International Diabetes Federation

75 YEARS 1950 - 2025

IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes

2025

IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes

2025

In Memoriam

We are deeply saddened by the passing of Professor Akhtar Hussain (IDF President 2022-2024), who served as Chair of this initiative and led its development. His leadership, dedication, and expertise significantly shaped this publication. We respectfully dedicate this work to his memory.

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Acknowledgements

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Sponsors' duality of interest

This update of the 2005 International Diabetes Federation (IDF) Global Guideline on type 2 diabetes was supported by educational grants from Sanofi and Servier.

These companies did not take part in any aspect of the development of these clinical practice recommendations.

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ISBN 978-2-930229-97-3

Please cite this report as International Diabetes Federation. IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes – 2025. https://idf.org/t2d-cpr-2025

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IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes – 2025

Foreword

On behalf of the International Diabetes Federation (IDF), it is my great pleasure to present this 2025 edition of the *IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes*. These recommendations reflect our ongoing commitment to improving the lives of people living with diabetes worldwide by equipping healthcare providers with the tools to help them deliver high-quality, evidence-based care.

Diabetes remains a serious and fast-growing public health challenge. The IDF Diabetes Atlas estimated that 589 million adults aged 20–79 years were living with diabetes in 2024 and that this number is projected to reach 853 million by 2050. Type 2 diabetes mellitus (T2DM), which accounts for between 90% and 95% of all diabetes cases, places a substantial burden on individuals, families, and healthcare systems. Around half of all T2DM cases remain undiagnosed.

If not managed, T2DM can lead to severe complications, including cardiovascular disease, chronic kidney disease, retinopathy, neuropathy, and liver disease. With an early diagnosis and access to appropriate treatment and support, T2DM can be controlled and its associated complications prevented or delayed. Furthermore, there is increasing evidence that remission of T2DM may be possible in the early stages of the condition. Therefore, early detection, effective management, and preventive strategies are imperative to address the burden T2DM places on individuals and their families.

The 2025 IDF global clinical practice recommendations have been updated to incorporate the latest evidence and advancements in diabetes care. These recommendations provide a structured yet adaptable framework for healthcare professionals, ensuring they are equipped with practical guidance tailored to diverse clinical settings. A key feature of these recommendations is their unique approach to distinguishing between optimal and basic care strategies, allowing for context-specific adaptation while maintaining high standards of diabetes management.

This edition covers a broad range of critical topics, including epidemiology, glycaemic targets, blood glucose management (both non-insulin and insulin therapies), weight control, cardio-renal health, and the impact

of metabolic dysfunction-associated steatotic liver disease (MASLD) on diabetes outcomes. These recommendations prioritise a person-centred approach, ensuring that care is aligned with the individual needs, preferences, and circumstances of people living with diabetes.

The development of these recommendations has been a collaborative effort, bringing together leading experts from around the world. I extend my heartfelt gratitude to the co-chairs of the Technical Working Group, Professor Stephen Colagiuri and Professor Antonio Ceriello, and to all the contributors, reviewers, and editors who have dedicated their time and expertise to this initiative. I acknowledge the essential contribution of our past president, the late Professor Akhtar Hussain, whose vision and dedication were instrumental in shaping this project from the outset. He would be extremely proud that this document has been produced and launched in time for our congress, in keeping with his wishes. His contributions will remain a legacy in the field of diabetes care and education. Additionally, I extend my appreciation to the IDF Executive Office for their unwavering support in delivering this document.

The impact of these recommendations will be determined by their implementation. We urge healthcare providers, policymakers, and other key diabetes stakeholders to adopt and adapt these guidelines within their local contexts, ensuring they lead to meaningful improvements in diabetes care. By working together, we can alleviate the global burden of diabetes, prevent its complications, and move closer to achieving universal health coverage and health equity for all those living with or at risk of diabetes.

The International Diabetes Federation remains steadfast in its goal to support healthcare professionals, empower people living with diabetes, and drive innovation in diabetes care. We hope these recommendations will serve as a valuable resource for all those working to improve diabetes management in primary care settings.

Thank you for joining us in this vital effort. Together, we can create a world where everyone has access to the care they need to lead healthy, fulfilling lives.

Professor Peter Schwarz
IDF President, 2024–2027

IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes – 2025

Introduction

Antonio Ceriello & Stephen Colagiuri

Diabetes is a major global health challenge, with an estimated 589 million adults in 2024 living with diabetes, of whom almost one-in-two were undiagnosed. In addition, another 1.1 billion adults worldwide had impaired glucose tolerance or impaired fasting glycaemia predisposing them to an increased risk of developing type 2 diabetes mellitus (T2DM). These numbers are projected to increase significantly over the next two decades.[1]

T2DM is the most common type of diabetes, accounting for over 90% of all diabetes worldwide, and is associated with increased all-cause mortality and macrovascular and microvascular complications. There is strong evidence that the T2DM burden can be reduced by controlling hyperglycaemia and associated risk factors, diagnosing earlier, and preventing high-risk individuals from progressing to T2DM.

The global burden of T2DM continues to increase despite the wealth of existing evidence on diabetes care and prevention. Optimal diabetes management is not reaching the majority of individuals who could benefit. Poor glycaemic control is common in T2DM and does not meet the World Health Organization (WHO) goal of 80% of people with diagnosed diabetes achieving good glycaemic control.[2]

INTEGRATED DIABETES CARE

The principles of T2DM care are as follows:

- **An holistic approach to delivering evidence-based care centred around the person with diabetes, empowered through self-management education and support**
- **A well-trained multidisciplinary health professional team**
- **Decision support systems (registries, reminders, audits, and feedback)**

Providing this care requires a comprehensive, integrated, individual-centred strategy supported by a health system structured to deliver care in the context of a chronic care model which addresses the multifaceted challenges inherent to this complex condition. Structured diabetes care is an essential aspect of integrated care and underscores the significance of systematic and organised processes, including assessment as a crucial component of quality assurance. Regular evaluation of the person with T2DM's progress and adherence to agreed care plans creates a foundation for data-driven decision-making.

International Diabetes Federation guidelines

The first International Diabetes Federation (IDF) Global Guideline for Type 2 Diabetes was published in 2005[3,4] and an update for primary care physicians was published in 2017.[5] Since then, T2DM management has undergone considerable transformation marked by noteworthy developments. New medications have emerged, offering a broader range of therapeutic options and a more personalised approach to care aligning interventions with individual needs. Concurrently, tests for assessing and monitoring diabetes have evolved.

The integration of technology into diabetes care has transformed the interaction between individuals with T2DM and their providers. Wearable devices, continuous glucose monitoring systems, and mobile applications are available for the daily management of T2DM in well-resourced healthcare systems. Coupled with the adoption of virtual care, including telemedicine and digital health platforms, these technological advancements have expanded access to care, fostering engagement and facilitating ongoing monitoring and support.

The IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes - 2025

IDF is a global umbrella organisation of more than 240 national diabetes associations from 161 countries and territories, representing a diverse range of health systems and populations. Developing global clinical practice recommendations which are relevant, applicable, and equitable across these various healthcare settings presents a unique challenge.

Clinical guidance recommendations of national and international learned societies are formulated on the highest level of available evidence in relatively well-resourced health

systems with universal health coverage or at least coverage of essential health services. This does not reflect global reality, with an estimated 4.5 billion people not covered by essential health services and exposed to out-of-pocket health expenses and impoverishing financial hardship. Regrettably, the recent global pattern is one of stagnating progress in service coverage with catastrophic health spending increasing across all regions and most countries.[6] In this context, current clinical guidance may be of limited practical use in countries with resource-challenged health systems.

This new *IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes - 2025* attempts to strike a balance, embracing the latest therapeutic and technological evidence while acknowledging the realities of providing diabetes care in a diverse global healthcare environment. These guidelines aspire to provide healthcare professionals and policy makers with an effective and contemporary framework for navigating the complexities of diabetes management that is sensitive to resource, affordability, access, and equity.

Levels of diabetes care and prevention approach

All people with or at risk of diabetes should have equitable and affordable access to the best available evidence-based, cost-effective integrated diabetes care and prevention. However, it is widely recognised that many countries and health systems around the world do not currently have the workforce or financial resources to provide this level of diabetes care.

An imperative in formulating IDF guidance is recognising the limitations and opportunities presented in the context of varying healthcare systems globally. This is pivotal in guiding recommendations that cater to diverse settings, and which can evolve and be adapted to encourage and facilitate healthcare system reform.

The 2005 IDF guideline adopted a Levels of Care approach to formulate recommendations for diabetes care and prevention to address the challenges of global variations in available healthcare resources, expertise, and funding across different countries and localities.[3,4] Unlike national guidelines formulated for a particular healthcare system, this perspective is necessary to increase the global relevance and applicability of IDF recommendations.

To serve its global membership, the IDF has developed this global guidance that is resource-, capacity-, and cost-sensitive while ensuring an appropriate level of care which will improve outcomes relative to the current situation.

Standards of diabetes care and prevention

IDF clinical and prevention recommendation advice is now based on two levels of standards of diabetes care and prevention which recognise the diversity of global healthcare systems and inherent resource constraints.

Optimal Care sets the standard for evidence-based care which would ideally be universally available and represents the most desirable care to achieve best outcomes. This care requires well-resourced health systems which would usually include some form of universal health coverage. It may be available to subgroups of the population in less well-resourced health systems but is not generally available. It should be the aim of all healthcare systems to achieve this standard of care.

Basic Care aims to achieve the main objectives of "Optimal Care" but is provided in a healthcare setting with limited resources. It serves as a foundational level or starting point to ensure that, even with limited resources, individuals receive essential care and establishes a pathway towards Optimal Care.

Table 1. Standards of diabetes care and prevention

	Optimal Care	Basic Care
Definition	Evidence-based care and prevention provided in well-resourced settings	Evidence-based care and prevention adapted for resource-constrained settings. Serves as a starting point towards Optimal Care
Target audience	Healthcare professionals and policy makers in well-resourced settings	Healthcare professionals and policy makers in resource-constrained settings
Accessibility	All individuals with or at risk of diabetes	Essential care for all individuals regardless of resource limitations
Scope	• Comprehensive • Individual-centred • Multidisciplinary care • Decision support systems	• Focus on essential services and prioritised programmes • Adapted to challenges of local healthcare settings • Individual-centred • Best available multidisciplinary care approach

The intended users of these guidelines are all healthcare professionals involved in the management of people with T2DM (and those at risk of developing T2DM) and policy makers who are responsible for healthcare services to improve individual and population health. The focus on policy makers is particularly important to ensure that healthcare and health system reform is implemented to provide universal optimal care.

Methodology

This guidance focuses on recent advances in diabetes care and prevention. An IDF expert panel was appointed to guide the development of these recommendations, which were formulated using an evidence-based consensus approach. The process included proposing pertinent questions deemed most relevant for the effective management of individuals with, or at risk of, T2DM. These questions were systematically categorised into various topics. Experts in their respective field compiled evidence summaries for each section. The entire group convened to discuss the synthesised evidence on the various topics and draft recommendations. A preliminary document was shared with external reviewers for broader input. Feedback received was carefully reviewed, and revisions made to address duplications and consolidate the evidence and recommendations. The International Centre for Professional Development in Health and Medicine (ICPDHM.com), a not-for-profit physician organisation based in Canada, provided medical writing, editorial, and logistical support throughout the development.

Acknowledgements

The *IDF Global Clinical Practice Recommendations for Managing Type 2 Diabetes - 2025* was supported by educational grants from Sanofi and Servier. These companies did not take part in any aspect of the development of these clinical practice recommendations.

Medical writing support was provided by, Bhavadharini Balaji, PhD and Alanna Grant, PhD of the International Centre for Professional Development in Health and Medicine (ICPDHM), Quebec, Canada.

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Chapter 1

Detection of Diabetes and Intermediate Hyperglycaemia, and Prevention of Type 2 Diabetes

RECOMMENDATIONS

<table>
<tr><th></th><th>Optimal Care</th><th>Basic Care</th></tr>
<tr><td>Criteria for defining diabetes and intermediate hyperglycaemia</td><td colspan="2">
<table>
<tr><th></th><th>WHO criteria</th><th>ADA criteria</th></tr>
<tr><td colspan="3">Diabetes</td></tr>
<tr><td>Fasting plasma glucose (FPG)</td><td>≥7.0 mmol/L (126 mg/dL)</td><td>≥7.0 mmol/L (126 mg/dL)</td></tr>
<tr><td>2 h plasma glucose*</td><td>≥11.1 mmol/L (200 mg/dL)</td><td>≥11.1 mmol/L (200 mg/dL)</td></tr>
<tr><td>HbA1c</td><td>≥6.5% (48 mmol/mol)</td><td>≥6.5% (48 mmol/mol)</td></tr>
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<tr><td colspan="3">Intermediate hyperglycaemia</td></tr>
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<tr><td>Fasting plasma glucose</td><td>6.1–6.9 mmol/L
(110–125 mg/dL)</td><td>5.6–6.9 mmol/L
(100–125 mg/dL)</td></tr>
<tr><td colspan="3">Impaired glucose tolerance (IGT)</td></tr>
<tr><td>2 h plasma glucose*</td><td>7.8–11.0 mmol/L
(140–199 mg/dL)</td><td>7.8–11.0 mmol/L
(140–199 mg/dL)</td></tr>
<tr><td colspan="3"></td></tr>
<tr><td>HbA1c</td><td>–</td><td>5.7%–6.4%
(39–47 mmol/mol)</td></tr>
</table>
</td></tr>
<tr><td>Options for screening for diabetes and intermediate hyperglycaemia</td><td colspan="2">Target group: determine locally
Risk assessment:
• Risk scores – developed locally or adapted to local factors
• Risk factors – excessive weight, family history, gestational diabetes history, etc.
Biochemical testing options:
• FPG
• 2 h OGTT
• HbA1c
1 h PG during 75 g OGTT is an emerging option
Select the screening protocol based on available resources and capacity to intervene (in those identified as high-risk) with a diabetes prevention programme</td></tr>
<tr><td>Diabetes prevention programmes for high-risk individuals</td><td>• Offer a locally developed or adapted 6–12-month structured lifestyle modification diabetes prevention programme aiming for 5% weight loss if overweight/obese.
• Consider metformin as additional intervention
• Provide regular reassessment of individuals
• Support the programme with data systems
• Regularly monitor and evaluate the programme</td><td>Consider the feasibility of implementing a community-based lifestyle modification diabetes prevention programme</td></tr>
<tr><td>Diabetes prevention population strategies</td><td>Implement population programmes to encourage healthier eating, increased physical activity, and healthy weight</td><td>Consider population programme to encourage healthier eating, increased physical activity, and healthy weight</td></tr>
</table>

*Following a 75 g oral glucose tolerance test.

ADA, American Diabetes Association; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test; WHO, World Health Organization.

KEY POINTS

- Globally, there is a high number of people with diabetes, which is predicted to continue to increase; almost one in two people living with diabetes are undiagnosed.
- Diabetes can be diagnosed by fasting plasma glucose, 2 h oral glucose tolerance test (OGTT), and glycated haemoglobin (HbA1c) with universally agreed diagnostic criteria. However, there is a lack of congruence between these measures.
- Screening for undiagnosed diabetes will identify individuals who will benefit from early treatment.
- Intermediate hyperglycaemia (IH) (also referred to as "prediabetes") includes impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and intermediate HbA1c. The WHO and ADA criteria for defining IH differ for IFG and WHO does not have an HbA1c criterion.
- The prevalence of IH is higher than diabetes but varies with the screening test – these tests lack congruence. IGT can only currently be detected by a 2 h OGTT.
- The 1 h OGTT test has recently been advocated as another option.
- Screening for IH identifies individuals who can benefit from interventions to prevent type 2 diabetes mellitus (T2DM).
- Strategies for diabetes prevention include the individual-based high-risk approach and the population approach.
- Structured lifestyle modification programmes are effective in preventing or delaying T2DM in people with IGT but not isolated IFG. Data for HbA1c-detected IH are limited. Some medications can prevent or delay T2DM.
- Prevention strategies have been successfully translated in community or national programmes in a number of countries.
- The design of programmes has differed in relation to target group, screening process and test, and intensity and method of delivery of the lifestyle intervention. Little data are available on the impact on diabetes prevention, but weight reduction and increased physical activity are encouraging.
- A decision to implement a high-risk individual diabetes prevention programme should be guided by local resources, health system capacity, and cost. Local design and adaptation are important.
- Population approaches aiming to reduce modifiable diabetes risk factors in the whole population include healthier eating, regular physical activity, and preventing and managing overweight and obesity.
- Encouragingly, there appears to be a stabilisation or decline in diabetes incidence in many higher-income countries.

BACKGROUND

In 2024, an estimated 589 million adults aged 20 to 79 were living with diabetes, giving a prevalence of 11.1%. Almost one-in-two (42.8%; 251.7million) adults with diabetes were undiagnosed, with considerable regional differences.[1]

In addition, the global prevalence of impaired glucose tolerance (IGT) was 12.0% and that of impaired fasting glucose (IFG) was 9.2%.[1] Individuals with undiagnosed type 2 diabetes mellitus (T2DM) and intermediate hyperglycaemia (IH) are at increased risk of adverse outcomes and premature mortality.

Type 2 diabetes is a silent, progressive disease with chronic hyperglycaemia often preceded by IH. Earlier detection of T2DM provides an opportunity to intervene with evidence-based care and studies over the last three decades confirm that progression from IH to T2DM can be prevented or delayed. Tests used for the early detection of diabetes and IH include fasting plasma glucose (FPG), 2 h PG during a 75 g oral glucose tolerance test (OGTT), or glycated haemoglobin (HbA1c). Programmes for the detection of undiagnosed T2DM and the prevention of progression to T2DM in high-risk individuals are well-accepted strategies to reduce the burden of diabetes.

