlier onset of cardiovascular disease

17.7 Long-term management of women with gestational diabetes mellitus

Women with a history of GDM have a 50-60% lifetime risk of diabetes and an almost ten-fold increased risk of developing type 2 diabetes when compared with women who were normoglycaemic during pregnancy (45-47). Several demographic, obstetric, anthropometric, and metabolic factors, such as a family history of diabetes, non-White ethnicity, multiparity (≥3 pregnancies), high pre-pregnancy BMI, women requiring insulin therapy during pregnancy, and high HbA1c levels in pregnancy, independently predict the progression to overt diabetes (45). Because of this evidence, women with a history of GDM are advised to repeat an OGTT between 6-12 weeks postpartum and perform lifetime screening for diabetes every 1-3 years using either FBG, HbA1c, or OGTT (1, 2, 25).

It is important to note that a small, but significant proportion of women with GDM may develop slowly progressive type 1 diabetes, especially in the presence of elevated islet-cell autoantibodies (48-51).

17.8 Pre-gestational or pre-existing diabetes: an overview

Pre-gestational diabetes, which consists of type 1 and type 2 diabetes and other forms of diabetes present before pregnancy, accounts for ~10% of cases of HIP. Importantly, women with type 1 and 2 diabetes should receive preconception counselling, underscoring the need to achieve optimal glycaemic control to reduce the risk of congenital anomalies

and obstetric complications such as pre-eclampsia and intrauterine foetal death (2, 52). They should also be counselled about the increased risk of developing diabetic ketoacidosis in pregnancy at lower blood glucose levels because pregnancy is a ketogenic state (2).

Pregnancy has also been shown to increase the risk of new-onset diabetic retinopathy and the progression of pre-existing diabetic retinopathy in women with type 1 and type 2 diabetes. The risk of diabetic retinopathy in pregnancy is further increased in cases of longer duration of diabetes, suboptimal glycaemic control, pre-eclampsia, and the presence of diabetic nephropathy (53, 54). Because of this evidence, screening for diabetic retinopathy before conception and in the first trimester is recommended in women with type 1 and type 2 diabetes. The screening can be repeated 3-12 months later, depending on the severity or grading of the diabetic retinopathy (2, 55).

17.9 Management of pre-gestational diabetes

Optimal glycaemic control is essential before conception and early pregnancy to reduce the risk of congenital anomalies, abortion, perinatal mortality, and foetal overgrowth (56, 57).

Management of pre-gestational diabetes involves both lifestyle intervention and pharmacological management. A balanced diet of complex high-fibre carbohydrates, protein, unsaturated fat, and increased physical activity is encouraged (2, 24, 58).

Women with pre-gestational diabetes should start aspirin 150mg at bedtime daily from 12–16 weeks of gestation to reduce the risk of preeclampsia (59).

Concerning glycaemic management, insulin therapy delivered in a basal-bolus approach (use of basal and pre-meal insulin) is the preferred approach for managing pre-gestational diabetes because it closely mimics the normal physiology of insulin secretion in the body. The insulin requirements generally increase during pregnancy. The recommended total daily insulin dose is based on a woman's body weight and trimester of pregnancy. Therefore, the initial total daily insulin dose in the first, second, and third trimesters is 0.7-0.8 units/kg/day, 0.8-1.0 units/kg/day, and 0.9-1.2 units/kg/day, respectively (58). Adjustments to the insulin doses should then be made based on blood glucose profiles, either on home self-monitoring of blood glucose levels or inpatient blood glucose levels (FBG and 2-hour postprandial glucose levels).

The insulin dosing approach and glycaemic goals (plus HbA1c <6% or 42 mmol/mol) are similar to what is recommended in the management of GDM. Rapid-acting and long-acting analogue insulins are preferred to short-acting, intermediate-acting, and premixed human insulins due to the rapid onset of action and better safety profile (less hypoglycaemia and glycaemic variability) (2, 24, 58). However, short-acting and intermediate-acting human insulins can be used in settings where analogue insulins are expensive and unavailable.