GLOBAL CONSIDERATIONS

The capacity to detect individuals with undiagnosed T2DM and IH and implement diabetes prevention programmes varies considerably between countries and health services and systems, especially in low- and middle-income countries (LMIC). The World Health Organization (WHO) periodically conducts a country capacity survey on non-communicable diseases (NCDs) to assess the national-level response to the NCD burden, which includes information on health system capacity for diabetes detection, treatment, and care. The most recent survey in 2019 collected data from 160 countries; 75% reported having an operational policy, strategy, or action plan for diabetes. Specific details on diabetes screening and prevention were not reported. The percent of countries with guidelines utilised in at least 50% of healthcare facilities was 22% for overweight/obesity and 33% for physical activity. Fifty-two percent of countries had an OGTT generally available in 50% of their primary care facilities in the public and private health sector; 53% of countries had HbA1c tests.[2] The Pan American Health Organization separately reported its survey results and found that 33 of 35 countries (94%) had blood glucose measurement equipment, 22 of 35 countries (63%) had OGTT testing, and 18 of 35 countries (51%) had HbA1c testing generally available in 50% of public primary healthcare facilities.[3] A survey of individuals from LMICs showed that the reach of any diabetes prevention-related activities was low: 40% for physical activity counselling, 37% for weight loss counselling, 43% for dietary counselling, and 37% for blood glucose screening. The lowest receipt of these activities was among people in low-income countries and people with no formal education.[4]

EVIDENCE SUMMARY

Criteria for diabetes and intermediate hyperglycaemia

Criteria for diabetes and IH have evolved since the first WHO guidelines were published in 1965, with significant changes made by expert panels of WHO and the American Diabetes Association (ADA) to reflect evolving evidence and its interpretation.[5] Since there is no specific marker which unequivocally defines diabetes, the diagnosis is based on cut-points derived from the relationship between various measures of glycaemia associated with risk of diabetes microvascular complications, particularly retinopathy.[5] Without a true gold standard among the biochemical tests for diagnosing diabetes (FPG, 2 h OGTT PG, HbA1c), comparisons of these tests are questionable. It has been suggested that the closest to a gold standard would be a combination of FPG, 2 h PG, and HbA1c assessments with confirmatory testing for all parameters, but this is not feasible.[6] This also applies to tests and comparisons of tests for IH.

There are significant differences in the attributes of tests used to diagnose diabetes and IH which influence the testing method adopted in different health settings and services.[7,8] These include requirement for fasting, global access and affordability, analytic stability, biologic variation, and factors affecting the assay (Table 1.1).

Table 1.1 Comparison of tests to diagnose diabetes and define intermediate hyperglycaemia

	FPG	OGTT	HbA1c
Fasting required	Yes	Yes	No
Test preparation	Fasting	Pretest CHO intake	Nil
Convenience	Reasonable	Low	Good
Global access and affordability	Highest	Intermediate	Intermediate
Pre-analytic stability	Poor – influenced by sample handling		Good
Assay standardisation	Not standardised		Standardised but varies globally
Biological variation	Intermediate	High	Low
Within-person variation	High		Low
Acute factors affecting result	Food intake, stress, activity		Not affected
Other factors affecting results	Diurnal variation Older age Medications		Haemoglobinopathies Altered red cell turnover, uraemia Ethnicity
Diagnostic sensitivity (compared to OGTT)	Lower	Highest	Lower
Identifies IGT	No	Yes	No
Lifestyle prevention intervention effect	Negative (for isolated IFG)	Positive (for IGT +/– IFG)	Limited data

CHO, carbohydrate; FPG, fasting plasma glucose; IFG, impaired fasting glucose; HbA1c, glycated haemoglobin; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Diabetes

Criteria

Definitions of diabetes are universally agreed, with both WHO and ADA adopting the same FPG, 2 h PG, and HbA1c diagnostic values (Table 1.2).

In asymptomatic individuals, two abnormal values either in the same setting or on separate occasions are recommended for clinical management.[5]

Table 1.2 Criteria for defining diabetes and intermediate hyperglycaemia

	WHO criteria	ADA criteria
Diabetes		
Fasting plasma glucose (FPG)	≥7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
2 h plasma glucose*	≥11.1 mmol/L (200 mg/dL)	≥11.1 mmol/L (200 mg/dL)
HbA1c	≥6.5% (48 mmol/mol)	≥6.5% (48 mmol/mol)
Intermediate hyperglycaemia		
Impaired fasting glucose (IFG)		
Fasting plasma glucose	6.1–6.9 mmol/L (110–125 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)
Impaired glucose tolerance (IGT)		
2 h plasma glucose*	7.8–11.0 mmol/L (140–199 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)
HbA1c	–	5.7%–6.4% (39–47 mmol/mol)

*Following a 75 g oral glucose tolerance test.
ADA, American Diabetes Association; HbA1c, glycated haemoglobin; WHO, World Health Organization.

Prevalence

Prevalence data for diabetes vary and are influenced by the method used to identify individuals with diabetes, which may include diabetes based on self-report, and/or taking diabetes-specific medication, and/or testing of people without known diabetes, and/or testing people with self-report diabetes but not taking medication. Furthermore, there is a well-recognised lack of congruence between FPG, 2 h PG, and HbA1c tests in identifying individuals as having diabetes.[9]

In 2024, the International Diabetes Federation (IDF) reported a global diabetes prevalence in 20–79-year-olds of 11.1% (589 million people), which was predicted to increase to 853 million by 2050. Diabetes prevalence was similar in men and women, highest in those aged 75–79 years, higher in urban (12.7%) than rural (8.8%) areas, and in high-income (12.4%) compared to low-income countries (6.1%). Regional differences were also noted, with the highest prevalence in the Middle East and North Africa IDF region (19.9%) and the lowest in the Africa IDF region (5.0%), and the largest numbers of people with diabetes in China (148 million) and India (90 million).[1] Methods for diabetes diagnosis included any of the three glucose measures, self-report, medical record or clinic diagnosis, and extrapolations for countries without data.[10]

In 2022, the NCD Risk Factor Collaboration estimated that 828 million adults aged 18 years and older had diabetes, an increase of 630 million from 1990, with the largest increases in low- and middle-income countries. The global age-standardised diabetes prevalence was 13.9% for women and 14.3% for men. These estimates were based on defining diabetes as an FPG ≥7.0 mmol/L (126 mg/dL) or an HbA1c ≥6.5% (48 mmol/mol), or taking medication for diabetes.[11]

Previously undiagnosed diabetes

In 2024, almost one in two (42.8%; 251.7 million) adults aged 20–79 years old living with diabetes were undiagnosed. There were significant regional disparities in undiagnosed diabetes, and 86.9% of all undiagnosed cases were in low- and middle-income countries. Low-income countries had the highest proportion of undiagnosed cases (58.7%), followed by middle-income countries at 45.5%, and high-income countries at 28.9%.[1]

The lack of congruence between glycaemic measures impacts reported prevalence of undiagnosed diabetes. An analysis of previously undiagnosed diabetes detected by an elevated FPG, HbA1c, or both reported that globally 29% of individuals with screen-detected diabetes had an isolated elevated FPG, 37% had an isolated elevated HbA1c, and 34% had elevated levels of both, with substantial variation across regions. In most low- and middle-income regions, isolated elevated HbA1c was more common than isolated elevated FPG.[12] Some of this disparity may relate to ethnic variations in the FPG-HbA1c relationship.[13]

Intermediate hyperglycaemia

Intermediate hyperglycaemia, also referred to as "prediabetes", includes impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and intermediate HbA1c. IGT was introduced in 1979 to describe a category of increased risk of progressing to diabetes.[14] IFG was introduced in 1997 to describe the FPG zone, which was believed to equate to IGT.[15]

There are differences in the pathogenesis of IFG and IGT, with IGT associated with muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during the OGTT; IFG is associated with impaired insulin secretion and impaired suppression of hepatic glucose output.[16]

Criteria

WHO and ADA criteria are the same for IGT but are different for defining IFG (Table 1.2), with WHO using an FPG range of 6.1–6.9 mmol/L (110–125 mg/dL) and the ADA using an FPG range of 5.6–6.9 mmol/L (100–125 mg/dL). Based on an OGTT with measurement of both FPG and 2 h PG, IH can be subdivided into those with isolated IFG, isolated IGT, and combined IFG/IGT.

IFG and IGT are not clinical entities but rather risk factors for future diabetes and adverse outcomes, and regression to normoglycaemia is common, ranging from 33% to 59% over 1–5 years of follow-up for IFG and 17% to 42% over 6–11 years of follow-up for IGT.[17]

In 2009, an International Expert Committee (IEC) recommended using an HbA1c of 6.0%–6.4% (42–47 mmol/mol) to identify people with IH.[18] An HbA1c intermediate hyperglycaemia category termed "prediabetes" was adopted by ADA in 2010, defined as an HbA1c of 5.7%–6.4% (39–47 mmol/mol).[19] To date, WHO has not made a recommendation on HbA1c for IH. Other groups

such as the UK National Institute for Health and Care Excellence recommends an HbA1c of 6.0%–6.4% (42–47 mmol/mol).[20]

Prevalence of intermediate hyperglycaemia

In 2024, IDF estimated the global prevalence of IGT was 12.0% and that of IFG was 9.2% among adults aged 20–79 years, with marked regional differences. Age-adjusted IGT prevalence was highest in Southeast Asia region (13.8%) and lowest in Europe region (5.9%). North America and the Caribbean region showed the highest IFG prevalence (13.6%) while Europe had again the lowest (5.4%).[1]

There are significant differences in prevalence and congruence of IH identified by different criteria, and overlap between the various biochemical tests is only moderate. Although IFG and intermediate HbA1c were introduced to achieve alignment with IGT, individuals with IGT who also had ADA-IFG was 58%, WHO-IFG was 23%, and ADA-HbA1c was 32%.[21] In addition, the percentage of people without IGT who have IFG increases substantially with ADA-FPG versus WHO-FPG.[22] The 2015–2016 US NHANES survey reported IH prevalences ranging from 4.3% with IEC-HbA1c to 43.5% with ADA-IFG. If a combination of ADA-HbA1c, ADA-FPG, and 2 h PG was used, the prevalence was 2.5% compared with 51.3% if any of the three tests was used.[23]

Progression to diabetes

All measures of IH predict progression to T2DM without intervention, and incident rates of T2DM increase with longer periods of follow-up.

Randomised controlled trials (RCTs) of diabetes prevention in people with IGT in Asia,[24] Europe,[25] India,[26] and the United States[27] reported a cumulative diabetes incidence of 23%–68% in the control group in this high-risk group mostly defined by two abnormal OGTTs.

A Cochrane review reported a cumulative diabetes incidence in individuals with IGT of 13% after one year and 60% after 20 years follow-up. The risk of diabetes was highest with combined IFG and IGT compared to people with normal glucose tolerance and with isolated IGT. The cumulative diabetes incidence after 12 years follow-up was 31% for both ADA-IFG and WHO-IFG; for ADA-HbA1c it was 31% at 10 years follow-up and 29% at 15 years follow-up for IEC-HbA1c.[17] A recent Danish population study reported a 21% 5-year cumulative T2DM incidence for IEC-HbA1c.[28]

Older age is an important consideration. A study of older adults with a high prevalence of ADA-FPG and ADA-HbA1c-defined IH reported that regression to normoglycaemia or death was more frequent than progression to diabetes.[29]

Prediction of adverse outcomes

The association between adverse outcomes and the various definitions of IH has been examined in two systematic reviews. The first included 129 studies with 10,069,955 individuals[30] and the second included 106 prospective studies and nearly 1.85 million people from 27 countries.[31] Overall, IH was associated with a significantly increased risk of mortality, cardiovascular disease (CVD), stroke, and chronic kidney disease compared with normoglycaemia across the different definitions of IH, albeit with some minor, inconsistent differences.

Summary

There are considerable differences in prevalence with the various individual tests for IH. Although the absolute reported prevalence varies, the pattern is consistent, with the highest prevalences found with ADA-IFG, ADA-HbA1c, and IGT and the lowest with WHO-IFG and IEC-HbA1c.[32, 33]

Differences in IH prevalences and progression to T2DM may reflect differences in pathophysiology and the myriad of ecological and external factors (e.g., environment, ecosystem, awareness, cultures, access to care, and standard of care) as well as host factors (e.g., ancestry, ethnicity, sex, age, gender, genetics, life course events, education, lifestyles, cognitive/psychological behaviours, coexisting risk factors, and comorbidities) and their complex interactions. As such, context and phenotyping are important considerations in attempts to improve the precision of risk assessment to maximise the impacts and cost-effectiveness of interventions.[34, 35]

There are well-documented differences across ethnic groups based on OGTT, with Asians highly insulin-sensitive, Africans most insulin-resistant, and Caucasians in-between along the hyperbolic curve between glucose sensitivity and insulin secretion.[36] Data from Uganda indicate that nearly one-third of people with incident diabetes have a body mass index (BMI) <25 kg/m^2, with a predominant phenotype of

reduced pancreatic secretory function.[37] These differences contribute to sub-phenotypes within the spectrum of dysregulation of glucose metabolism, which may stem from interethnic differences in biological responses, influenced by differences in population-specific genetic and ecological factors.[38]

Screening for undiagnosed diabetes and intermediate hyperglycaemia

Screening for undiagnosed T2DM or for IH are commonly recommended strategies. Earlier diagnosis and treatment reduce the risk of adverse outcomes, and identifying people with IH provides an opportunity to prevent progression to diabetes.

The usual approach to screening for undiagnosed T2DM or IH is based on well-recognised clinical risk factors (e.g., increasing age, family history of diabetes, overweight/obesity, previous history of gestational diabetes, ethnicity) and/or using formal risk scores composed of clinical information, followed by blood testing of glucose or HbA1c.[39,40] Risk scores have been demonstrated to enhance the performance of biochemical testing.[32] Use of local data to develop a risk score to estimate absolute risk prediction for diabetes may also increase precision.

Testing method and frequency of screening

There are considerable differences in the performance of individual tests for IH and consequently differences in country and international recommendations. If a decision is made to screen, the choice of test procedure and frequency of testing will need to be determined by a country's health services, taking into account available resources. Within-country differences in recommendations underscore the lack of universal consensus.[7, 41] While guidelines recommend repeat testing to confirm a diagnosis of diabetes in an asymptomatic individual, there are no guidelines regarding repeat testing to confirm IH.[42]

The 1 h OGTT – a proposed new approach to testing for intermediate hyperglycaemia

Decades ago, the 2 h OGTT was a five-sample test with glucose measured at 0, 30, 60, 90, and 120 minutes. Later the 30-, 60-, and 90-min samples were eliminated, leaving the modern day OGTT with only FPG and 2 h PG. Recently, the value of the 1 h PG during an OGTT has been revisited in an IDF Position Statement. Epidemiological data demonstrate the value of a 1 h PG ≥8.6 mmol/L (155 mg/dL) in predicting diabetes and associated complications, even in people with otherwise normal glucose tolerance, and a 1 h PG ≥11.6 mmol/L (210 mg/dL) for diagnosing T2DM. The IDF Position Statement suggests the 1 h PG as a more sensitive and practical method than other current biochemical tests and calls for redefining current diagnostic criteria for IH and T2DM by adding the 1 h PG as a diagnostic option.[43] The evidence supporting the utility of the 1 h PG during an OGTT is comprehensively detailed in the IDF Position Statement and is therefore not reviewed further in this Chapter.

In time, the 1 h PG OGTT may be adopted for detecting IH. Using a 1 h OGTT may not necessarily overcome the practical and health system challenges of the 2 h OGTT, even though it is a shorter test. An additional test for detecting IH may find increased prevalence rates and incongruence in classifying individuals with IH evident with currently available tests. While it is likely that individuals with an elevated 1 h PG will benefit from diabetes prevention interventions similar to those with IGT, there are currently no supporting clinical trial data.

Diabetes prevention

There are two complementary approaches to reducing the incidence of type 2 diabetes:

- **The individual-based high-risk approach with interventions in higher risk individuals**
- **The population approach to reduce diabetes risk factors across the entire population**

The individual-based high-risk approach

This strategy involves identifying individuals at higher risk of developing T2DM by screening and testing for IH, followed by offering lifestyle interventions. Successful randomised diabetes prevention studies have targeted individuals with IGT, and a recent review reported a lack of effect of lifestyle intervention in individuals with isolated IFG.[44] However, the situation may be different for

pharmacological interventions to prevent diabetes for glucose- or HbA1c-defined IH.[45, 46]

There are limited data on the effectiveness of lifestyle intervention in individuals with IH identified by HbA1c. The US Diabetes Prevention Program (DPP) evaluated treatment effects (in participants with IH identified by HbA1c) on incident diabetes, defined by HbA1c ≥6.5% (48 mmol/mol). Lifestyle intervention and metformin reduced diabetes incidence by 49% and 44%, respectively, during the DPP, and by 29% and 38%, respectively, during the 10-year follow-up. In contrast to the superiority of the lifestyle intervention on glucose-defined diabetes, metformin and lifestyle interventions had similar effects in preventing HbA1c-defined diabetes.[47]

Interventions to prevent or delay development of T2DM in high-risk individuals

Several systematic reviews and meta-analyses have demonstrated an association between incident T2DM and diet or dietary components, including:

- **High glycaemic index (GI) foods and high glycaemic load (GL) diets increase risk.[48]**
- **Consumption of foods and dietary components from plant-based sources, such as whole grain products, fibre, vegetable fats, and plant proteins, reduces risk.[49]**
- **A higher intake of red meat, processed meat, and sugar-sweetened beverages increases risk.[50]**
- **A high intake of vegetable fat lowers T2DM incidence but total fat intake is not associated with incident T2DM.[50]**
- **Substituting plant protein for animal protein may decrease T2DM risk.[51]**
- **Vegetarian diets are associated with reduced T2DM incidence.[52]**

Randomised controlled studies

Diet and physical activity
Lifestyle changes are effective in preventing or delaying the development of T2DM. A Cochrane review reported a significant reduction in incident T2DM in people with IGT with or without IFG (but not in isolated IFG) who received diet and exercise counselling.[53] The lack of effect in IFG has been confirmed in a more recent systematic review of data from other studies.[44]

Diabetes prevention or delay persists but decreases over time as demonstrated after 20 years in the China Da Qing Diabetes Prevention Study, with intervention participants having 3.6 fewer years with diabetes. However, residual risk of progression to diabetes was high: 80% in the intervention group and 93% in the control group after 20 years.[54] The Finnish DPS reported an ongoing reduction in incident T2DM over the 13-year follow-up. The cumulative incidence of diabetes was 44% in the intervention group and 64% in the control group, with an estimated five-year delay in deterioration from IGT to overt T2DM.[55] The US Diabetes Prevention Program Outcomes Study also showed sustained diabetes prevention in the intervention versus control group after 12 years.[56]

Emerging data from long-term observational studies of RCTs suggest a possible beneficial effect on vascular complications,[57] including a lower risk of severe retinopathy after 20 years of follow-up,[58] and a significant 41% risk reduction in CVD and 29% reduction in all-cause death in the intervention group after 23 years.[59]

Pharmacotherapy
Several studies have assessed the effect of various glucose-lowering medications on T2DM prevention. A Cochrane review reported the superiority of metformin in reducing incident T2DM compared with standard diet and exercise but it was not different compared with intensive diet and exercise, acarbose, thiazolidinediones, or when combined with intensive lifestyle compared with intensive lifestyle alone.[60] However, a recent RCT reported a 17% significantly lower risk of incident T2DM with metformin plus lifestyle intervention compared with lifestyle intervention alone, but with more adverse gastrointestinal side effects.[61] Data on long-term outcomes are limited except for the US DPP which showed no difference in microvascular complications in the metformin versus the comparative group after 15 years follow-up.[62]

Other agents which significantly reduced diabetes incidence include acarbose,[63] thiazolidinediones,[45] glucagon-like peptide-1 receptor agonists,[64] and sodium-glucose cotransporter-2 inhibitors.[46]

Community and national programmes

Several programmes have translated the high-risk individual lifestyle-based T2DM diabetes prevention RCTs into large-scale community and national prevention programmes.

The US National Diabetes Prevention Program (US NDPP)

US NDPP is a lifestyle intervention programme to prevent T2DM in at-risk people age ≥18 years old identified by HbA1c, FPG, or OGTT, or previous gestational diabetes, or positive ADA risk test. The programme is overseen by the Centre for Disease Control (CDC) and promotes ≥5% weight loss over one year delivered via in-person classes, distance learning, online programming, or a combination of modalities. There are a total of 26 sessions and at least 22 must be completed for the individual to achieve CDC recognition for completing the programme. Analysis of 14,747 adults enrolled in the programme reported that 36% achieved the 5% weight loss goal (average weight loss 4.2%). As yet, incident T2DM has not been systematically evaluated.[65]

The Finnish National Diabetes Prevention Programme (FIN-D2D)

FIN-D2D is a community-based lifestyle modification T2DM prevention programme delivered in primary and occupational health care, predominantly through groups.[66] Individuals are screened for high risk with the Finnish Diabetes Risk Score (FINDRISC) and are then referred for OGTT. Evaluation of 2,730 individuals with complete follow-up data showed that in those who lost 2.5%–4.9% body weight and ≥5% during the first year, risk for incident medication-treated diabetes after 7.4 years was significantly reduced by 37% and 29%, respectively, compared with those with stable weight. There were no significant differences in CVD events or all-cause mortality.[67]

The UK National Health Service Diabetes Prevention Programme (NHS DPP)

This programme is offered to individuals aged ≥18 years with an HbA1c 6.0–6.4% (42–47 mmol/mol) or FPG 5.5–6.9 mmol/L (100–125 mg/dL) through 13 lifestyle modification education sessions delivered by face-to-face groups or a digital service. An assessment of 17,252 individuals who completed the programme demonstrated a mean weight loss of 3.3 kg and an HbA1c reduction of 0.19% (2.04 mmol/mol). T2DM incident was not reported.[68]

Australian Victorian Life! Taking Action on Diabetes Program

This is a community-based diabetes prevention programme with individuals at risk of developing diabetes identified by a national risk score. An evaluation of 8,412 participants who commenced a Life! Program (of whom 37% completed all six education sessions) showed an average weight loss of 2.4 kg (2.7%) in completers and 1.4 kg weight loss in those attending 1–5 sessions.[69]

Middle-income countries

A review of six RCTs of community-based lifestyle interventions included three studies (Chennai and Kerala, India, and one from rural China) reported diabetes incidence in 1,921 individuals. The review found a non-significant reduction in diabetes incidence at 12 months compared with controls. Significant reductions were observed in weight (2.3 kg) and in FPG and HbA1c.[70]

A lifestyle diabetes prevention programme in primary care settings in Thailand in 1,093 individuals with IGT reported a significant 28% reduction in incident diabetes after two years compared with the control group, accompanied by body weight reduction of 1.5 kg in the intervention group and a 0.4 kg increase in the control group.[71]

South Africa

Lifestyle Africa is a culturally adapted version of the US DPP with a lifestyle intervention of 17 video-based group sessions delivered by trained community health workers. An assessment of 494 enrolled participants reported a mean weight change of 0.6% in the intervention group, not significantly different to the 0.4% in the control group. However, HbA1c was significantly lower (mean difference 0.24% [2.58 mmol/mol]).[72]

The population approach

Strategies to improve the health of the entire population by reducing modifiable risk factors for NCDs are an integral part of T2DM prevention. Reducing population diabetes risk factors results in a small downward shift in average population levels of diabetes risk, which can lead to a significant reduction in diabetes. This can be achieved by encouraging a healthy diet and regular physical activity, preventing overweight and obesity, and reducing other

health risks such as smoking, excessive alcohol intake, improving sleep, and minimising climate-related health effects.

Common strategies to drive population change include increasing health-promoting environments, embedding health-promoting activities in everyday life, education and social media campaigns, and reducing marketing and the promotion of unhealthy foods, especially to children. Effective societal strategies include legislation (e.g., sugar tax) to reduce consumption of sugar-sweetened beverages, food reformulation, improved food labelling, and changing the physical environment (e.g., reduce pollution, provide living and leisure space). Broader population-based measures are also important, including improving general education, reducing poverty, ensuring food security, and raising health awareness – all underpinned by universal health coverage and a robust primary care and health system.[38] These interventions can be incorporated in diabetes prevention programmes.[66]

Summary

Randomised controlled studies have demonstrated the effective prevention of T2DM in people with IGT across different populations but a lack of effect in people with isolated IFG. The effect on incident diabetes persists but declines over time. Emerging evidence suggests a decline in some adverse diabetes outcomes.

Several countries and settings have translated this evidence into community-based programmes, with differences in target population, method of identifying high-risk individuals, and the intervention content and delivery. Overall, the degree of weight loss is less than in RCTs and data on incident diabetes are lacking.

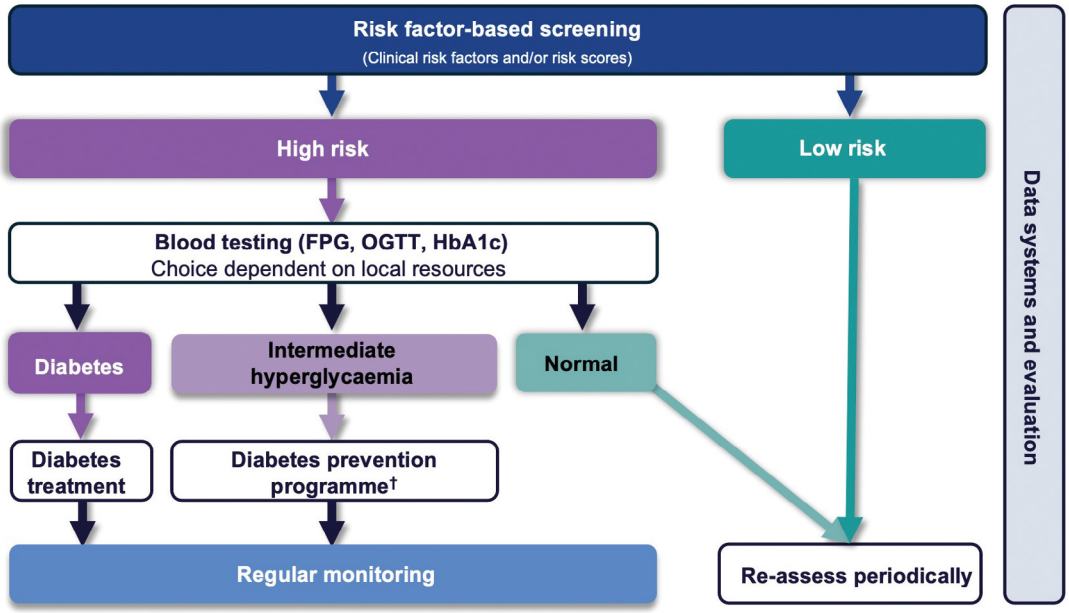
Including strategies to reduce population diabetes risk is an important component of diabetes prevention programmes.

Implementing diabetes prevention programmes

Diabetes prevention programmes should ideally include both high-risk and population strategies. Encouragingly, the incidence of diagnosed diabetes appears to be stabilising or declining in many higher-income countries, with a reported annual estimated change in incidence ranging from –1.1% to –10.8% since 2010. Multifaceted T2DM prevention activities in individuals at high risk of T2DM and population-wide approaches may be factors in this observation.[73] Population strategies require lobbying and influencing national policy makers. The focus of this section is implementing programmes for high-risk individuals.

The essential components of programmes targeting high-risk individuals are universally agreed (Figure 1.1). However, there are a number of questions which need to be considered in developing and implementing a community or

Figure 1.1 Overview of high-risk type 2 diabetes screening and prevention programmes



†Programme content and delivery dependent on local resources.
FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; OGTT, oral glucose tolerance test.

national diabetes prevention programme for high-risk individuals.

Risk assessment and screening

Most programmes target a specific age group for screening rather than offering universal screening but differ in the selected age, which is decided based on local risk and resources. Many guidelines suggest initial screening with a risk score to identify high-risk individuals. Developing or adapting a risk score using local data may increase predictive precision.

Screening for high risk is complex and challenging on a large scale. The strongest evidence for successful lifestyle intervention is for people with IGT, which can only be diagnosed by an OGTT.[44] However, OGTT screening has practical limitations for both the health system and participants, especially if it is also to be used for routine follow-up assessment. Given these practical challenges, many national programmes use HbA1c or FPG to identify high-risk individuals for interventions to reduce progression to T2DM. While the US DPP includes testing with any of the three tests for identifying IH, the most used tests are HbA1c and FPG rather than an OGTT. The UK DPP advocates blood testing with HbA1c or FPG. The Hong Kong Chronic Co-Care Pilot Scheme includes screening for IH based on an HbA1c of 6.0%–6.4% (42–47 mmol/mol) or FPG 6.1–6.9 mmol/L (110–125 mg/dL).[74]

Advances in understanding the heterogenous nature of IH and in technology may increase the precision with which the highest-risk individuals can be identified for a programme based on selective use of OGTT, depending on available resources. Options include stratifying levels of risk and recommending OGTT testing in the younger highest-risk category.[75] Another option is the 1 h OGTT PG.

Screening for diabetes prevention programmes requires balancing the evidence, practicalities, potential impact, and cost. A comparison of a range of screening scenarios, including OGTT, FPG, and HbA1c alone or following risk score assessment explored the potential impact on reducing incident diabetes and cost. Compared with OGTT testing, costs of screening and prevention were substantially lower with an initial assessment with a risk score, followed by a blood test, but the potential for diabetes prevention was reduced by 35% to 75%. With all scenarios, there will be some lower-risk individuals who will develop diabetes.[76]

Programme delivery

Established programmes have varied widely with respect to number of education sessions (ranging from 4–22), the way the programme is delivered (face-to-face individual or group, online), and the follow-up support offered. Programmes have also differed with respect to training, qualifications, and accreditation of the education trainers who deliver the programme.

Awareness, enrolment, and retention

In Finland, 25% of men and 48% of women reported being aware of the FIN-D2D programme in the area where it was being rolled out, compared with 20% men and 36% of women in the control area.[77] Community-based programmes have consistently highlighted the challenge of enrolment and retention. In the Victorian Diabetes Program, over 29,000 individuals showed interest in the programme, 15,000 were referred, approximately 8,500 commenced the programme, and 3,000 attended all six programme sessions.[69] In the UK NHS Diabetes Prevention Programme by December 2018, nearly 325,000 people were referred, approximately 150,000 attended the initial assessment, and approximately 95,000 attended at least one of 13 group-based intervention sessions with approximately half completing the intervention (attending >60% of sessions).[68]

Attendance may be influenced by the mode of programme delivery, with assessment of over 330,000 US National DPP participants showing that the average number of sessions attended was highest for in-person participants (68%), online (57%), distance learning (55%), and combination (49%), with a similar pattern for average weeks in the programme. Among participants who remained in the programme for all sessions, average weight loss exceeded the programme goal of 5% for all delivery modes.[78] Results were similar for the South African programme – average attendance across all sessions and groups was 54%, with 35% attending at least 75% of sessions across all groups.[79]

Scalability

Scalability and reach remain a challenge. The US National DPP has been successful in offering the programme to over 700,000 at-risk participants since it began in 2012 but there are an estimated nearly 100 million Americans with IH. One approach which has been taken to improve reach is to incorporate diabetes prevention

into broader NCD prevention initiatives. Some programmes offer financial incentives to encourage risk assessment and subsidise lifestyle educational interventions.

Implementation

If a decision is made to have a diabetes prevention programme for high-risk individuals, the design will need to be decided according to local practice, local resources, feasibility, and cost. Data systems and evaluation are important components of the programme to facilitate quality improvement.

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Chapter 2

Glycaemic Control Assessment and Targets In Type 2 Diabetes

RECOMMENDATIONS

<table>
<tr><th></th><th>Optimal Care</th><th>Basic Care</th></tr>
<tr><td rowspan="2">Glycated haemoglobin (HbA1c)</td><td>• Measure HbA1c at regular intervals
• HbA1c general target 7.0% (53 mmol/mol)
• Personalise HbA1c
- higher in the elderly
- lower in the newly diagnosed
• Measure fructosamine if HbA1c cannot be measured accurately</td><td>• Measure HbA1c at regular intervals
• HbA1c general target 7.0% (53 mmol/mol)
• Personalise HbA1c (especially in the elderly)
• If HbA1c assay not available, use any available glucose measure</td></tr>
<tr><td rowspan="2">Self-monitoring of blood glucose (SMBG)</td><td>• Routinely recommend SMBG to all insulin-treated people with type 2 diabetes mellitus (T2DM)
• Consider SMBG in other people with T2DM
• Provide education in structured SMBG</td><td>• Routinely recommend SMBG to people with T2DM treated with multiple daily insulin regimens
• Consider SMBG in other people with T2DM treated with other insulin regimens
• Provide education in structured SMBG</td></tr>
<tr><td colspan="2">• SMBG targets:
Fasting and pre-prandial glucose
- 4.0–8.0 mmol/L (70–144 mg/dL)
Postprandial glucose†
- 4.0–8.0 mmol/L (70–144 mg/dL) (preferable)
- 4.0–9.0 mmol/L (70–160 mg/dL) (acceptable)</td></tr>
<tr><td rowspan="2">Continuous glucose monitoring (CGM)</td><td>• Consider CGM in all insulin-treated people with T2DM and in others on an individual basis</td><td>• Consider short-term CGM in select people with T2DM on intensive insulin regimens or insulin pump, if available and affordable</td></tr>
<tr><td colspan="2">• CGM targets (refer to Table 2.1)</td></tr>
</table>

†Measure postprandial glucose 1–2 h after beginning a meal.

KEY POINTS

- Glycaemic control reduces the risk of both micro- and macrovascular complications in type 2 diabetes mellitus (T2DM).
- Assessing and monitoring glycaemia is an essential component of guiding treatment decisions to achieve and maintain target glycaemic control.
- Setting glycaemic targets is based on established associations with adverse outcomes.
- HbA1c is the established gold standard for assessing glycaemic control in T2DM.
- The general HbA1c target of <7.0% (<53 mmol/mol) should be personalised, balancing reducing complications, minimising hypoglycaemia and an individual's characteristics.
- HbA1c measurement may be affected by a variety of factors – in these situations, fructosamine and glycated albumin are alternatives for monitoring glycaemic control.
- Improving HbA1c improves diabetes outcomes in the short- and longer-term.
- HbA1c variability may be important but has not been definitively confirmed as an independent risk factor for diabetes complications.
- The contribution of fasting plasma glucose (FPG) and postprandial glucose (PPG) to overall glycaemia varies according to HbA1c levels, being greater for PPG at lower HbA1c levels and greater for FPG at higher HbA1c levels.
- In select individuals with T2DM, HbA1c measurement may be complemented with self-monitoring of blood glucose (SMBG) or continuous glucose monitoring (CGM).
- SMBG and CGM may provide additional useful clinical information on glycaemic metrics relevant to diabetes management, including periods of hyperglycaemia and hypoglycaemia.
- SMBG is recommended in insulin-treated T2DM but may be useful in other situations.
- SMBG use (intensity and frequency) should be structured and individualised.
- The proposed SMBG targets are adapted to align with CGM metrics.
- CGM is currently used mainly in people with type 1 diabetes mellitus (T1DM) but use is increasing in insulin-treated T2DM in high-resource health settings. Data supporting its use in non-insulin treated people with T2DM are limited.
- Key CGM metrics include glycaemic variability and time in defined glucose ranges.
- Target CGM metrics are based on international consensus.
- Most of the global diabetes population lives in low-income and middle-income countries (LMICs) where access and affordability to HbA1c testing, SMBG, and CGM are limited.

BACKGROUND

Glycaemic control is a treatment pillar for reducing the risk of both micro- and macrovascular complications in type 2 diabetes mellitus (T2DM),[1] and early and intensive glycaemic control has a legacy effect in reducing cardiovascular and kidney disease events and all-cause mortality even after 24 years.[2] Assessing and monitoring glycaemia are essential components of guiding treatment decisions to achieve and maintain target glycaemic control.

Measurement of glycated haemoglobin (HbA1c) underpins the assessment of long-term glycaemic control in people with T2DM. In select individuals with T2DM, this may be complemented with self-monitoring of blood glucose (SMBG) by finger-stick capillary devices or continuous glucose monitoring (CGM) devices which measure interstitial glucose. SMBG and CGM may provide additional useful clinical information on other dimensions of glycaemia relevant to diabetes management, including periods of hyperglycaemia and hypoglycaemia.