The basal insulin using long-acting or intermediate insulin such as insulin glargine or Neutral Protamine Hagedorn (NPH) insulin given at bedtime or both before breakfast and at bedtime (for NPH insulin) and pre-meal short-acting insulin (to control the post-meal glucose excursions) such as soluble insulin (given 30 minutes before a meal), insulin aspart, and lispro (given 10-15 minutes before a meal) can be used in controlling the blood glucose levels in women with pre-gestational diabetes (58).

Metformin can be used as a second-line agent or an add-on to insulin in the management of pre-gestational diabetes (pre-existing type 2 diabetes), especially in obese women and women with polycystic ovarian syndrome (58, 60). Its use in women with pre-gestational diabetes has been reported to be associated with less

maternal weight gain, fewer maternal and neonatal hypoglycaemic episodes, and caesarian deliveries, use of lower insulin doses, and lower risk of large-for-gestation age infants (58, 60-62).

Glucose-lowering therapies such as dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, thiazolidinediones, and injectable glucagon-like peptide 1 agonists are not recommended in the management of pre-gestational diabetes due to a lack of evidence about their safety when used in pregnancy. As discussed above, the use of sulfonylureas is also discouraged due to the associated risk of increased neonatal hypoglycaemia and macrosomia (58).

17.9.1 Foetal monitoring, surveillance, and timing of delivery of women with pre-gestational diabetes

The 1st trimester ultrasound scan should be carried out at 11-14 weeks' gestation to assess foetal viability, gestation dating, diagnosis of multiple pregnancy, as well as chorionicity and nuchal translucency as part of prenatal aneuploidy screening. Major foetal malformations can also be excluded at 13-14 weeks' gestation (44). A detailed anatomical scan should be performed at 18-24 weeks to detect any foetal anomalies, followed by regular obstetric ultrasound scans performed every four weeks from 28-36 weeks. These are essential in monitoring foetal viability and growth, amniotic fluid volume, and assessing foetal anatomy to rule out congenital anomalies such as congenital heart defects (24, 63).

Although there are no universally recommended antepartum fetal surveillance tests for GDM or pre-gestational DM, a weekly non-stress test (NST) is appropriate for both GDM and pre-gestational DM, starting at 36 weeks' gestation. Biophysical profiles should start at 28-32 weeks' gestation, followed by evaluations every 2-4 weeks till delivery. Fetal Doppler studies are indicated in high-risk pregnancies such as intrauterine growth restriction or development of preeclampsia (64).

In the case of foetal macrosomia (estimated foetal weight ≥4.5 kg) on ultrasound scan, consider caesarian delivery to avert related complications such as birth trauma, vaginal tears, shoulder dystocia, and obstructed labour.

In women with diabetes complications (diabetic nephropathy, macrovascular complications, suboptimal glycaemic control, and history of intrauterine foetal death), the delivery should be planned between 36 weeks and <37 weeks. If well controlled by lifestyle intervention and pharmacological therapy, delivery should be planned at 39 weeks. Delivery planned after 40 weeks is not recommended (24).

17.9.2 General management of pre-term labour, premature rupture of membranes, and labour in women with hyperglycaemia in pregnancy

In cases of preterm labour, HIP does not preclude the use of antenatal corticosteroids (ACS) for purposes of lung maturation. However, ACS should be used with caution in women using insulin. The use of ACS leads to increased maternal blood glucose levels up to 5 days after the first dose and will require insulin dose adjustments (65, 66).

The following protocol is recommended after the first dose of ACS to prevent severe hyperglycemia and diabetic ketoacidosis (65):

1. Day 1: Increase the night insulin dose by 25%
2. Days 2 and 3: Increase all insulin doses by 40%
3. Day 4: Increase all insulin doses by 20%
4. Day 5: Increase all insulin doses by 10% to 20%
5. Days 6 and 7: gradually taper insulin doses to pre-betamethasone doses

In case of premature rupture of membranes, the obstetric management is similar in both women with and without

HIP. Because of an increased risk of infection, appropriate antibiotics should be used (65).

Regarding labour, even in women with optimal glycaemic control, the induction of labour should be performed at 38 weeks. However, if a woman prefers to continue with the pregnancy, careful weekly foetal monitoring should be performed and the delivery of the baby planned by 40 weeks (24, 25, 65).