Determining glycaemic targets is based on the established association of adverse diabetes outcomes derived from epidemiological studies or post-hoc analyses of intervention studies. Observational studies have shown a relationship between HbA1c and macro- and microvascular complications, and death in people with T2DM.[3] Interventional randomised controlled trials (RCTs) examining the effect of intensive glycaemic control have achieved HbA1c levels ranging from 6.5%–7.1% (48–54 mmol/mol).[4-8]

Identifying actual "thresholds" in the HbA1c/complications relationship has given differing results. For example, post-hoc analyses of the ADVANCE trial suggest an HbA1c "threshold" of below 7.0% (53 mmol/mol) for macrovascular events and death, and 6.5% (48 mmol/mol) for microvascular events.[9] However other analyses of observational data suggest a continuous increase in risk of major adverse cardiovascular disease (CVD) outcomes down to an HbA1c of 5.7% (39 mmol/mol).[10]

Setting clinical target recommendations should consider both the individual and population-level impact. The global prevalence of poor glycaemic control is high, ranging from between 45% and 93% in one systematic review[11] and another reporting that the proportion with adequate control was 22% since 2010.[12] These estimates are considerably lower than the World Health Organization (WHO) goal of 80% of people with diagnosed diabetes achieving good control of glycaemia.[13] The greatest population impact on complications will be achieved by reducing HbA1c from very high to moderate glycaemic levels. Although lowering HbA1c from 7.0% to 6.0% (53 mmol/mol to 42 mmol/mol) is associated with a further reduction in the risk of microvascular complications, the absolute risk reductions become much smaller and numbers needed to treat to benefit an individual increase.[14] Setting lower targets has implications for the impact on health services in different resource settings.

General glycaemic targets (e.g., HbA1c <7.0% [<53 mmol/mol]) are proposed as guides that are appropriate for many people but need to be personalised, balancing reducing complications and minimising hypoglycaemia and taking into account a range of factors relevant to the individual with T2DM, including comorbidities, age, duration of diabetes, risk of hypoglycaemia, life expectancy, individual preferences, and available resources.[14,15] Setting specific glycaemic (and other) goals during consultations are also helpful in improving outcomes for individuals with diabetes.[16]

Advances in technology, such as continuous glucose monitoring (CGM), have provided more detailed information on glycaemia in both healthy individuals without diabetes and people with diabetes, and these data can be used to inform glycaemic targets in people with diabetes.[17] To date, CGM has largely been applied to people with type 1 diabetes mellitus (T1DM) but is increasingly being considered in T2DM in high-resource health settings.

GLOBAL CONSIDERATIONS

Approximately 80% of the global diabetes population lives in low-income and middle-income countries (LMICs) where healthcare resources are often limited, which impacts access, availability, and affordability to many established evidence-based diabetes interventions.[18] These considerations are relevant to formulating practical clinical recommendations and implementation strategies for assessment of glycaemic control in resource-limited settings.

Regular periodic measurement of HbA1c is the gold standard for assessing longer-term glycaemic control, and health systems should

aim to ensure that it is available throughout their services. However, at present it is not available in many health services.

The 2019 periodic WHO country capacity survey on non-communicable diseases (NCDs) of 160 countries reported that overall HbA1c testing was generally available in only 53% of primary care facilities in the public and private health sectors.[19] The Pan American Health Organization separately reported that 18 of 35 countries (51.4%) had HbA1c testing generally available in >50% primary healthcare facilities in the public sector.[20] In these situations, other less satisfactory methods of assessing glycaemia (e.g., fasting, random, and postprandial glucose measurement) remain the only option for assessing glycaemic control. An additional important consideration for HbA1c testing is that the assay is not currently well-enough standardised in many countries.[21]

SMBG systems have been the standard method of self-assessment of glycaemia for many years in well-resourced settings. However, access to SMBG in LMICs is often hindered by unavailability, high costs, inadequate coverage by national health services, and even when available, usage is compromised by poor diabetes education.[22] Approximately 95% of SMBG expenses is attributable to testing strips. Consequently, SMBG is only widely used if subsidised, but the availability of subsidised supplies varies considerably. One survey reported that full provision by government of two or more blood glucose test strips per day for children with diabetes aged less than 15 years occurred in 18 of 20 high-income countries (HIC), five of 15 upper MIC countries, and none of 37 LMIC and LIC countries.[23]

Access in LMIC is further hindered because out-of-pocket prices to individuals are often much higher than prices in HIC, making SMBG mostly unaffordable.[24] An Indonesian study reported that public sector facilities did not supply devices for self-testing and in the private sector, a low-income worker required nine to 12 days' wages to purchase a meter and a month's supply of test strips.[25]

The 2023 WHO's Essential Diagnostics List recognised the role of blood glucose meters and test strips for SMBG in home settings and added a new recommendation for glucose measurement for use in community settings "to self-monitor type 1 and type 2 diabetes mellitus at home".[26] This significant step should help increase access to SMBG in LMICs.

CGM has emerged as an option for self-monitoring which provides more detailed glycaemic information but is considerably more expensive than SMBG systems. There are few data on the global use or availability of CGM, which is at present largely restricted to well-resourced health settings. The Indonesian study assessed the financial impact of CGM and reported that it would require spending 31 days' salary of a low-income worker to purchase a CGM reader, meaning no salary would remain for basic daily needs. Moreover, buying a month's supply of CGM sensors would require 61 days' salary, effectively making access to CGM financially impossible for many individuals.[25]

EVIDENCE SUMMARY

HbA1c (glycated haemoglobin)

Measurement of HbA1c is the established gold standard marker to assess glycaemic control in T2DM and has prognostic value for the development of diabetes complications and is routinely used to measure glycaemia in outcome-related clinical studies.[27] HbA1c integrates the mean glycaemia from the past two to three months. It can be measured in the laboratory or by point-of-care testing. Point-of-care technology can give HbA1c results of sufficient quality to enable clinical decision-making and can be used in community and primary care settings.[28]

HbA1c measurement may be affected by a variety of genetic, haematologic, and illness-related factors. The most common worldwide important factors affecting HbA1c levels are haemoglobinopathies, certain anaemias, and disorders associated with accelerated red cell turnover, such as malaria.[21]

Serum glycated proteins (fructosamine and glycated albumin) are an alternative to monitor glycaemic control, especially in people with diabetes where measurement or interpretation of HbA1c is problematic. Fructosamine reflects total glycated serum proteins and glycated albumin, the proportion of total albumin that is glycated. These measures reflect glycaemia over the past two to four weeks and are associated with long-term complications but lack definitive outcome data.[14]

HbA1c and diabetes complications

Glycaemia measured by HbA1c is associated with increased risk of microvascular and macrovascular complications in T2DM.[29] Interventions to reduce HbA1c significantly reduce macrovascular and microvascular complications in the short and longer-term.[1,7] One meta-analysis suggested a 15% relative risk reduction in non-fatal myocardial infarction with every 1.0% (11 mmol/mol) reduction in HbA1c[30] and another that an absolute HbA1c reduction of 0.9% (10 mmol/mol) reduced the relative risk of kidney events by 20% and eye events by 13%.[31]

HbA1c variability

Serial measurements of HbA1c can be used to assess long-term glycaemic variability.[32,33] While HbA1c variability has not been definitively confirmed as an independent risk factor for diabetes complications, observational studies[34,35] and post-hoc analysis of diabetes outcomes studies have reported an association between HbA1c variability and diabetes complications, including macrovascular events in the ADVANCE study,[36] CVD death in the EMPAREG study,[37] and all-cause mortality in the ACCORD study.[38] However in the VADT study, no HbA1c measures were associated with CVD.[39] High variability in HbA1c, even among individuals with T2DM whose average HbA1c was at target levels, has been associated with an increased risk of CVD complications and other adverse outcomes.[40,41]

HbA1c target

Setting general HbA1c targets is based on observational studies and post-hoc analyses of interventional RCTs showing a relationship between HbA1c levels and macrovascular and microvascular complications, and death in people with T2DM. However, the nature of the relationship has varied. The UKPDS showed a curvilinear relationship between HbA1c and microvascular complications.[3] The ADVANCE trial showed a non-linear relationship between mean HbA1c during follow-up and the risks of macrovascular events, microvascular events, and death with evidence of HbA1c 'thresholds' below 7.0% (53 mmol/mol) for macrovascular events and death, and 6.5% (48 mmol/mol) for microvascular events.[9] An Italian registry-based study examined 251,339 newly diagnosed T2DM without CVD at baseline and assessed major CVD outcomes-based mean HbA1c. After a mean follow-up of 4.6 years, compared with mean HbA1c <5.7% (39 mmol/mol) during the first year after diagnosis, CVD risk increased progressively to 56% for individuals with HbA1c >8.0% (>64 mmol/mol).[10]

Interventional RCTs examining the effect of intensive glycaemic control have achieved HbA1c targets ranging from of 6.5%–7.1% (48–54 mmol/mol).[4-8] These data are the basis for the general target of HbA1c <7.0% (<53 mmol/mol) in people with T2DM recommended by most guidelines for minimising risk of diabetes complications and hypoglycaemia. This target is proposed as a guide, which is appropriate for many people, but it is important to consider personalising targets, based on a range of factors relevant to the individual with T2DM. These factors include the presence of comorbidities, age, duration of diabetes, risk of hypoglycaemia, life expectancy, individual preferences, and available resources.[14,15] Increasing age and declining functional and cognitive capacity are particularly relevant when setting less stringent goals, as treatment burden and risk of harm outweigh potential benefits.[42] It is also important to adjust targets as required if circumstances change.

Setting glycaemic targets should consider not only the impact on the individual but also the broader population-level effects. Considering the high global levels of poor glycaemic control,[11,12] the greatest population impact on complications will be achieved by reducing HbA1c from high to moderate glycaemic levels. Although further lowering of HbA1c is associated with an additional reduction in the risk of complications, the absolute risk reductions become much smaller, and number needed to treat to achieve a benefit for an individual increases.[14] For example, if the annual incidence of a diabetes complication is 5% at an HbA1c of 9.0% (75 mmol/mol) and lowering HbA1c by 1.0% (11 mmol/mol) is associated with a 50% reduction in the annual incidence of that complication, 40 people would need to have their HbA1c lowered from 9.0% (75 mmol/mol) to 8.0% (64 mmol/mol) to benefit one individual. The equivalent numbers for lowering HbA1c from 8.0% (64 mmol/mol) to 7.0% (53 mmol/mol) is 80 individuals and from 7.0% (53 mmol/mol) to 6.5% (48 mmol/mol) is 270 individuals. Therefore, setting low HbA1c population targets has implications for the impact on health services in different resource settings.

Postprandial and fasting glucose

The contribution of fasting plasma glucose (FPG) and postprandial glucose (PPG) to overall glycaemia in people with T2DM varies according to HbA1c levels. The relative contribution of PPG decreased progressively from approximately 70% in the lowest to approximately 30% in the highest quintile of HbA1c, whereas the opposite is observed for the relative contribution of FPG – approximately 30% in the lowest compared with approximately 70% in the highest quintile.[43,44]

A short-term study assessed the relative contribution of controlling FPG and PPG in people with T2DM with an HbA1c ≥7.5% (58 mmol/mol). Only 64% of people achieving an FPG <5.6 mmol/L (100 mg/dL) achieved an HbA1c <7.0% (53 mmol/mol) compared with 94% who achieved a PPG of <7.8 mmol/L (140 mg/dL).[45] However, the contribution of FPG to HbA1c may also be influenced by the intervention to improve glycaemia with basal insulin reducing the contribution of basal hyperglycaemia to approximately 35% with lowering mean FPG to 6.5 mmol/L (117 mg/dL) and HbA1c to 7.0% (53 mmol/mol).[46]

Postprandial and fasting glucose and diabetes complications

Atherosclerotic disease accounts for much of the increased mortality and morbidity associated with T2DM, and PPG may have a direct toxic effect on the vascular endothelium, mediated by oxidative stress that is independent of other CVD risk factors.[47]

The HEART2D RCT in people with T2DM after acute myocardial infarction compared controlling PPG with three premeal doses of insulin lispro (PRANDIAL strategy) versus a basal strategy (BASAL) of twice daily NPH insulin or once daily insulin glargine. After 2.6 years, the trial was stopped due to lack of efficacy.[48]

The Kumamoto study which used multiple daily insulin injections to control both fasting and post-meal glycaemia in people with T2DM, reported a curvilinear relationship between retinopathy and microalbuminuria with both FPG and two-hour PPG control with no development or progression of retinopathy or nephropathy with FPG <6.1 mmol/L (110 mg/dL) and two-hour post-meal PG <10 mmol/L (180 mg/dL). This suggests that both reduced PPG and reduced FPG are strongly associated with reductions in retinopathy and nephropathy.[8]

RCTs have examined CVD outcomes with glucose-lowering medications (GLMs) which target PPG. The NAVIGATOR trial examined the effect of the short-acting insulin secretagogue, nateglinide, on risk of CVD events in 9,306 people with impaired glucose tolerance. CVD outcomes were not significantly reduced in the participants taking nateglinide compared with placebo after a median of five years.[49] Three studies have examined alpha glucosidase inhibitors on CVD outcomes. The ACE (Acarbose Cardiovascular Evaluation) study examined the effect of acarbose in people with coronary artery disease and impaired glucose tolerance and failed to show a difference in outcomes between acarbose and placebo.[50] The UKPDS randomised 1,946 people with T2DM to acarbose or placebo. After three years, there was no difference in the primary aggregated outcome or microvascular disease.[51] The ABC study assessed the effect of voglibose on the recurrence of myocardial infarction in people with a previous myocardial infarction and impaired glucose tolerance but was terminated early after an interim analysis suggested a low probability of a positive outcome.[52]

Fasting plasma and postprandial glucose variability

Long-term glycaemic variability can be assessed by serial measurements of HbA1c or other measures of glycaemia, including FPG and PPG.[32,33]

Post-hoc analyses of diabetes outcomes studies have examined the relationship between FPG variability and diabetes complications. In the ADVANCE study intensive treatment group, an increase in visit-to-visit variation in FPG was associated with an increased risk of both macrovascular and microvascular events.[36] In the DEVOTE study, higher day-to-day fasting glycaemic variability was associated with increased risks of severe hypoglycaemia and all-cause mortality.[53] In the VADT study, variability measures of FPG were significantly associated with CVD events after adjusting for other risk factors. Considered separately, this relationship was evident in the intensive treatment group but not in the standard group.[39] In the EMPAREG study, higher FPG variability was associated with an increased risk for CVD death in both treatment arms.[37] There are no equivalent in-depth data analyses examining PPG variability.

Postprandial and fasting glucose targets

The Kumamoto study showed no development or progression of retinopathy or nephropathy with FPG <6.1 mmol/L (110 mg/dL) and two-hour post-meal PG <10 mmol/L (180 mg/dL).[8]

Intervention RCTs on the effects of glycaemic control used different glycaemic targets to intensify treatment in the intensive treatment groups. The UKPDS aimed for an FPG <6.0 mmol/L (108 mg/dL);[7] the ACCORD study intensified treatment in the intensive glycaemic control group every month if required, if HbA1c levels were ≥6.0% (42 mmol/mol) or if >50% of premeal or post-meal capillary glucose readings were >5.6 mmol/L (100 mg/dL) or >7.8 mmol/L (140 mg/dL), respectively;[54] and the VADT started or adjusted insulin based on achieving SMBG fasting glucose of 4.4 to 6.4 mmol/L (80 to 115 mg/dL).[55]

SMBG targets recommended by diabetes organisations have also differed but are generally in the same range. The IDF recommended target levels for capillary plasma glucose levels of <6.0 mmol/L (<108 mg/dL) before meals, and <8.0 mmol/L (<144 mg/dL) one to two hours after meals;[42] the ADA recommends a pre-prandial capillary plasma glucose level of 4.4–7.2 mmol/L (80–130 mg/dL) and a peak post-prandial capillary plasma glucose level of <10 mmol/L (180 mg/dL);[14] and the Research Society for the Study of Diabetes in India recommends an FPG ≤6.4 mmol/L (115 mg/dL) and a postprandial glucose ≤8.9 mmol/L (160 mg/dL).[56]

CGM-derived glycaemic data are also useful in informing glycaemic targets. In 153 healthy children and adults, all without diabetes and not overweight, CGM showed that 96% of glucose readings were between 3.9 and 7.8 mmol/L (70 and 140 mg/dL during the day [6 am to 11:59 pm]) and 99% during the night (12 am to 5:59 am). No glucose levels exceeded 10 mmol/L (180 mg/dL) and 1.4% and 0.4% of readings fell below this level during the day and night, respectively.[17]

Taking into account available data and in particular aligning with CGM data, Table 2.1 shows suggested general targets for SMBG glucose levels. Algorithms based on similar targets have been used to safely and successfully adjust basal insulin in people with T2DM.[57]

Glycaemic profiles / other measures of glycaemia

While measurement of HbA1c is the established gold standard biomarker for assessing glycaemic control, it does not provide information on short-term glycaemic variability or hypoglycaemia. The advent of CGM has enabled a more comprehensive assessment and understanding of glycaemia.[27]

A number of glycaemic metrics are recommended for assessment of CGM-derived glycaemia. Short-term glycaemic variability refers to how much glucose levels fluctuate between peaks and nadirs within or between the day and is usually described as the percent coefficient of variation (%CV) of glucose within-day (%CV over 24 hours) and between-day (%CV over several days).[34] CGM-derived time in range (TIR), time above range (TAR), and time below range (TBR) of defined glycaemic levels are useful measures of glycaemic status and in clinical management. Time in a defined range is assessed using a 14-day CGM assessment with a CGM wear of 70% or higher.[58]

While there is a correlation with HbA1c, CGM metrics provide additional information on glycaemic status. For example, a retrospective analysis examined the relationship between end-of-study HbA1c levels and CGM data in 530 adults with T1DM or insulin-requiring T2DM from four randomised trials. HbA1c was strongly correlated with mean glucose value, TIR in the

Table 2.1 Suggested general SMBG targets

Measure	Target*	
Fasting and pre-prandial glucose	4.0–8.0 mmol/L	70–144 mg/dL
Post-prandial glucose**	4.0–8.0 mmol/L (preferable) 4.0–9.0 mmol/L (acceptable)	70–144 mg/dL (preferable) 70–160 mg/dL (acceptable)

* The mg/dL and mmol/L values are not strictly identical but have been rounded for ease of use, noting that SMBG-generated values have an inbuilt accuracy error.
**Measure post-prandial glucose 1–2 h after beginning a meal.
SMBG, self-monitoring of blood glucose.

3.9–10.0 mmol/L (70–180 mg/dL) range, and percentage of glucose values >13.9 mmol/L (250 mg/dL) but weakly correlated with the percentage of glucose values <3.9 mmol/L (70 mg/dL) or <3.0 mmol/L (54 mg/dL). The median percentage glucose <3.0 mmol/L (70 mg/dL) was 1.2% across all HbA1c ranges while the percentage of glucose values >13.9 mmol/L (250 mg/dL) varied from 2.5% (0.6 h/day) to 27.8% (6.7 h/day) in the lowest and highest HbA1c groups, respectively.[59]

CGM metrics and diabetes complications

CGM-derived metrics are associated with diabetes outcomes. A review of 34 publications, including 663 people with T1DM and 19,909 with T2DM, reported an association of higher glycaemic variability and lower TIR with diabetes microvascular and macrovascular complications. Higher TIR was associated with reduced risk of albuminuria, retinopathy, cardiovascular disease mortality, all-cause mortality, and abnormal carotid intima-media thickness. However, the authors acknowledged several limitations, including 30 of the 34 papers being cross-sectional studies and most studies using only a short period of CGM (48 to 72 hours).[60]

In prospective cohort studies in people with T2DM, greater %CV was associated with increased risk for all-cause mortality even among people with seemingly well-controlled diabetes (mean HbA1c of 7.3% [56 mmol/mol]).[61] Lower TIR was also associated with increased risk of all-cause and CVD mortality in people with T2DM.[62]

A systematic review of 11 studies in 13,987 people with T2DM examined the association between CGM-derived TIR and microvascular complications of diabetic retinopathy (DR) (n = 4 studies), diabetic nephropathy (DN) (n = 4 studies), and diabetic peripheral neuropathy (DPN) (n = 7 studies). The majority of studies (10 of the 11) were conducted in Asia. A 10% increase in TIR was associated with a reduction in albuminuria, severity of DR, and prevalence of DPN and cardiac autonomic neuropathy.[63]

CGM metrics targets

An international consensus has proposed targets for key glycaemic metrics as summarised in Table 2.2.[58]

Table 2.2 Key metrics for assessing glycaemic status using continuous glucose monitoring (CGM) in non-pregnant adults with diabetes[58]

Metric	Interpretation	Goal
Number of days of CGM		14 days
Percentage of time CGM device is active		70% data
Coefficient of variation	Percentage coefficient of variation Intraday (i.e., within 24 h) and Interday (i.e., over multiple days)	≤36%
Time in range 70–180 mg/dL (3.9–10.0 mmol/L)	Percentage readings and time in range	>70% (most adults) >50% (older adults)
Time below range <70 mg/dL (<3.9 mmol/L) including readings <54 mg/dL (<3.0 mmol/L)	Percentage readings and time below range	<4% (most adults) <1% (older adults)
Time below range <54 mg/dL (<3.0 mmol/L)	Percentage readings and time below range	<1%
Time above range >180 mg/dL (>10.0 mmol/L) including readings >250 mg/dL (> 13.9 mmol/L)	Percentage readings and time above range	<25% (most adults) <50% (older adults)
Time above range >250 mg/dL (> 13.9 mmol/L)	Percentage readings and time above range	<5% (most adults) <10% (older adults)

CGM, continuous glucose monitoring.

Methods for self-assessment of glycaemia

Two approaches are available for self-assessment of glycaemia.

Self-monitoring of blood glucose (SMBG)

Self-monitoring of capillary (finger-stick) blood glucose (SMBG) is a common component of diabetes care and is commonly recommended in people treated with a multiple-daily insulin regimen or insulin pump, including those with T2DM.[64] Recommendations for SMBG use in less intensively insulin-treated people with T2DM (e.g., on basal insulin) varies, although self-measurement of fasting glucose appears helpful in adjusting basal insulin dose and improving glycaemic control.[65]

SMBG is generally not routinely recommended in people with non-insulin-treated T2DM. A 2012 Cochrane review concluded that when diabetes duration is more than one year, the overall effect of SMBG on glycaemic control in people with T2DM not using insulin is small up to six months after initiation and subsides after 12 months while acknowledging that more research is needed to explore the impact of SMBG on hypoglycaemia and diabetes complications.[66]

An IDF Guideline on SMBG use in non-insulin-treated T2DM suggested that in RCTs, SMBG data are only likely to be an effective self-management tool when results are reviewed and acted on by healthcare providers and/or people with T2DM to actively modify behaviour and/or adjust treatment. The principal IDF recommendation was that SMBG should be used only when individuals with diabetes, their caregivers, and/or their healthcare providers have the knowledge, skills, and willingness to incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals and that its use should be individualised and structured.[67]

RCTs have examined the effects of structured SMBG in people with non-insulin-treated T2DM.

In a 12-month RCT, 483 poorly controlled (HbA1c ≥7.5% [58 mmol/mol]) insulin-naïve people with T2DM were randomised to a control enhanced usual care group or enhanced usual care group with structured SMBG. After 12-months, structured SMBG significantly improved glycaemic control (HbA1c reduction 0.3% [3 mmol/mol]) and facilitated more timely and aggressive treatment changes.[68]

Another 12-month RCT randomised 1,024 people with non-insulin-treated T2DM (median baseline HbA1c 7.3% [56 mmol/mol]) to intensive structured SMBG and an active control group. A small but significantly greater reduction in HbA1c (0.12% [1.3 mmol/mol]) was observed over 12 months in the structured SMBG group and more participants achieved clinically meaningful reductions in HbA1c (>0.3% [3 mmol/mol]).[69]

A recent RCT examined the impact of structured SMBG, with or without TeleCare support, on glycaemic control in people with non-insulin-treated T2DM that was suboptimally controlled (HbA1c ≥7.5% to ≤13% [≥58 to ≤119 mmol/mol]) and a diabetes duration of more than one year. After 12 months, HbA1c was significantly lower by 0.8% (8.9 mmol/mol) in both the structured SMBG groups compared with the control group. No additional benefit to structured SMBG was observed with the addition of once-monthly TeleCare support.[70]

SMBG protocols (intensity and frequency) should be individualised to address each individual's specific educational, behavioural and clinical requirements, specific needs, and goals and provider requirements for data on glycaemic patterns to monitor impact of therapeutic decision-making.

In addition to those with insulin-treated T2DM, SMBG may be considered for people using GLMs who have an increased risk of hypoglycaemia, experience hypoglycaemia unawareness, have poor metabolic control despite multiple medications, and/or temporarily as an aid to education in newly diagnosed people with T2DM.[42,71]

Continuous glucose monitoring (CGM)

Personal CGM systems have evolved rapidly in recent years and are increasingly used to manage diabetes. CGM systems continuously measure interstitial glucose concentrations at intervals of one to five minutes, which correlate well with blood glucose levels. CGM provides the user with immediate glucose information on asymptomatic hypoglycaemia or hyperglycaemia to make treatment decisions and health professionals with more detailed information on glycaemia to guide therapeutic advice. CGM can also help to educate and support healthier lifestyle choices.

There are two basic types of CGM systems:

- **Realtime CGM (rtCGM): automatically and continuously transmits data to the user, provides alerts and active alarms and glucose data in real-time to a receiver (e.g., smart watch or phone)**
- **Intermittently scanned CGM (isCGM): provides the same type of glucose data but requires the user to scan the sensor to obtain information and does not have alerts and alarms.[72]**

There are currently limited data on CGM use in people with T2DM. The IMMEDIATE study randomised 116 people with non-insulin-treated T2DM to isCGM with diabetes self-management education (DSME) or DSME alone (which included SMBG). After 16 weeks, the isCGM and DSME group had significantly greater mean TIR, significantly less TAR, and a greater reduction in mean HbA1c by 0.3% (3 mmol/mol) compared with the DSME alone arm. TBR and hypoglycaemia were lower but not significantly different. Glucose monitoring satisfaction was higher among isCGM users.[73]

The RELIEF study was a retrospective analysis of 74,011 people with T1DM or T2DM initiating flash glucose monitoring identified from the French national claims database. After 12 months, hospitalisations for acute diabetes complications decreased by 39% in people with T2DM following initiation of flash glucose monitoring, although the absolute change was small – overall 2.67% versus 1.62%, hospitalisations for diabetic ketoacidosis 1.70% versus. 0.82%, severe hypoglycaemia 0.7% versus 0.62%, and hyperglycaemia 0.12% versus 0.09%.[74] These differences persisted after two years.[75]

CGM use is currently not widely recommended or adopted as part of routine care for people with T2DM. Wider use of CGM will require healthcare system adaptations, including training and education of both people with diabetes and clinicians in guiding day-to-day management decisions. Further research is also needed to inform optimal CGM usage guidelines and address cost-effectiveness challenges in people with T2DM. Although CGM technology offers potential advantages, it is expensive and global availability and access are limited. Incorporating CGM use in health systems where there are many challenges and barriers to achieving recommended standards of diabetes care will test policy makers and it is likely their use will be limited to those who can privately afford them until costs are substantially lower.

SMBG and CGM compared

CGM has the potential to provide more detailed glycaemic information than SMBG. However, to date, reported clinical differences in studies comparing CGM and SMBG have been small. A systematic review of 12 RCTs compared SMBG and CGM in 1,248 people with T2DM. Compared with SMBG, CGM use (rtCGM or isCGM) resulted in small but significantly lower HbA1c (mean difference 0.31% [3.4 mmol/mol]) with the effect being similar in individuals using insulin with or without oral agents or oral agents only. A larger effect was noted with rtCGM than isCGM. CGM was associated with a 6.4% increased TIR, a 0.7% decreased TBR, a 5.9% decreased TAR, and a 1.5% decreased glycaemic variability. CGM was associated with a non-statistically significant difference in the incidence of severe hypoglycaemia and macrovascular complications. No trials reported data on microvascular complications.[76]

A systematic review of 26 RCTs involving 2,783 people with T2DM compared CGM (real-time/retrospective data analysis CGM or isCGM) versus usual care (which may have included SMBG). Compared with usual care/SMBG, CGM reduced HbA1c by 0.19% (2 mmol/mol) and isCGM by 0.31% (3.4 mmol/mol) but increased risk of mainly device-related adverse events. Unlike CGM, isCGM was associated with improved user satisfaction.[77]

More CGM data are expected to become available as CGM is increasingly integrated into clinical trials. A recent consensus statement detailed how CGM might be incorporated in diabetes RCTs, especially with new pharmaceutical agents, and could help identify treatment differences related to hypoglycaemia and glycaemic metrics while minimising the potential confounding effect of CGM use.[78] Applying these consensus recommendations in LMICs presents challenges and may require different approaches in resource-limited settings to ensure such technology does not widen the resource-driven digital divide.[79]

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Chapter 3

Blood Glucose-Lowering Therapies – Non-Insulin Options for Type 2 Diabetes

RECOMMENDATIONS

	Optimal Care	Basic Care
At diagnosis		
No complications or low cardio-renal risk	• Lifestyle modification • Metformin • Combination therapy is an option	• Lifestyle modification • Metformin
In obese persons	• Consider metformin and GLP-1RA	• Consider metformin and SGLT2i*
Risk of or with cardio-renal complications	• Lifestyle modification • Metformin and SGLT2i or GLP-1RA (SGLT2i preferred in HF)	• Lifestyle modification • Metformin and SGLT2i*
On therapy and not at glycaemic target		
No complications or low cardio-renal risk	• Reinforce lifestyle modification *If only on metformin* • Add SGLT2i *In obese persons* • Add GLP-1RA *If on combination therapy* • Add an SGLT2i or GLP-1RA • If already taking an SGLT2i or GLP-1RA, add an agent from another BGL therapy	• Reinforce lifestyle modification *If only on metformin* • Add SGLT2i* or any available BGL therapy *If on combination therapy* • Add SGLT2i* or any available BGL therapy
Risk of or with cardio-renal complications	• Reinforce lifestyle modification *If only on metformin:* • Add SGLT2i or GLP-1RA *In obese persons* • Add GLP-1RA *If on combination therapy* • Add an SGLT2i or GLP-1RA • If already taking an SGLT2i or GLP-1RA, add an agent from another BGL therapy	• Reinforce lifestyle modification *If only on metformin:* • Add SGLT2i* or any available BGL therapy *If on combination therapy* • Add SGLT2i* or any available BGL therapy

* SGLT2 inhibitors are increasingly available in several low- and middle-income countries at generally affordable cost.

BGL, blood glucose- lowering; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

KEY POINTS

- Globally, poor glycaemic control is common in people with type 2 diabetes mellitus (T2DM) and improving glycaemic control remains an unmet need and a key diabetes care priority.
- Early and intensive glycaemic control in T2DM not only reduces micro- and macrovascular complications but also has a legacy effect that lower risk for decades.
- Intensive multifactorial risk management, including blood glucose, blood pressure, and lipids, decreases long-term cardio-renal events and overall mortality.
- Recent cardiovascular outcome trials with sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have demonstrated significant cardio-renal protection, prompting debate about balancing the focus on glycaemic control and organ protection, particularly for individuals at low risk of cardio-renal complications.
- Global availability, access, and affordability of blood glucose-lowering therapies (BGL) vary widely and impact treatment options in lower resource settings.
- The majority of cardio-renal outcome studies have added trial therapies to usual care with placebo as the comparator and outcome data from head-to-head studies comparing blood glucose-lowering therapies are limited.
- Initiating therapy should be personalised based on individual characteristics, comorbidities, and shared decision-making, with lifestyle interventions (e.g., self-management education, nutrition, and exercise) as essential components.
- Metformin remains the recommended first-line monotherapy due to its global availability, efficacy, safety profile, low hypoglycaemia risk, and cost-effectiveness, along with demonstrated long-term cardiovascular benefits.
- Emerging data support the early use of SGLT2 inhibitors and GLP-1 receptor agonists, usually added to metformin, to mitigate the adverse consequences of poor glycaemic control and improve cardio-renal outcomes, although evidence supporting their role as first-line monotherapy is limited.
- Initial combination therapy may increase durability of glycaemic control compared with stepwise addition of BGL therapies.
- Timely treatment intensification is crucial to overcome clinical inertia, while deintensification should be considered in individuals at or near glycaemic targets, especially in the elderly and those prone to hypoglycaemia.
- Therapy choices should factor in management of coexisting conditions such as cardio-renal complications, metabolic dysfunction-associated steatotic liver disease, and weight control.

BACKGROUND

Early and intensive glycaemic control

Evidence strongly suggests that good glycaemic control is the key to decreasing the risk of both micro- and macrovascular complications in type 2 diabetes mellitus (T2DM).[1] Furthermore, early and intensive glycaemic control has a legacy effect in decreasing the risk of developing complications even after 24 years, compared to non-intensive glycaemic control.[2] This legacy effect underscores the long-term benefits of early and intensive glycaemic control in reducing cardiovascular and kidney disease events and all-cause mortality.

Globally, poor glycaemic control in people with T2DM is common, being observed in 45%–93% of individuals, with considerable inter- and within-country variations.[3] Consequently, improving glycaemic control remains an unmet need and a key diabetes care priority. In addition, intensive multifactorial risk factor management (blood glucose, blood pressure, lipids) reduces microvascular complications and long-term cardio-renal events and mortality.[4,5]

Cardio-renal protection

Several sodium-glucose cotransporter-2 (SGLT2) inhibitor and glucagon-like peptide-1 (GLP-1) receptor agonist cardiovascular outcome trial (CVOT) randomised controlled trials (RCTs) have demonstrated cardio-renal protection with benefits in cardiovascular disease (CVD), heart failure, and renal outcomes. These findings have stimulated a paradigm shift to focusing on organ protection with less emphasis on glycaemic control. As a result, there is debate about the relative importance of glycaemic control in the management of T2DM and potential unintended consequences for the many individuals with poor glycaemic control without or at low risk of cardio-renal complications.[6] Separating an effect of intensive glucose control and the cardio-renal protection of newer blood glucose-lowering (BGL) medications is limited by a lack of dedicated RCTs. CVOT RCTs have been mainly performed in people with T2DM with prior cardiovascular and/or kidney disease or multiple risk factors, and the majority of participants in the CVOTs of SGLT2 inhibitors and GLP-1 receptor agonists were treated with conventional BGL medications and renin–angiotensin–aldosterone system inhibitors, statins, and antiplatelet therapy. Of note, these newer agents have no demonstrated benefits on diabetes microvascular complications of retinopathy and neuropathy, which are known to be influenced by improved glycaemic control.

Achieving glycaemic control is a universally accepted goal. Complimenting this with specific cardio-renal protection interventions in a low-resource health environment will be determined by availability, accessibility, and affordability of newer BGL medications.

GLOBAL CONSIDERATIONS

A number of classes of non-insulin BGL therapies are available and their attributes have been reviewed and summarised elsewhere.[7,8]

The global availability, access to, and affordability of BGL therapies vary widely. The World Health Organization (WHO) periodically publishes an Essential Medicines List (EML).[9] This includes a core list of minimum medicine needs for a basic healthcare system of the most efficacious, safe, and cost-effective medicines for priority conditions, including diabetes, selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. The current list for diabetes is shown in Table 3.1.

Table 3.1 World Health Organization Model List of Essential Medicines – 23rd List (2023)

Medicines for Diabetes	
Oral hypoglycaemic agents	
Empagliflozin Therapeutic alternatives: • canagliflozin • dapagliflozin	**Tablet:** 10 mg; 25 mg.
Gliclazide* Therapeutic alternatives: • 4th level ATC chemical subgroup (A10BB Sulfonylureas)	**Solid oral dosage form:** (controlled-release tablets) 30 mg; 60 mg; 80 mg. *glibenclamide not suitable above 60 years.
Metformin	**Tablet:** 500 mg (hydrochloride).

ATC, Anatomical Therapeutic Chemical.
Adapted from World Health Organization, 2023[9]

The WHO EML is reviewed and updated every two years, and in 2023, SGLT2 inhibitors were included. In some low- and middle-income countries (LMICs), generic SGLT2 inhibitors are becoming available at affordable prices.