Deliveries of women with HIP should be planned and conducted in a healthcare facility, preferably with a NICU. Vaginal delivery is preferred and a caesarian section is only performed based on an obstetrician indication. In cases of foetal weight >4 kg, an elective caesarian section should be planned to reduce maternal and foetal trauma and morbidity (24, 25, 65).

During labour, monitor the blood glucose levels every hour and aim to maintain them between 4.0 and 7.0 mmol/l either with a slow intravenous 5% dextrose infusion or oral feeding. If the random blood glucose is >7.0 mmol/l, initiate short-acting insulin at 1.25 units per hour. If the patient is not feeding orally, start a maintenance infusion of 10 IU of short-acting insulin in a 5% dextrose solution and administer 100 mls per hour (24, 65).

17.9.3 Post-delivery care of the baby and women with hyperglycaemia in pregnancy

All babies of women with HIP should be closely monitored for neonatal hypoglycaemia for at least 24 hours post-delivery. Mothers should be encouraged to initiate breastfeeding immediately following delivery. Before discharge from the hospital, the baby should be thoroughly examined for any congenital anomalies and hyperbilirubinemia (24, 65).

Because insulin requirements greatly reduce following delivery of the placenta, insulin doses should be reduced. The mothers who were previously on insulin therapy can either use 50% of the late-trimester insulin dose or revert to the pre-pregnancy insulin dose (24, 65).

For women previously not on insulin therapy, insulin infusion or injections should be immediately stopped following placental delivery, and blood glucose levels monitored every 4 hours until they resume oral feeding. On initiating oral feeding, blood glucose levels can then be monitored before each meal and at bedtime, aiming at blood glucose levels of 4.0-10.0 mmol/l. All glucose-lowering therapies should be stopped in women with GDM, and close blood glucose monitoring performed for 24 hours to detect new-onset diabetes (fasting glucose >7.0 mmol/l and post-meal blood glucose >11.1 mmol/l) (24, 25, 65).

17.9.4 Postpartum care of women with hyperglycaemia in pregnancy

Women with HIP should be counselled about the need to use safe, effective contraceptive methods to avoid unplanned pregnancies. They should be advised to plan future pregnancies when glycaemic control is optimal (HbA1c <6.5% or 48 mmol/mol) (2, 65).

For women with a prior diagnosis of GDM, measurement of the FBG level should be performed at 6-12 weeks post-delivery to diagnose postpartum diabetes. This should be followed by lifelong screening for type 2 diabetes by FBG, RBG, and/or HbA1c measurement every 1-3 years (2, 65). For women with a history of GDM and a clinical phenotype signifying an increased risk of developing type 1 diabetes, the screening can be performed every 1-3 years for 7-10 years (48, 67).

All women with pre-gestational type 1 diabetes should undergo screening for postpartum thyroiditis by measuring the thyroid stimulating hormone concentrations at 3 and 6 months postpartum (65).

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CHAPTER 18. MANAGEMENT OF DIABETES - HIV AND TUBERCULOSIS COMORBIDITY