The WHO EML serves as a basis for National EMLs (NEML) with approximately 70% of the 194 WHO member states having NEMLs. The congruence of NEMLs with the WHO EML varies considerably across conditions, with the median of listed diabetes drugs being 0.60.[10] In another study, the total number of diabetes medicines listed on NEMLs ranged from 0 to 16 across 127 countries (median: 4; interquartile range: 3–6) and diabetes health outcome scores were associated with the number of diabetes medicines on NEMLs.[11]

As reviewed in Chapter 2, assessment of glycaemic control is important in monitoring the effectiveness of BGL medications. Global consensus is that measurement of glycated haemoglobin (HbA1c) should be used to initiate and modify BGL therapy. Other tests, such as fasting and postprandial self-blood glucose, glucose variability, and time in range measurements, provide additional information about glycaemic status and underlying pathophysiology, and influence therapeutic choice.[12] Unfortunately, HbA1c measurement and other technologies are not available in many health facilities throughout the world and therefore healthcare providers should remain flexible in using alternative methods for glucose monitoring and treatment planning as per local resources and capabilities.

EVIDENCE SUMMARY

Initiating therapy

Determining the optimal timing for initiating and choosing BGL therapy in drug-naïve individuals with unsatisfactory diabetes control requires assessment of individual characteristics (advanced age), personal circumstances (financial constraints, living alone or in a care facility), glycaemic targets, and the presence of comorbidities and cardio-renal disease or risk. Shared decision-making should include an evaluation of benefits and risks such as hypoglycaemia and is a continuous process.[13]

Lifestyle intervention

Lifestyle interventions, including diabetes self-management education, medical nutrition therapy, and regular physical activity, play a pivotal role in managing T2DM regardless of BGL medication,[14] and contribute to improved outcomes, including quality of life,[15] reduced all-cause mortality,[16] hospitalisation, and lower healthcare costs,[17,18] emphasising their importance in initial management. Individuals should be encouraged to aim for specific lifestyle goals, such as at least 150 minutes of moderate exercise per week and a reduction in excess body weight of 5%–10%. Weight loss can improve

glycaemic control, induce diabetes remission, and lead to improvements in various metabolic and cardiovascular risk factors (see Chapter 5).

Globally, there is considerable variation in local diets, influenced by tradition, local customs, religion, and the availability and affordability of food. Consequently, the applicability of nutrition-related studies to a particular environment will vary, although some overarching observations are relevant. Most intervention studies of different diets and dietary components associated with benefits in diabetes control have been short-term. Beneficial effects diminish over time and are not consistently maintained in studies with follow-up periods longer than 12 months.

Carbohydrate in foods comprises the major nutrient component in most diets worldwide. Many less economically secure communities rely on carbohydrate foods for their sustenance. Wealthier nations have selected types of carbohydrate foods that have contributed to obesity, diabetes, and ill health. A systematic review and meta-analysis of RCTs on varying carbohydrate quantity reported a dose-dependent effect. Each 10% decrease in carbohydrate intake reduced HbA1c by 0.2% (3 mmol/mol) after six months, compared to a carbohydrate intake between 55%–65%.[19] A recent RCT compared a healthy low-carbohydrate diet with a usual diet in adults with HbA1c between 6.0%–6.9% (42–52 mmol/mol) who were not taking BGL medications. After six months, the low-carbohydrate diet group had a significantly lower HbA1c (0.23% [3 mmol/mol]) compared to the usual diet group.[20]

Diets that improve carbohydrate quality by using low glycaemic index foods may help improve glycaemic control, with a systematic review reporting a statistically significant reduction of HbA1c of 0.19% (2 mmol/mol) compared with a range of other diets.[21] The more restrictive vegan diet (low-fat, excluding all animal-based products) demonstrated an HbA1c reduction of 0.41% (4 mol/mol) compared with a conventional diet.[22]

The diets to be advised for the management of T2DM must be culturally and economically appropriate. Dietitians with local experience must be part of the team. Foods such as legumes, fresh fruit and non-starchy vegetables, nuts and seeds in acceptable form should be encouraged, and advice against consumption of soft drinks and sugars should be given, together with reducing amounts of starchy foods, especially those that are highly processed. Such diets will not only benefit people with T2DM but human health globally and reduce the environmental impact of human food production.

Understanding how nutrition therapy and pharmacotherapy interact in real-world diabetes management remains a challenge. The lack of clear evidence of complementarity between diet quality and the intensity of BGL medications highlights the challenge and need for better integration between diet and pharmacologic approaches.[23]

First-line monotherapy

Metformin

When pharmacologic intervention is necessary, metformin is traditionally recommended as first-line monotherapy based on its blood glucose-lowering efficacy, low hypoglycaemia risk, weight neutrality with the potential for modest weight loss, good safety profile, general availability, and low cost.[8,13] In addition, there is a long experience with its use, and long-term CVD benefits were observed in the UKDPS.[24] Metformin's safety profile extends to individuals with reduced estimated glomerular filtration rates (eGFR), supporting its use in those with an eGFR $\geq$30 mL/min/1.73 m^2.

Other therapies

Other therapies are also effective as first-line treatments, with some well-recognised class effect differences. Reductions in HbA1c were similar across monotherapies except that dipeptidyl peptidase 4 (DPP4) inhibitors had smaller effects. Body weight was reduced or maintained with metformin, DPP4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors and increased with sulfonylureas and thiazolidinediones. Hypoglycaemia was more frequent with sulfonylureas. Gastrointestinal adverse events were highest with metformin and GLP-1 receptor agonists. Genital mycotic infections were increased with SGLT2 inhibitors.[25] Within each class, there are also differences between individual agents. Of particular relevance to *Basic Care Recommendations* where the range and choice of therapeutic options are limited due to access, availability, and affordability, there are well-documented differences in sulfonylureas with regard to hypoglycaemia risk and impact on weight.[26]

SGLT2 inhibitors and GLP-1 receptor agonists

T2DM significantly increases the risk of cardio-renal complications. The findings of cardio-renal protection in recent RCTs with SGLT2 inhibitors and GLP-1 receptor agonists have led to guidelines and consensus statements proposing the use of these agents as first-line therapy in individuals with or at high risk of cardio-renal disease, either in combination with metformin[13] or as monotherapy.[27]

At present, the evidence supporting these agents as first-line monotherapy is inconclusive.[28] All CVOT RCTs demonstrating cardio-renal protection have added the study medication to existing therapy of study participants, with the majority taking metformin. Post-hoc analyses have shown no evidence of heterogeneity in the CV efficacy of the GLP-1 receptor agonist liraglutide based on background metformin[29] or with SGLT2 inhibitors for reductions in cardiovascular, kidney, and mortality outcomes regardless of whether individuals were receiving or not receiving metformin. However, it should be noted that baseline metformin users had an approximately 30% lower risk of the primary outcome than metformin non-users.[30] A meta-analysis of newer BGL medications in metformin-naïve people with T2DM reported beneficial effect of GLP-1 receptor agonists and SGLT2 inhibitors.[31]

A recent observational registry-based study using the AMD Annals Initiative assessed the association between the early introduction of SGLT2 inhibitors and consequences of poor glycaemic control in newly diagnosed individuals with T2DM without CVD.[32] The early introduction of SGLT2 inhibitors in people with T2DM, 90% of whom were also taking metformin, eliminated the association between poor glycaemic control in the first two years after T2DM diagnosis and later CVD events, suggesting that SGLT2 inhibitors may attenuate the consequences of poor glycaemic control after T2DM diagnosis.

To date, there have not been any direct comparisons of metformin versus newer agents on diabetes-related outcomes as first-line monotherapy. A registry-based randomised trial (SMARTEST) is underway to directly assess dapagliflozin versus metformin on a primary composite endpoint of macro- or microvascular events in approximately 4,300 participants with early T2DM.[33]

Combination therapy

There are numerous combinations of non-insulin BGL therapies, and it is beyond the scope of this document to review all potential combinations. This section highlights some aspects of combination therapy.

Combination first-line therapy

Metformin serves as the cornerstone for combination therapy. While conventional approaches have favoured stepwise addition of therapy, some individuals may require combination therapy (two BGL medications) to achieve glycaemic control early in the course of their diabetes. Dual initial oral therapy can be considered in those with HbA1c levels exceeding 9%–10% (75–86 mmol/mol) without symptoms. In some cases, insulin may be required as part of initial pharmacotherapy, particularly in those with clear symptoms and/or signs of significant hyperglycaemia.[7,34] In these situations, combination therapy may be temporary. A decision to reduce hyperglycaemia quickly through combination therapy should also consider potential detrimental effects such as the risk of retinopathy progression.[35] The primary focus should not be rapid reduction but rather reaching glycaemic goals and maintaining them over time.

Initial combination therapy may increase durability of glycaemic control compared with stepwise addition of BGL therapies. The VERIFY trial demonstrated the superiority of initial combination therapy over sequential addition in slowing the decline of glycaemic control. Participants with T2DM diagnosed within two years prior to enrolment with HbA1c of 6.5%–7.5% (48–58 mmol/mol) received either combination treatment with metformin and vildagliptin or initial metformin monotherapy with the subsequent addition of vildagliptin if required to improve diabetes control. The endpoint, time from randomisation to initial treatment failure (HbA1c ≥7.0% [53 mmol/mol]), occurred in 43.6% in the combination treatment group and 62.1% in the monotherapy group.[36] The VERIFY study was not designed or powered to assess the effect of combination treatment on cardiovascular outcomes.

The effect of initial triple therapy on long-term glycaemic control has also been studied. In the EDICT study, drug-naïve individuals with new-onset T2DM were randomly assigned to receive either 1) combination therapy with

metformin, pioglitazone, and exenatide (triple therapy) or 2) sequential addition of metformin followed by glipizide and insulin (conventional therapy) aiming to maintain HbA1c below 6.5% (48 mmol/mol). After three years, HbA1c was significantly lower with initial triple therapy compared with conventional therapy (6.4% [47 mmol/mol] versus 6.9% [52 mmol/mol]).[37] The TRIPLE-AXEL study randomised individuals with drug-naïve T2DM to triple combination therapy with metformin, dapagliflozin, and saxagliptin or conventional stepwise add-on therapy (initiated with metformin, followed by glimepiride and sitagliptin). The primary outcome, the proportion who achieved an HbA1c <6.5% (48 mmol/mol) without hypoglycaemia, weight gain of 5% or higher, or discontinuation of drugs because of adverse events at 104 weeks, was achieved in 39.0% and 17.1%, respectively, although HbA1c reduction from baseline was similar in both groups.[38] However, in both triple therapy studies, the treatment regimens differed between the two groups.

There are no dedicated outcome studies comparing treatment initiation with combinations of BGL therapies.

Combination SGLT2 inhibitors and GLP-1 receptor agonists

Some guidance suggests combining SGLT2 inhibitor and GLP-1 receptor agonist therapies. However, this combination has not been evaluated in an outcome RCT and the results of analyses of administrative datasets are not convincing. Nested case-control studies of individuals with T2DM in England and Wales of primary care data from the Clinical Practice Research Datalink and Secure Anonymised Information Linkage Databank reported on the association of SGLT2 inhibitors, GLP-1 receptor agonists, or their combination regimens on major adverse cardiac and cerebrovascular events (MACCE) and heart failure (HF) compared to other BGL regimens. Use of SGLT2 inhibitor was associated with an 18% lower odds of MACCE, and the odds of HF were 51% lower with SGLT2 inhibitors and 18% lower with GLP-1 receptor agonists, but the combination was not superior to either agent used alone.[39]

The addition of either SGLT2 inhibitors or sulfonylureas to baseline GLP-1 receptor agonists on CVD outcomes was explored in an analysis of three US claims datasets in 12,584 people with T2DM and showed significant reductions in the risk of MACCE and HF hospitalisations in the SGLT2 inhibitor/GLP-1 receptor agonist combination compared to the sulfonylureas/GLP-1 receptor agonist combination.[40] However, the magnitude of the CVD risk reduction was comparable to the benefit seen in CVOTs of SGLT2 inhibitors versus placebo, where baseline GLP-1 receptor agonist use was minimal.

Treatment intensification, deintensification, or modification

Early intervention is required in people with T2DM not reaching or maintaining their individualised glycaemia targets. Clinical inertia is one of the most difficult barriers to overcome in clinical practice and has a dramatic impact on the prognosis of complications and quality of life.[41,42] Timely treatment intensification with additional BGL therapy when required is crucial to avoid clinical inertia. Failure to reach or maintain glycaemic targets should be a trigger to consider a change in therapy. The presence or emergence of comorbidities also influence this decision. Any change or intensification of therapy should be reassessed within three months.

Meta-analyses suggest that any drug added to an initial therapy, particularly with metformin, can improve glycaemic control.[43,44]

Conversely, deintensification of therapy should be considered in people at or near glycaemic target who are prone to hypoglycaemia, especially the elderly.[45] The use of sulfonylureas (and glinides) should be minimised where alternatives are available and affordable, or dose should be reduced.[46]

Achieving glycaemic targets does not mandate treatment deintensification, especially with newer agents such as GLP-1 receptor agonists and SGLT2 inhibitors, which not only manage hyperglycaemia but also provide additional cardio-renal benefits in high-risk individuals without increasing hypoglycaemia, as well as supporting weight control.

Managing coexisting cardio-renal complications, metabolic dysfunction-associated steatotic liver disease (MASLD), and weight control are addressed in specific chapters. In brief, therapies with demonstrated benefits in managing these comorbidities should be preferred considering that they are also efficacious in controlling hyperglycaemia, if they are available, affordable, and accessible.

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Chapter 4

Blood Glucose-Lowering Therapies – Insulin Options for Type 2 Diabetes

RECOMMENDATIONS

	Optimal Care	Basic Care
Insulin initiation	• Begin insulin therapy when optimised glucose-lowering medications and lifestyle interventions do not maintain target blood glucose control	• Begin insulin therapy when optimised available glucose-lowering medications and lifestyle interventions do not maintain target blood glucose control
Support	• Provide education, continuing lifestyle management, and regular review, including telehealth	• Provide education, continuing lifestyle management, and regular review
Monitoring	• Self-monitoring of blood glucose • Consider CGM with complex insulin regimens and insulin pump therapy • Regular HbA1c measurement	• Self-monitoring of blood glucose • Regular HbA1c measurement
Insulin regimen	• Select from a broad range of affordable insulins and insulin delivery devices • Access to insulin pump therapy available	• Select from a limited range of affordable and continuously available insulin
Insulin initiation	• Commence with single daily injection of basal analogue insulin • Continue metformin (if tolerated and not contraindicated) • Continue with other blood glucose-lowering therapies if appropriate	• Commence with single daily injection of affordable human, analogue, or biosimilar insulin • Continue metformin (if tolerated and not contraindicated) • Continue with other affordable and available blood glucose-lowering therapies if appropriate
Insulin intensification	• Options include: - Basal bolus - Premixed insulin - Add GLP-1RA (either separately or switch to FRC) - Insulin pump	• Options include: - Basal bolus - Premixed human insulin - Other affordable and available blood glucose-lowering therapies
Insulin deintensification	• Regularly review insulin dose, need for insulin, and complex insulin regimens, especially in the elderly and individuals at target glycaemia or experiencing hypoglycaemia • Deintensify and simplify treatment as required	

CGM, continuous glucose monitor; FRC, fixed-ratio combinations, GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin.

KEY POINTS

- Insulin therapy is a key option for type 2 diabetes mellitus (T2DM) when non-insulin treatments fail to achieve glycaemic targets.
- Long term outcome studies confirm insulin's efficacy in improving glycaemic control and its legacy effect on reducing micro- and macrovascular complications in T2DM.
- The decision to use insulin should consider the individual's views on safety, cultural values, social and religious influences, health literacy and language barriers.
- A diverse range of insulin types (human, analogue, and biosimilar) is available.
- The clinical effects of these insulin types in T2DM are similar except for small differences in hypoglycaemia between intermediate human and long-acting analogue insulins.
- Global access to insulin remains a significant challenge and only about half of those with T2DM who could benefit have access to appropriate insulin therapy due to regulatory, supply chain, cost, and device access barriers.
- Biosimilar insulins offer the potential for cost reduction and improved accessibility.
- The different insulin pharmacokinetic profiles, ultra rapid-acting, rapid-acting, short-acting, intermediate-acting, and long-acting, facilitate personalised and tailored treatment.
- Premixed insulins offer a range of fixed-ratio combinations of rapid- or short-acting with intermediate- or long-acting insulins aiming to control fasting and postprandial glucose.
- Combining insulin with other agents such as glucagon-like peptide-1 (GLP-1) receptor agonists (including fixed-ratio combinations) or sodium-glucose cotransporter-2 (SGLT2) inhibitors has the potential to enhance glycaemic control, promote weight loss, reduce insulin dosage, and lower hypoglycaemia risk.
- Insulin initiation typically begins by adding once daily basal insulin and continuing some oral blood glucose lowering medication(s), with treatment intensification options including adding prandial insulin, switching to premixed regimens, adding a GLP-1 receptor agonist or an SGLT2 inhibitor, tailored to the individual glycaemic responses and preferences, and resource considerations.
- Regular reassessment of insulin therapy is essential and insulin deintensification or simplification should be regularly considered, especially in older or frail individuals, to minimise hypoglycaemia risk, reduce treatment burden, and improve quality of life.

BACKGROUND

Insulin therapy is an often-used therapeutic option in people with type 2 diabetes mellitus (T2DM) when glycaemic control is not achieved with non-insulin blood glucose-lowering therapies. The decision to use insulin therapy should not only consider glycaemic control but also take into account the individual's views on insulin safety, cultural values and beliefs, social influences, religious considerations, health literacy, and language barriers. The diverse landscape of insulin types allows for customisation to address specific requirements of the individual. Advances in the manufacture and design of commercial insulin have guaranteed supplies and led to insulins with different pharmacokinetics as well as the potential for more flexible and personalised treatment regimens. The emergence of biosimilar insulins provides an opportunity to decrease cost and increase global insulin access. The development of fixed-ratio combinations (FRCs) of basal insulin and glucagon-like peptide-1 (GLP-1) receptor agonists adds to the range of insulin-related treatments.

GLOBAL CONSIDERATIONS

Global access to insulin remains a challenge. The World Health Organization (WHO) estimated that 15% of people with T2DM require insulin, but only half are appropriately treated because of barriers to insulin availability such as regulatory challenges and issues with supply chains and cost.[1]

A range of insulins are listed in the WHO Model List of Essential Medicines (Table 4.1).