SUMMARY OF RECOMMENDATIONS

- HIV and its treatment, especially some protease inhibitors and integrase strand transfer inhibitors, are associated with an increased risk of developing type 2 diabetes and related cardiometabolic disorders such as dyslipidaemia, obesity, and hypertension **(Level of evidence: A).**
- Individuals living with HIV should be screened for risk factors of diabetes before the initiation of ART and while on treatment. Screening for diabetes should be performed every six months **(Level of evidence: B).**
- The criteria for diagnosing, evaluating, monitoring, and managing diabetes in individuals with and without HIV are similar. However, the use of glycated haemoglobin measurement in diagnosing diabetes in individuals living with HIV is not recommended because the test is affected by certain HIV-related comorbidities and drugs **(Level of evidence: A).**
- Metabolically neutral antiretroviral therapies such as abacavir, tenofovir, emtricitabine, lamivudine, darunavir, and atazanavir are preferred in managing individuals with HIV and diabetes **(Level of evidence: A).**
- Diabetes increases the odds of developing tuberculosis disease, and it adversely affects the clinical presentation and treatment outcomes of tuberculosis (TB) **(Level of evidence: A).**
- The International Union against TB and Lung Disease recommends timely bidirectional screening and integrated management of diabetes and tuberculosis at the time of diagnosis **(Level of evidence: A).**
- Sputum-smear microscopy, the WHO-approved rapid molecular tests such as gene Xpert, and the chest radiograph can be used to screen and diagnose TB disease in individuals with diabetes **(Level of evidence: A).**
- The approach involving initial random blood glucose measurement followed by fasting blood glucose measurement should be used in the diagnosis of diabetes in adult Ugandans with recently diagnosed tuberculosis **(Level of evidence: C).**
- Treatment of diabetes in adult Ugandans with recently diagnosed tuberculosis should be individualised. Insulin therapy should be used as the first-line glucose-lowering therapy in individuals with severe hyperglycaemia **(Level of evidence: C).**
- Non-insulin therapies such as sulfonylureas or dipeptidyl peptidase-IV inhibitors may be used as the first-line agents in individuals with mild to moderate hyperglycaemia. Metformin should only be used as the first-line agent in individuals with an insulin-resistant phenotype and TB **(Level of evidence: C).**

18.1.0 Introduction

Globally, there is a steadily growing dual burden of non-communicable diseases such as diabetes and infectious diseases such as HIV and tuberculosis (TB). According to the Uganda AIDS Commission statistics, the HIV prevalence among adults aged 15-49 years in Uganda in 2022 was 5.5%. The prevalence was higher in females than males (6.5% vs. 3.6%) (1).

Uganda has a national antiretroviral therapy (ART) roll-out program supported by the Ministry of Health with multilateral donations from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the Centers for Disease Control and Prevention (CDC), and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) (2). This national ART roll-out program has enabled free universal access to HIV

treatment, therefore improving the life expectancy of people living with HIV and reducing the frequency of HIV-related acute complications. However, with the increasing life expectancy and the long-term effect of ART, the prevalence of chronic cardiometabolic disorders such as type 2 diabetes, prediabetes, dyslipidaemia, hypertension, unhealthy weight gain, and obesity has greatly increased in individuals living with HIV (3, 4).

18.1.1 Burden of type 2 diabetes and related cardiometabolic disorders in individuals with HIV

Generally, type 2 diabetes and related cardiometabolic disorders such as prediabetes, dyslipidaemia, obesity, and hypertension are highly prevalent in individuals living with HIV. This is due to several associated risk factors such as increasing age, longer duration of HIV, high viral load, HIV-associated chronic low-grade pro-inflammatory state, hepatitis B and C co-infection, the effect of ART such as protease inhibitors (PIs), integrase strand transfer inhibitors (INSTI), and tenofovir alafenamide (TAF) (4-9).

A high frequency of diabetes and prediabetes has been widely documented in adult Africans living with HIV. In one systematic review and meta-analysis that reviewed 63 studies reporting information on the prevalence and associated factors of diabetes in Africans living with HIV, the pooled prevalence of diabetes and prediabetes in 53 studies was 5.1% (95% confidence interval [CI] 4.3-5.9) and 15.1% (95% CI 9.7-21.5%), respectively. The meta-analysis reported a statistically non-significant association between diabetes and increasing age >39 years (6.0%, 95% CI 4.5–7.6 vs. 4.5%, 95% CI 3.5–5.7 for age ≤39 years), higher BMI (>23 kg/m2: 7.1%, 95% CI 4.7–9.9 vs. 4.5%, 95% CI 2.8–6.6 for BMI ≤23 kg/m2), and living in an urban area (4.8%, 95% CI 3.8–5.9 vs. 3.8%, 95% CI 0.9–8.4 for those living in rural areas). No association was reported between diabetes and ART use, duration of ART, and CD4 count (10).

In Uganda, several studies have reported a high prevalence of type 2 diabetes and related cardiometabolic disorders such as obesity, dyslipidaemia, and hypertension in individuals living with HIV (11-15). In one study by Amutuhaire et al conducted on 309 adult ART naïve Ugandans (with median age and CD4 count of 34 [28-40] years and 318 [163-550] cells/mm3, respectively) receiving HIV treatment from a health centre IV in Kampala Uganda, the prevalence of diabetes, dyslipidaemia, abdominal obesity, and hypertension was 18.4%, 93.6%, 34.0%, and 8.1%, respectively (11). This high frequency of diabetes and related cardiometabolic disorders underscores the need to proactively screen, monitor, and optimally manage these chronic conditions in adult Ugandans living with HIV.

18.1.2 Effect of HIV and antiretroviral therapy on glucose metabolism

Evidence shows that ART, especially PIs, INSTI such as dolutegravir, and non-nucleoside reverse transcriptase inhibitors such as efavirenz are associated with increased odds of developing type 2 diabetes in some adult populations living with HIV (16-18). This increased risk is due to their effect of inducing peripheral insulin resistance, mitochondrial toxicity, weight gain, and inhibition of the glucose transporter-4 activity, hence blocking insulin-mediated glucose uptake and utilisation (6, 7).

In one meta-analysis of 41 observational studies with 20,178 participants, compared with ART naïve participants, ART-exposed participants had higher odds of having diabetes (pooled odds ratio [OR] of 3.85, 95% CI 2.93-5.07, n=10 studies) and metabolic syndrome (pooled OR of 1.45, 95% CI 1.03-2.03, n=18 studies). Additionally, ART-exposed participants had higher mean fasting blood glucose (FBG) concentrations (pooled mean difference of 4.66 mg/dl, 95% CI 2.52 to 6.80, n= 24

studies) (16).
Regarding the association between INSTI and new-onset diabetes, one systematic review and meta-analysis of 13 studies assessing the association between the use of INSTI, insulin resistance, and incident type 2 diabetes reported a 20% reduced risk of incident diabetes with the use of INSTI (relative risk [RR] 0.80, 95% CI 0.67 to 0.96, I2=29%). However, in two African populations, INSTI therapy was associated with a threefold increase in the risk of incident diabetes (RR 2.99, 95% CI 2.53-3.54, I2=0%) in two studies conducted in Cameroon and South Africa (17). This reflects heterogeneity in some key risk factors for diabetes across populations.

18.1.3 Dolutegravir and risk of new-onset diabetes in adult Ugandans living with HIV

In 2018, the Ministry of Health in Uganda rolled out new HIV treatment guidelines that recommended the use of a tenofovir-lamivudine-dolutegravir fixed-dose combination (FDC) as the first-line therapy for the management of HIV. This necessitated a switch of all patients receiving ART from an efavirenz-based FDC to a dolutegravir-based FDC (19). Following this switch in the ART regimens, clinicians providing care in some HIV treatment centres started observing cases of new-onset diabetes in individuals without a prior history of diabetes. For example, at the HIV treatment and care clinic at the Infectious Diseases Institute, Mulago, Kampala, Uganda, a total of 16 cases of new-onset diabetes were described. Phenotypically, compared with those with normoglycaemia, participants with new-onset hyperglycaemia were mainly male (81.3% vs. 35.9%, p<0.0001), aged ≥50 years (50.0% vs. 25.2%, p=0.02), hypertensive (50.0% vs. 14.4%, p<0.0001), previously on a stavudine-based ART regimen (56.3% vs. 16.8%, p<0.0001), and ART exposed for a duration >10 years (56.3% vs. 26.0%, p=0.016) (20).
This increase in the risk of hyperglycaemia due to the use of dolutegravir was further reported in a case-control study conducted on 435 individuals living with HIV receiving treatment from the Mulago ISS clinic, Kampala Uganda (204 cases with HIV and hyperglycaemia versus 231 controls with HIV and normoglycaemia). Prior use of dolutegravir increased the odds of being diagnosed with hyperglycaemia by sevenfold (adjusted odds ratio [AOR] of 7.01, 95% CI 1.96–25.09). Being ≥56 years (AOR 12.38, 95% CI 3.79–40.50) and hypertensive (AOR 5.78, 95% CI 2.53–13.21) were also associated with increased odds of hyperglycaemia in this study (21).
To fully understand the effect of dolutegravir on glucose metabolism, the glucose metabolism changes in Ugandan people living with HIV on dolutegravir (GLUMED) study was conducted. In this prospective cohort study, 309 adult ART naïve Ugandans initiated on a dolutegravir-based ART regimen at Kisenyi Health Centre IV, Kampala Uganda, were enrolled and followed up for 48 weeks. Participants underwent serial FBG measurement and an oral glucose tolerance test (OGTT) with measurement of the 2-hour post-glucose load blood glucose concentrations during the study period. A total of 243 participants completed the follow-up period (22).
The incidence of type 2 diabetes and prediabetes in this study was 4 cases per 1000-person years (1/243) and 240 cases per 1000-person years (54/243). Dolutegravir use was associated with a significant increase in FBG from baseline to week 48 (median change from baseline of 3.6 mg/dl, interquartile range [IQR]−3.6, 7.2, p=0.005) and a significant reduction in the 2-hour blood glucose at week 36 (mean change from baseline of−7.26 mg/dl, IQR:−21.6, 14.4, p=0.024). A high CD4 count (adjusted median change of 0.01, 95% CI 0.0002–0.021, p = 0.045) and increased waist circumference (adjusted median change of 12.85, 95% CI 4.80–20.89, p = 0.002) were associated with an increase in the 2-hour post-glucose load