Insulin (soluble and intermediate) has been listed since the first WHO Essential Medicine List in 1977. In 2021, long-acting insulin analogues (insulin glargine, detemir, degludec, and their quality-assured biosimilars, as therapeutic alternatives) were added, with the WHO Expert Committee on the Selection and Use of Essential Medicines noting that access to affordable human insulin remained a critical global priority.[1] In addition, appropriate use of insulin is hampered by a lack of access to affordable medical devices for safe administration and optimal glucose monitoring to guide insulin use.[1] The challenges of global access to insulin are experienced in most regions of the world.[3]

EVIDENCE SUMMARY

Insulins can be described by the method of manufacture and their pharmacokinetic characteristics.

Methods of modern-day insulin manufacture

Human insulin

In the past, insulin was obtained from pig and beef pancreas. These were replaced in the 1980s

Table 4.1 World Health Organization Model List of Essential Medicines – 23rd List (2023)

Medicines for Diabetes	
Insulins	
Insulin injection (soluble)* **including quality-assured biosimilars*	**Injection:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen.
Intermediate-acting insulin* **including quality-assured biosimilars*	**Injection:** 40 IU/mL in 10 mL vial; 100 IU/mL in 10 mL vial; 100 IU/mL in 3 mL cartridge or pre-filled pen (as compound insulin zinc suspension or isophane insulin).
Long-acting insulin analogues* Therapeutic alternatives: • insulin degludec • insulin detemir • insulin glargine **including quality-assured biosimilars*	**Injection:** 100 IU/mL in 3 mL cartridge or pre-filled pen.

Adapted from World Health Organization, 2023.[2]

by genetically engineered human insulin made by recombinant DNA technology using fermentation in micro-organisms (bacteria or yeast). Consequently, human insulin can be produced in large quantities with a high level of purity and consistent quality at relatively low cost.[4]

Analogue insulin

The first insulin analogue (insulin Lispro rDNA) was approved for human therapy in 1996. Analogue insulins are genetic modifications of human insulin, produced using recombinant DNA technology, and designed to alter the absorption of subcutaneously injected insulin. Following subcutaneous injection, insulin molecules form a depot from which absorption into the systemic circulation occurs. All insulin molecules have a tendency to self-aggregate into hexameric complexes, and these clusters must dissociate into dimers and monomers to enter the bloodstream. The pharmacologic features of individual insulin analogue preparations largely alter the rate of hexamer dissociation and insulin movement into the circulation. Fast-acting analogues either have less tendency to aggregate after injection or dissociate quickly and enter the bloodstream faster; long-acting analogues aggregate more, remain aggregated for longer, and enter the bloodstream slowly.

Biosimilar insulin

Biosimilar insulin is also developed through recombinant DNA technology and is highly similar to an already approved reference insulin.[5] Criteria for approval of a biosimilar require a quality assessment; demonstration of similarity in physicochemical and biological characterisation, including receptor binding, metabolic potency, and mitogenicity; pharmacokinetic/pharmacodynamic profiles in phase 1 studies; and assessment of safety endpoints in phase 3 clinical trials, with an emphasis on immunogenicity.[6]

The first biosimilar insulin, Abasaglar, was approved in the European Union in 2014 and in the US, the first biosimilar insulin (Basaglar) was approved in 2016.[6] Semglee (insulin glargine-yfgn) received FDA approval in July 2021 as the first interchangeable insulin glargine biosimilar.[7]

Studies consistently demonstrate the efficacy and safety of biosimilar insulin analogues in glycaemic control, with no notable differences in insulin antibody formation compared to reference.[8] Biosimilar insulins present an option for lower-priced and efficacious insulin alternatives.[9]

Categorisation of insulin by pharmacokinetic characteristics

Insulin can be categorised into five groups: ultra rapid-acting analogue (URAA) insulins, rapid-acting analogue insulins (RAAI), short-acting human insulins, intermediate-acting human insulins, and long-acting analogue insulins. Notable examples are shown in Table 4.2.

The pharmacokinetic profiles of insulin analogues are significantly altered by changing the amino acid sequence compared with native human insulin. Increasing the onset of action is designed to better control postprandial glucose excursions, whereas the long-acting insulins are designed to control fasting plasma glucose levels. The main anticipated beneficial consequences include improved glycaemic control and reduced hypoglycaemia compared with human insulin.

However, this has not been clearly established in T2DM. A Cochrane systematic review concluded that overall, there were no clear benefits of rapid-acting analogue insulin over regular short-acting human insulin in people with T2DM in change in glycated haemoglobin (HbA1c) or number of non-severe hypoglycaemic episodes.[10]

There is limited evidence on ultra rapid-acting analogue (URAA) insulins in T2DM. A recent

Table 4.2 Types of insulins

Ultra rapid-acting analogue insulins (URAA)	Rapid-acting analogue insulins (RAAI)	Short-acting human insulins	Intermediate-acting human insulins	Long-acting analogue insulins
Faster aspart (URAsp) Insulin lispro-aabc (URLi)	Insulin lispro Insulin aspart Insulin glulisine	Regular human insulin	NPH human insulin	Insulin glargine Insulin detemir Insulin degludec Insulin glargine-yfgn (Semglee)

NPH, neutral protamine Hagedorn.

meta-analysis showed no difference in HbA1c compared with RAAI but a small reduction in 1-hour (but not 2-hour) postprandial glucose in people with T2DM, and consequently concluded that they are not routinely recommended.[11]

Another Cochrane systematic review in people with T2DM compared long-acting analogue insulins (insulin glargine and insulin detemir) with intermediate-acting human insulin (NPH insulin) and showed that while the effect on HbA1c was comparable, treatment with insulin glargine and insulin detemir was associated with fewer participants experiencing hypoglycaemia compared with NPH insulin. Treatment with insulin detemir also reduced the incidence of serious hypoglycaemia; however, serious hypoglycaemic events were rare.[12]

Premixed insulins

Premixed insulins (Table 4.3) offer a diverse array of fixed component formulations designed to address both fasting and postprandial glycaemia.[13,14] These formulations combine rapid or short-acting insulin with intermediate- or long-acting insulin and their pharmacokinetic profile is designed to strike a balance between 24-hour efficacy and convenience for the person with T2DM.[14]

The efficacy of premixed insulins in improving glycaemic control is well-established. Premixed analogues were found to be similar to premixed human insulin in lowering fasting glucose, HbA1c, and the incidence of hypoglycaemia, but more effective in lowering postprandial glucose. Compared to long-acting insulin analogues, premixed analogues were superior in lowering postprandial glucose and HbA1c (mean difference –0.39% [-4 mmol/mol]) but inferior in lowering fasting glucose, and had higher incidence of hypoglycaemia.[16]

Premixed and basal bolus regimens (defined as any basal injection with at least a single bolus injection per day) have been compared in randomised controlled trials (RCTs) and real-world settings. There were no significant differences between the insulin regimens but there was a discordance between real-world and RCT data. Both insulin regimens were associated with HbA1c reductions (real-world data –0.28% [-3 mmol/mol]; RCT data, –1.4% [-15 mmol/mol]) and weight gain (real-world data, +0.27 kg; RCT data, +2.96 kg), demonstrating greater changes in RCTs compared with real-world conditions.[17]

Combining insulin and a GLP-1 receptor agonist

Treatment can be intensified in a person with insulin-treated T2DM by adding a GLP-1 receptor agonist. A systematic review comparing basal plus/basal bolus and adding a GLP-1 receptor agonist to insulin combinations was associated with a similar HbA1c reduction (-0.06% [-0.7 mmol/mol]) but greater weight loss (-3.72 kg), a lower incidence of hypoglycaemic events (relative risk [RR] -0.46), and a reduction in insulin dosage of 30.3 units/day.[18]

Fixed-ratio combinations (FRC) of insulin and a GLP-1 receptor agonist are available. IDegLira is a combination of insulin degludec (IDeg) and liraglutide with one unit of IDeg combined with 0.036 mg of liraglutide. IGlarLixi is a combination of insulin glargine and lixisenatide with one unit of insulin glargine combined with 0.33-to-1 µg of lixisenatide. These products are administered once daily and aim to optimise efficacy and minimise drawbacks associated with individual components.[19] Compared with a control group (mostly the individual components or another

Table 4.3 Formulations of premixed insulin

Type of premixed insulin	Low-mixed formulations	Mid-mixed formulations	High-mixed formulations
Premixed human regular insulin-NPH insulin	30% regular insulin/70% NPH insulin	50% regular insulin/50% NPH insulin	75% regular insulin/25% NPH insulin
Premixed insulin analogues	30% insulin aspart/70% insulin aspart protamine 25% insulin lispro/75% insulin lispro protamine	50% insulin aspart/50% insulin aspart protamine 50% insulin lispro/50% insulin lispro protamine	75% insulin lispro/25% insulin lispro protamine
Coformulation	70% insulin degludec/30% insulin aspart		

NPH, neutral protamine Hagedorn.
Adapted from Kalra et al. 2018[15]

insulin regimen), IDegLira significantly lowered HbA1c by 0.63% (7 mmol/mol) but there was no difference in body weight change. The percentage of those achieving HbA1c <6.5% or <7.0% (<48 mmol/mol or <53 mmol/mol) without weight gain and hypoglycaemia episodes was higher with IDegLira.[20] Similar results were reported for iGlarLixi, which achieved an HbA1c reduction of 0.56% (6 mmol/mol).[21]

A meta-analysis of RCTs compared free or FRC combinations of a GLP-1 receptor agonist plus basal insulin versus insulin intensification on glycaemic control in people with T2DM. Compared with insulin uptitration, insulin and GLP-1 receptor agonist combined therapy resulted in a significantly greater decrease in HbA1c (-0.53% [-6 mmol/mol]), more individuals at HbA1c target, greater reduction in body weight (-1.9 kg) but similar hypoglycaemic events. Results did not differ in either the free or FRC subgroups.[22] Use of FRC has been associate with increased treatment persistence and improved adherence.[23]

Combining insulin and sodium-glucose cotransporter-2 inhibitors

Insulin can also be effectively combined with sodium-glucose cotransporter-2 (SGLT2) inhibitors as reported in a systematic review and meta-analysis. Compared with the control group of insulin plus placebo or insulin alone, SGLT2 inhibitor reduced HbA1c by 1.4% (15 mmol/mol), body weight by 2.3 kg, and decreased the dose of insulin without increasing the risk of hypoglycaemia.[24]

Insulin outcome studies

Numerous studies have examined the impact of insulin therapy on glycaemic control in people with T2DM. However, there are limited data on clinical outcomes focused specifically on insulin treatment, rather than its use as a component of an intensified glycaemic control strategy in RCTs. The UKPDS is the main long-term study which assessed insulin treatment and randomised people with newly diagnosed T2DM to intensive glycaemic control (with sulfonylurea or insulin, or metformin if overweight) or conventional glycaemic control (primarily diet). Over 10 years, mean HbA1c was 7.0% (53 mmol/mol) in the intensive group compared with 7.9% (63 mmol/mol) in the conventional group, with no differences in agents in the intensive group. Compared with the conventional group, the risk in the intensive group was 12% significantly lower for any diabetes-related endpoint, driven by a significant 25% risk reduction in microvascular endpoints. There was no difference in endpoints between sulfonylureas and insulin.[25] In the 10-year post-trial follow-up study, participants randomised to the intensive group with sulfonylurea or insulin showed a continued 9% risk reduction for any diabetes-related endpoint and 24% reduction in microvascular disease. Risk reductions of 15% for myocardial infarction and 13% in death from any cause emerged over time, despite an early loss of glycaemic differences. Outcome results for insulin and sulfonylureas were not reported separately.[26]

The UKPDS results have recently been reported for another 14 years of follow up. The beneficial effects of early intensive glycaemic control with sulfonylurea or insulin therapy, compared with conventional glycaemic control, persisted with risk reductions of 10% for death from any cause, 17% for myocardial infarction, and 26% for microvascular disease.[27]

The ORIGIN study randomised individuals to insulin glargine to normalise fasting glucose (targeting a fasting blood glucose level of ≤5.3 mmol/L [≤95 mg/dL]) or standard care to assess the impact on cardiovascular events. After a median follow up of 6.2 years, incident cardiovascular outcomes were similar in the insulin glargine and standard care groups.[28]

The GRADE study assessed the comparative effectiveness of insulin glargine U-100, glimepiride, liraglutide, and sitagliptin added to metformin in achieving and maintaining an HbA1c <7.0% (<53 mmol/mol) in people with T2DM. During a mean 5.0 years of follow up, the incidences of microvascular complications and death were not materially different among the four treatment groups. There was a possible non-significant difference among the groups in the incidence of any cardiovascular disease, favouring the GLP-1 receptor agonist.[29]

Overall, insulin is an established and safe long-term treatment for improving glycaemic control in people with T2DM and is associated with a legacy effect of improved micro- and macrovascular outcomes in newly diagnosed people with T2DM.

Initiating and optimising insulin therapy in individuals with T2DM

Although insulin therapy is a treatment option at any stage of T2DM, it is usually initiated after other treatments have failed to achieve

personalised glycaemic targets. It may be introduced earlier if diabetes control is poor (e.g., HbA1c >10% [>86 mmol/mol], blood glucose consistently >16.7 mmol/L [>300 mg/dL]) and the person has symptomatic hyperglycaemia.

For most people with T2DM, insulin is usually used as a third or fourth blood glucose-lowering therapy in combination with metformin and/or other blood glucose-lowering therapies, taking into account level of diabetes control, diabetes duration, obesity, age, comorbidities, personal preferences, and medication attributes such as efficacy, hypoglycaemia risk, adverse events, availability, and cost.

An overview of insulin initiation and intensification options is shown in Figure 4.1. Choice will depend on availability and affordability of options, especially in resource-limited settings. The most frequently used options are basal insulin (with or without prandial insulin) or premixed insulin.

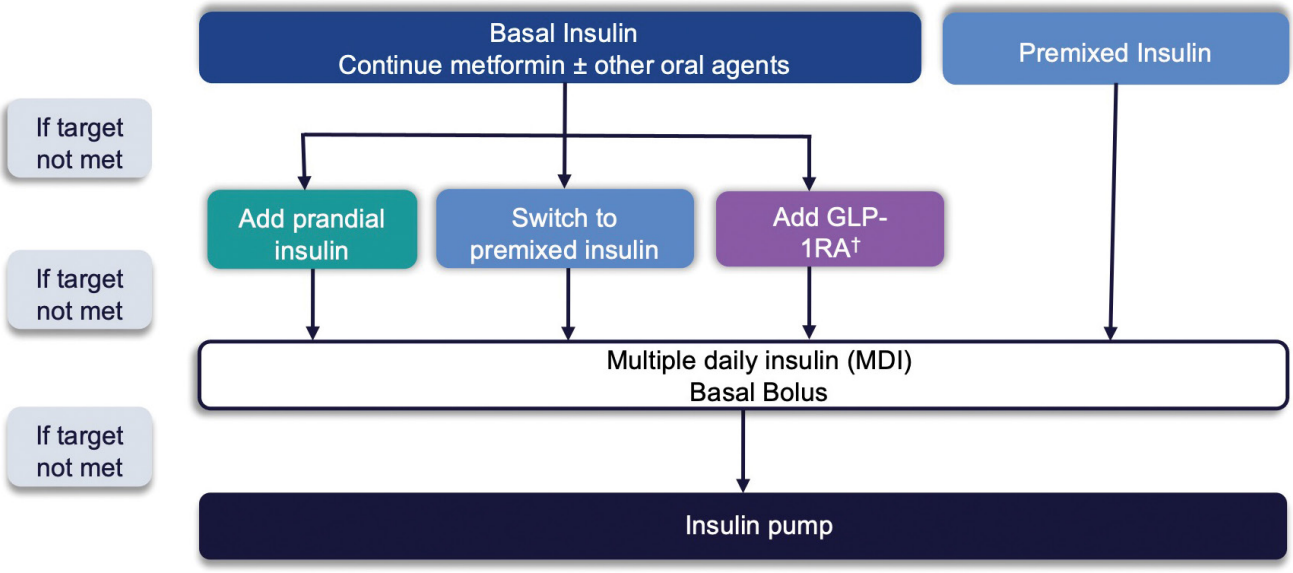
Insulin initiation and treatment intensification

Insulin treatment is usually initiated with once daily basal insulin. An alternate approach is to commence with once or twice daily premixed insulin. The commencing dose for basal insulin is 10 units/day or 0.1–0.2 units/kg/day and increasing 2–4 units or by 10%–15% units at agreed intervals (often once weekly) to achieve target fasting plasma glucose, unless hypoglycaemia occurs.

Care should be taken to avoid excessive increases in the dose of basal insulin ("overbasalisation"). There is a ceiling effect of basal insulin, where increasing doses result in proportionally smaller reductions in fasting blood glucose.[30] The plateau effect is observed at doses around 0.5 units/kg/day, with variations noted in different patient populations. Exceeding this threshold offers modest glycaemic benefits and may lead to weight gain and increased hypoglycaemia.[31,32] There is usually a linear response to increasing basal insulin doses up to 0.3 units/kg/day, but between 0.3 and 0.5 units/kg/day, the response diminishes non-linearly. Therefore, treatment intensification should be considered when basal insulin doses surpass 0.3 units/kg/day.[32]

Basal insulin treatment should be intensified in people who are taking a basal insulin dose of 0.3–0.5 units/kg/day or who have not attained their personalised HbA1c target and fasting blood glucose is below 7.0 mmol/L (126 mg/dL). Assessment of the difference between bedtime and morning blood glucose values (BeAM value) may assist in identifying individuals on basal insulin who need treatment intensification, with large positive BeAM values with fasting glucose at goal suggestive of poor control of postprandial glucose.[33]

Figure 4.1 Insulin initiation and intensification



†either separately or as a fixed-ratio combination
GLP-1RA, glucagon-like peptide-1 receptor agonist.