blood glucose concentrations at week 36. No factors were associated with increased FBG concentration (22). This study showed that incident diabetes related to the use of DTG was low in this study population.
Additionally, based on the glucose-insulin kinetic studies performed on a selected number of study participants, the study also showed that the use of dolutegravir was not associated with insulin resistance and beta-cell dysfunction, defined based on the homeostatic model assessment 2 (HOMA2)- insulin resistance and HOMA2-beta-cell function level as surrogate markers, respectively (23).

18.1.4 Screening and diagnosis of diabetes in an individual living with HIV

The Uganda Diabetes Association fully endorses the recommendations for screening and diagnosis of diabetes in individuals living with HIV as outlined in the 2022 Ugandan Ministry of Health guidelines for the prevention and treatment of HIV and AIDS in Uganda (24). Every individual living with HIV should be screened for risk factors of diabetes before the initiation of ART and while on treatment. Screening for diabetes should be performed every six months (24). The screening and diagnostic approach of diabetes in individuals with and without HIV is similar. The approach has been discussed in detail in Chapter 3 of this guideline. As elaborated in that Chapter, the use of HbA1c in diagnosing diabetes in individuals living with HIV is not recommended due to several prevalent clinical factors that can result in falsely low HbA1c levels (25-27).

18.1.4 Comprehensive evaluation, monitoring, and management of an individual with HIV and diabetes comorbidity

The approach of comprehensive evaluation, monitoring, and management of diabetes in individuals with and without HIV is similar. Broadly, lifestyle interventions such as appropriate dietary intake, weight management, and increased physical activity in addition to individualised pharmacological therapy are pivotal in the management of diabetes in individuals living with HIV. These aspects have been discussed in great detail in Chapters 3, 7, 9, 10, and 11 of this guideline.
Regarding the ideal ART to use, healthcare professionals are advised to use metabolically neutral nucleoside reverse transcriptase inhibitors such as abacavir, tenofovir, emtricitabine, and lamivudine, and PIs such as darunavir and atazanavir. The Ugandan Ministry of Health HIV treatment guidelines do not recommend the use of dolutegravir in individuals with diabetes and HIV comorbidity (24).
As discussed extensively in Chapter 11 of this guideline, in addition to optimal glycaemic management and control, individuals living with HIV should also receive a comprehensive cardiovascular risk evaluation and management. Because HIV is a recognised risk factor for cardiovascular disease (CVD), baseline and periodic screening and management of dyslipidaemia are highly recommended (5). Recent evidence shows that lipid-lowering agents such as statins are effective in reducing the rates of CVD such as myocardial infarction, stroke, and hospitalisation for unstable angina, and improving the lipid profile in individuals living with HIV and low- to moderate-risk of CVD (28, 29). The evidence supports the use of pravastatin, atorvastatin, and low-dose rosuvastatin. Simvastatin, Fluvastatin, and lovastatin should be avoided in patients on ART due to drug-drug interactions, related adverse events, and lack of clinical efficacy data (30).

18.2.0 Introduction: Burden and predictors of diabetes and tuberculosis comorbidity

Current estimates show a growing dual burden of diabetes and TB in sub-Saharan Africa, posing significant public health challenges (31, 32). Compelling evidence shows that diabetes increases the odds of developing TB disease (33-35). In one

systematic review and meta-analysis of 13 observational studies with >1.7 million participants, diabetes was associated with a threefold increase in the risk of developing TB disease (33). Another systematic review and meta-analysis of 16 observational studies investigating the prevalence of diabetes in Africans with tuberculosis reported a pooled prevalence of diabetes of 9.0% (95% CI 6.0-12.0%, I2=97.5%, p<0.001) (36).

In Uganda, studies that have investigated the prevalence of diabetes in adult patients with TB disease have reported a prevalence ranging from 1.3% to 13.8% (37-43). This varied prevalence could be explained by the differences in study populations (hospitalised vs. outpatient participants) and the number of diabetes diagnostic tests used (FBG, HbA1c, or random blood glucose [RBG]). In two hospital-based cross-sectional studies, age ≥40 years (adjusted odds ratio [AOR] 3.12, 95% CI 1.35-7.23, p=0.008) and a raised alanine transaminase concentration (OR-11.42 95%CI 2.15-60.59, p=0.004) were reported to independently predict diabetes in the study population of adult Ugandans with TB, while HIV positivity was associated with reduced odds of being diagnosed with diabetes in both studies (AOR- 0.17, 95% CI 0.06-0.51, p=0.002, and AOR- 0.27, 95% CI 0.10-0.74, p=0.01, respectively) (42, 43).

18.2.1 Effect of diabetes and tuberculosis comorbidity on clinical outcomes

Several studies have shown that diabetes directly affects the clinical presentation and treatment outcomes of TB. Individuals with TB and diabetes comorbidity usually present with more lung cavitation on chest X-ray, smear-positive or culture-positive pulmonary TB, higher bacillary loads, and increased risk of TB recurrence, multi-drug resistant TB, and mortality. Tuberculosis disease is often associated with suboptimal glycaemic control and worsening of some diabetes complications such as diabetic neuropathy (44-47).

18.2.2 Screening and diagnosis of diabetes and tuberculosis comorbidity

Because of the close interaction between diabetes and TB as discussed above, the International Union against TB and Lung Disease (The Union) recommends bidirectional screening and integrated management of DM and TB to improve early diagnosis, optimal management, and treatment outcomes (48, 49).

The approach for screening and diagnosing TB in patients with and without diabetes is similar. The Union guidelines recommend using sputum-smear microscopy, the WHO-approved rapid molecular tests, especially Gene Xpert, and the chest radiograph to screen and diagnose TB disease in individuals with diabetes at the time of diagnosis or on presentation with symptoms of TB. Screening for diabetes in individuals with TB should be performed at the time of diagnosis of TB. The diagnosis of diabetes can be made based on the measurement of the FBG, RBG, HbA1c, and 2-hour blood glucose level after a 75-gram OGTT (48). The Union guidelines recommend the use of RBG measurement as the initial screening test for diabetes and then followed by the measurement of either the FBG or HbA1c level if the RBG is ≥6.1 mmol/l (48). The diagnostic cut-offs for diabetes and prediabetes using the above tests have been discussed in Chapter 3 of this guideline.

The optimal follow-up diagnostic test for diabetes in adults with TB after the initial RBG measurement varies across populations. As part of the tuberculosis and diabetes comorbidity (TADIC) study that investigated the burden, phenotypic characteristics, and optimal diagnostic tests of diabetes and TB comorbidity in adult Ugandans with recently diagnosed TB, the diagnostic performance of FBG and laboratory-based HbA1c tests to diagnose diabetes (using an OGTT as the gold standard and reference test) in adult Ugandans with recently diagnosed TB was evaluated (50). A total of 75 adults (with an initial RBG ≥6.1 mmol/l)

underwent FBG, HbA1c, and 2-hour post-glucose load blood glucose measurement. The areas under the curve (AUC) for FBG and laboratory-measured HbA1c were 0.69 (95% CI 0.47-0.90) and 0.65 (95% CI 0.43-0.87), respectively. The sensitivity and specificity of a FBG level of ≥7 mmol/l were 57.1% (95% CI 18.4%-90.1%) and 74.6% (95% CI 62.5%-84.5%), respectively, while the sensitivity and specificity for laboratory-measured HbA1c of ≥6.5 mmol/l (48 mmol/mol) were 14.3% (95% CI 0.40%-57.9%) and 95.3% (86.9%-99.0%), respectively (50). The findings of this study showed that the FBG test may be a better follow-up test than laboratory-measured HbA1c in confirming diabetes in adult Ugandans with recently diagnosed TB. Because the sample size of the sub-study was small, larger studies are justified to confirm these findings.

18.2.3 Management of diabetes in individuals with tuberculosis

The management of diabetes in individuals with tuberculosis should be individualised based on an individual's phenotypic profile. The ABCD and 2Ps approach, as elaborately discussed in Chapter 9 of this guideline, should guide the healthcare professional in selecting the optimal glucose-lowering therapy (insulin or non-insulin-based therapy).

As a sub-study of the TADIC study, phenotypic characterisation of participants with and without diabetes and TB comorbidity was performed to inform how best to manage diabetes in adult Ugandans with TB. Phenotypically, participants with diabetes and TB comorbidity were noted to have severe hyperglycaemia (50% had a HbA1c ≥10% or 86 mmol/mol) with a low BMI (median BMI- 19.0 [17.5-22.5] kg/m2), HOMA2-beta-cell function (45.5 [28.3-60.6]%), and HOMA2-insulin resistance (1.08 [0.69-1.50]) level, in addition to a high frequency of insulin deficiency (25.0%) (51). These phenotypic features suggest a predominance of pancreatic beta-cell secretory dysfunction as opposed to insulin resistance (52).

Because the management of diabetes should be based on a detailed understanding of the phenotypic profile, the documented predominance of clinical features suggestive of pancreatic beta-cell secretory dysfunction supports the use of insulin as the first-line glucose-lowering therapy in Ugandan patients with TB and severe hyperglycaemia (HbA1c ≥10.0% or 86 mmol/mol, FBG ≥14.0 mmol/l or 250 mg/dl, and RBG ≥16.7 mmol/l or 300 mg/dl). In individuals with mild to moderate hyperglycaemia, oral agents that stimulate insulin secretion by the pancreatic beta-cells, such as sulfonylureas and dipeptidyl peptidase IV (DPP-IV) inhibitors, may be used as the first-line glucose-lowering therapy. Metformin should only be used as the first-line agent in individuals with TB and an obese insulin-resistant phenotype (BMI ≥25 kg/m2, with other features of metabolic syndrome such as hypertension and a dyslipidaemia profile) (53).

Because rifampicin is a potent inducer of cytochrome P450 enzymes, it reduces the plasma concentrations of most oral glucose-lowering therapies such as metformin, sulfonylureas, and DPP-IV inhibitors by 30-80% (54-56), resulting in suboptimal glycaemic control in individuals with diabetes and TB. Therefore, healthcare professionals must increase the doses of most of these oral therapies to achieve the optimal glycaemic targets.

The optimal glycaemic targets for individuals with and without diabetes and TB comorbidity are similar. These have been discussed in Chapter 8 of this guideline. Every individual with diabetes and TB comorbidity should also have a comprehensive cardiovascular risk evaluation and timely initiation of the recommended management as discussed in Chapter 11 of this guideline.

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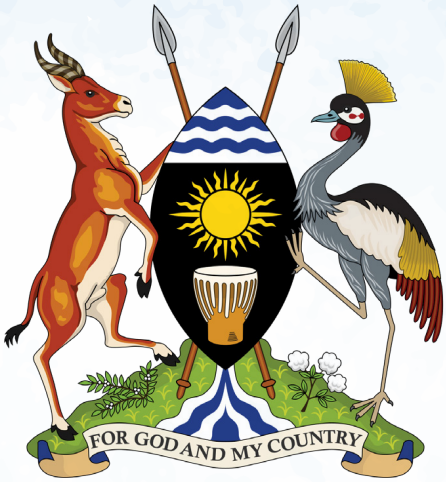

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