There are three main options for intensifying treatment, with the choice depending on the person's preference, blood glucose monitoring requirement, and medication availability and cost:

1. **Add prandial insulin: administer one rapid-acting insulin injection before the meal with the highest carbohydrate content.**
2. **Switch to premixed insulin: replace basal insulin with a premixed insulin, usually twice daily – before breakfast and before evening meal.**
3. **Add a GLP-1 receptor agonist.**

Adding prandial insulin allows for greater flexibility for individuals with variable daily routines but requires a higher level of cognitive and dexterity abilities, necessitates more frequent blood glucose monitoring, and may involve more frequent injections compared to premixed insulin regimens. An alternate approach to escalating basal insulin doses and avoiding additional injections is to add a blood glucose-lowering oral agent with reduced hypoglycaemia and weight gain potential such as a SGLT2 inhibitor.

Treatment intensification by switching from a basal to a premixed insulin is a simple, safe, and effective approach, especially in resource-limited settings.

For individuals on basal bolus insulin who do not achieve glycaemic targets, further intensification of insulin therapy involves increasing the number of bolus injections (multiple daily injections). This typically involves a basal insulin and a prandial insulin injection before each of the main meals. Other glucose-lowering medications can be continued but sulfonylurea should be discontinued. Access to blood glucose monitoring is essential to guide bolus prandial insulin adjustments.

Finally, insulin pump therapy may be considered. This is not common in T2DM and requires access to and affordability of blood glucose monitoring, preferably continuous glucose monitoring. However, the lack and cost of the required technology mean that these options are usually not available in resource-limited settings.

Insulin and treatment deintensification

As with all therapies, the dose and the continuing need for insulin should be periodically reassessed. This is particularly important in older individuals with T2DM. Deintensifying insulin treatment may include insulin discontinuation, dose reduction, or changing to an alternate medication when benefits outweigh harm, particularly in older people.[34] Real-world single-arm clinical trials in older individuals support the findings of improved quality of life, reduced stress, and fewer complications arising from hypoglycaemia.[35]

A particularly concerning trend of overtreatment relates to individuals with HbA1c below 6.5% (48 mmol/mol) not being considered or offered therapy simplification. A population-based retrospective cohort study using claims database data reported that over three-quarters of frail individuals or those with multiple comorbidities did not undergo therapy simplification, posing potential risks associated with polypharmacy.[36]

Treatment simplification should be considered for all individuals with T2DM on complex insulin regimens. Triggers for simplification include poor glycaemic control, adherence difficulties, hypoglycaemic episodes, substantial weight gain, comorbidities, cognitive impairments, frailty, limited life expectancy, a history of falls, and negative impacts on quality of life.[37] Deintensification of complex insulin regimens can be done by simplifying the regimen from a basal bolus regimen or with two premixed insulins to a basal regimen with or without non-insulin medications. The decision should be personalised, involving shared decision-making and continuous assessments. The BEYOND trial demonstrated the feasibility of switching individuals on basal bolus insulin with inadequate glycaemic control to basal insulin plus either a SGLT2 inhibitor or GLP-1 receptor agonist, which resulted in fewer injections, lower insulin dose, less hypoglycaemia, and improved glycaemic control.[38] In individuals with proven insulinopaenia (undetectable C-peptide or history of ketoacidosis or severe decompensation after insulin reduction or withdrawal), and in those with long-standing diabetes and treatment with complex insulin regimens due to proven ineffectiveness of other regimens, deintensification by reducing insulin dose should be performed gradually and cautiously with regular monitoring.

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Chapter 5

Weight Control in Type 2 Diabetes Management

RECOMMENDATIONS

	Optimal Care	Basic Care
Weight reduction	• Lifestyle change • VLCD • Incretin-based therapy • Metabolic bariatric surgery	• Lifestyle change • Low-calorie diet • Use weight-sparing BGL therapy • SGLT2i if available
Improving diabetes control	• Lifestyle change • Incretin-based therapy • Metabolic bariatric surgery	• Lifestyle change • Metformin • Add weight-sparing BGL therapy when indicated • SGLT2i if available
Diabetes prevention	• Lifestyle change • Consider: - Metformin - SGLT2i/incretin-based therapy - Metabolic bariatric surgery	• Lifestyle change • Consider metformin
Diabetes remission	• Lifestyle change • VLCD • Metabolic bariatric surgery	• Lifestyle change • Low-calorie diet • VLCD

BGL, blood glucose-lowering; SGLT2i, sodium-glucose cotransporter-2 inhibitor; VLCD, very low-calorie diet.

KEY POINTS

- Obesity is a major driver of type 2 diabetes mellitus (T2DM) accounting for an estimated 43% of cases globally and a major factor in the increase in childhood T2DM.
- People in many Asian countries develop T2DM at a lower body weight and a high proportion have an ideal body weight at diagnosis.
- A complex interplay of biological, genetic, socioeconomic, educational, environmental, and commercial factors underlies both obesity and T2DM.
- The health and economic burden of diabetes is immense accounting for around 12% of global health expenditure (nearly US $1.015 trillion annually); lower- and middle-income countries (LMICs) face the double burden of malnutrition and rising obesity rates.
- There is compelling evidence that strategies to reduce weight can prevent and reverse T2DM and other obesity-associated comorbidities.
- While several factors influence the relationship of weight and T2DM control, in general a 1 kg weight loss results in a 0.1% (1.1 mmol/mol) reduction in glycated haemoglobin (HbA1c).
- Ethnic-specific cut-offs for BMI and waist circumference should be used.
- A stratified, personalised approach to weight management, ranging from lifestyle interventions (nutrition, physical activity, behavioural counselling) to pharmacotherapy and metabolic bariatric surgery, is recommended based on the severity of overweight/obesity, associated comorbidities and available resources.
- Intensive lifestyle interventions, very low-calorie diets and metabolic bariatric surgery can result in T2DM remission but maintaining long term remission is challenging.
- Incretin-based therapies (such as semaglutide, tirzepatide, and retatrutide) show robust efficacy for weight loss and improved glycaemic control but their high cost and limited availability restrict their use in resource-limited settings.
- The choice of blood glucose-lowering therapies should consider their impact on body weight - agents like sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist and metformin promote weight loss, whereas sulfonylureas and glitazones tend to increase weight.
- Metabolic bariatric surgery is associated with longer term diabetes remission, improved glycaemic control and benefits on microvascular and macrovascular outcomes but availability and access are often restricted, especially in resource-limited settings.

BACKGROUND

There is a close relationship between diabetes and obesity. Obesity is estimated to be responsible for around 218 million cases of type 2 diabetes mellitus (T2DM) and is associated with a seven-fold increased risk of developing T2DM compared with a healthy weight. Globally, obesity is responsible for around 43% of T2DM cases. However, this relationship varies across countries. In the US and UK, obesity contributes to an estimated 80%–90% of T2DM while in many Asian countries people develop T2DM at a lower body weight, with one study showing that 63% of people with T2DM diabetes in India had an ideal body weight at diagnosis. The increasing rates of childhood obesity are a major factor in the increase of childhood T2DM.[1]

A complex interplay of common factors contributes to obesity and T2DM, including biology, genetics, food, education, social deprivation, social economic status, healthcare access, stigma, and commercial determinants of health.[1]

The health and economic burden of diabetes has profound repercussions, particularly in lower- and middle-income countries (LMICs),[2,3] where there is the paradoxical double burden of malnutrition and soaring obesity.[3] Diabetes consumes approximately 12% of global health expenditure, translating to US $1.015 trillion annually.[4] This cost has surged by 338% in the last 17 years and is projected to reach US $1.043 trillion by 2050.[4]

There is now compelling evidence that strategies to reduce weight can prevent and reverse T2DM and other obesity-associated conditions and comorbidities.

Overweight and obesity are commonly defined by body mass index (BMI). Since this measure alone may not provide information about the health of an individual, there has been a recent call to identify increased adiposity as an indicator of clinical obesity to guide management decisions. T2DM is an established obesity-related disorder and an indicator of clinical obesity and consequently management of overweight and obesity is an important aspect of diabetes care.[5]

Since Asians manifest T2DM at lower body weights, lower cut-offs are proposed for defining overweight and obesity in these populations (Table 5.1).

Unhealthy weight can also be characterised by measurement of waist circumference and should be interpreted using published ethnic-specific cut-points.[7] The routine measurement of waist circumference can also be used to guide management and determine the efficacy of weight reduction interventions.[7]

Weight management treatment options are usually guided by the severity of overweight/obesity assessed by weight anthropometry (BMI/waist circumference) and tailored to improve person-specific cardiovascular, renal, and metabolic outcomes using a personalised

Table 5.1 Classification of weight category by race/ethnic-appropriate body mass index (BMI)[6]

	General population	Asian populations
Obesity	BMI ≥30	BMI ≥27.5
Obesity class I	BMI 30–34.9	BMI 27.5–32.4
Obesity class II	BMI 35–39.9	BMI 32.5–37.4
Obesity class III	BMI ≥40	BMI ≥37.5
Overweight	BMI 25–29.9	BMI 23–27.4
Normal	BMI 18.5–25	BMI 18.5–22.9

BMI, body mass index.

Table 5.2 A stratified approach to weight management in people with T2DM

Intervention	25.0–26.9 (or 23.0–24.9*)	27.0–29.9 (or 25.0–27.4*)	≥30.0 (or ≥27.5*)
Nutrition, physical activity, and behavioural counselling	Indicated in all individuals	Indicated in all individuals as an adjunct to intensifying treatment	Indicated in all individuals as an adjunct to intensifying treatment
Pharmacotherapy		Preferred treatment intensification option if available	Initial treatment intensification option if available
Metabolic bariatric surgery (MBS)			Consider in individuals with comorbidities

* Refer to Table 5.1.
T2DM, type 2 diabetes mellitus.

treatment plan (Table 5.2). Success requires a combination of caring and supportive health professionals, a motivated person, and a flexible programme which uses the range of available options.

Treatment should always include supervised lifestyle interventions, which can be intensified with reduced or low energy diet, very low-calorie diet (VLCD), pharmacotherapy, or metabolic bariatric surgery (MBS). Unfortunately, the availability and affordability of weight control treatment options is limited globally.

GLOBAL CONSIDERATIONS

Weight control is complex and requires significant health resources. The relationship between weight and T2DM varies considerably across countries and many weight control recommendations have limited relevance where a significant proportion of the diabetes population is not overweight or obese. Large-scale weight control programmes are particularly challenging in countries faced with the double burden of malnutrition and increasing rates of overweight/obesity.

The emerging incretin-based anti-obesity medications are costly and not generally affordable or reimbursed in most countries and especially in resource-limited settings. Access is also an issue with metabolic bariatric surgery.

With limited availability and affordability of BGL medications with established weight loss potential in many countries throughout the world, alternate weight mitigating strategies become increasingly important including nutrition education and use of BGL medications with minimal negative impact on weight.

EVIDENCE SUMMARY

Weight loss results in improvement of a range of parameters relevant to improving outcomes in people with T2DM linked to the degree of weight loss.[8]

Weight loss and diabetes control

A number of factors influence the relationship of weight and diabetes control (glycated haemoglobin [HbA1c] change) in people with T2DM, including choice of blood glucose-lowering (BGL) therapy and baseline HbA1c. However, as a general guide, a 1 kg weight loss is estimated to result in a 0.1% reduction in HbA1c (approximately 1.1 mmol/mol), although a higher baseline HbA1c is associated with a greater reduction in HbA1c for the same degree of weight loss.[9]

Impact of weight loss in type 2 diabetes

Preventing type 2 diabetes

As reviewed in Chapter 1, lifestyle interventions and pharmacotherapy can prevent progression from intermediate hyperglycaemia, in particular impaired glucose tolerance (IGT), to T2DM and can also reverse intermediate hyperglycaemia to normoglycaemia.

In the US Diabetes Prevention Program (DPP), an average weight loss of 6.7% was associated with a 58% reduced incidence of T2DM in people with IGT.[10] A subsequent analysis showed that for every kilogram of weight lost there was a 16% reduction in risk for progression to diabetes, but after 10 kg weight loss, there was negligible benefit of further weight loss on diabetes risk reduction.[11] These data illustrate that even 1–2 kg of weight loss in people at risk for developing T2DM can have health benefits, although it is generally accepted that a weight loss of at least 2.5% or more is required, with maximal impact on T2DM prevention occurring at 10% weight loss.[12]

Type 2 diabetes remission

It has long been recognised that in some people with T2DM, glucose levels can improve into the normal range either spontaneously or after medical or surgical interventions, which can persist, at least temporarily, after glucose-lowering pharmacotherapy is withdrawn. This occurrence is now referred to as "remission" and is generally defined as an HbA1c <6.5% (48 mmol/mol) without blood glucose medications for a period of three months or more.[13] However, it should be noted that publications on diabetes remission have used various definitions and are therefore not always directly comparable. Furthermore, current definitions exclude those achieving remission while taking newer diabetes and weight loss glucagon-like peptide-1 (GLP-1) receptor agonists based therapies.[14] Since weight loss is strongly associated with diabetes remission, the introduction of these newer BGL medications with significant weight-lowering potential has raised the question of revisiting the diabetes remission definition to include a provision for continuing these medications, analogous to the situation of metabolic bariatric surgery where remission is defined in the presence of the intervention which induced weight loss.

Data from the National Diabetes Audit in England reported that 1.7% of 2,297,700 people underwent T2DM remission without specific intervention. The odds of remission was 2.87-fold greater in people diagnosed with T2DM within one year compared to three to five years, and a BMI reduction of ≥10%, as compared to <5%, was associated with 3.57 greater odds of remission.[15] A younger age, shorter duration of diabetes, lower baseline weight, and detectable C-peptide levels without insulin treatment are associated with the highest diabetes remission rates.[16]

Intensive lifestyle intervention (ILI), very low-calorie diet (VLCD), and MBS not only substantially enhance glycaemic control but may also induce T2DM remission.

Intensive lifestyle intervention

In the Look AHEAD (Action for Health in Diabetes) trial in 5,145 overweight or obese individuals with T2DM, greater weight loss was achieved in the group randomised to ILI compared to diabetes education at one year (-7.9%), which decreased to -3.9% at four years.[17] This translated into diabetes remission in 2% in the control group and 11.5% and 7.3% in ILI participants at one and four years, respectively.

Very low-calorie diet

VLCDs are effective interventions to induce rapid weight loss and improving glycaemia. Two randomised controlled trials (RCTs) of VLCD interventions in the UK (DiRECT-predominantly White European) and Qatar (DIADEM-1-predominantly Arab) reported significant reductions in body weight of 11.2%, with T2DM remission in 45%–60% at 12 months[18,19] and 35% in the DiRECT study at 24 months.[16] A small RCT, the South Asian Diabetes Remission Feasibility Trial (STANDby), of 25 South Asians in the UK, reported weight loss of 7.2% and T2DM remission in 38% at four months.[20] In a non-randomised, open-label primary care study from Australia (DiRECT-Aus), VLCD achieved a weight loss of 11.2% and T2DM remission in 55% of 155 participants at one year.[21] Maintaining these remission rates for a longer period is challenging, as reported by the five-year DiRECT extension study, with 13% overall remaining in remission at five years.[22]

In relation to weight loss required for T2DM remission, the DiRECT study showed that weight loss of 5–10 kg (baseline weight approximately 100 kg) resulted in remission rates of 34% at one year and 29% at two years. With weight losses of 10–15 kg, remission rates were 57% and 60% and with weight loss more than 15 kg, remission rates were 86% and 70%, respectively, at one and two years. After five years, remission rate was 19% for individuals maintaining a weight loss of more than 10 kg.[16]

Metabolic bariatric surgery (MBS)

MBS offers superior diabetes remission and blood glucose control compared to non-surgical interventions for people with T2DM.[23,24] In the

Alliance of Randomized Trials of Medicine Versus Metabolic Surgery in Type 2 Diabetes (ARMMS-T2D), people with T2DM aged 20–65 years and BMI 27–45 kg/m^2 reported diabetes remission at three years of 37.5% of participants after MBS compared with 2.6% with medical/lifestyle intervention.[25]

A recent systematic review included 85,473 people with T2DM, of whom 24,451 were in the surgical group, with follow-up durations between five and 15 years. Data on 972 people from seven studies (three cohort studies and four RCTs) were available for long-term assessment of diabetes remission. There was a significant increase in diabetes remission with MBS compared with conventional medical therapy with remission rates of 32% versus 6% over five to 15 years.[26]

The wide range of remission rates reported with MBS may be due to the diversity of surgical procedures, limited numbers in the RCTs, different lengths of follow-up, different definitions of diabetes remission, and difference in reporting of remission – cumulative remission (counted as any individual who ever achieved remission) and/or prevalent remission (counted as only individuals who were in remission at the time of measurement).[27]

MBS improves control of diabetes through both weight-dependent and weight-independent actions. Some degree of glycaemic improvement is associated with weight loss as reported in a meta-analysis of eight studies involving 1,247 participants who underwent MBS, which demonstrated that percentage excess weight loss was positively associated with remission rate.[28] Furthermore, 75% of participants who do not achieve diabetes remission had weight regain.[29] Improvement in insulin sensitivity following weight loss with MBS is a likely mechanism and changes in gut microbiome may also be a factor. A striking feature of MBS is the rapid improvement in glycaemic control that precedes weight loss with reports of individuals being insulin-free at the time of discharge. Mechanisms driving these rapid, weight-independent improvements in glucose homeostasis may be related to alterations in gut hormones.[27]

Mortality and diabetes-related complications

Accumulating data demonstrate that interventions leading to weight loss in people with T2DM are associated with reduced risk of premature mortality and diabetes-related microvascular and macrovascular complications. This may be the direct result of improved control of glycaemic and other risk factors (hypertension, lipids), or due to periods of diabetes remission, or a direct effect of pharmacotherapy used to induce weight loss.

Intensive lifestyle intervention

The primary aim of the LOOK AHEAD study was to examine whether an intensive lifestyle weight loss intervention would decrease cardiovascular morbidity and mortality in 5,145 overweight or obese people with T2DM. Despite greater weight loss in the intervention group than in the control group throughout the study (6.0% versus 3.5% at study end), after a median follow-up of 9.6 years, rates of cardiovascular disease (CVD) events were similar in both groups.[30] Secondary analyses showed a benefit on diabetic nephropathy[31] and symptoms of neuropathy.[32] Additionally, a recent analysis of study participants who achieved diabetes remission at any stage during the study had a 40% lower rate of CVD and 33% lower rate of chronic kidney disease after adjusting for HbA1c, lipids, blood pressure, and CVD history.[33] In a similar post-hoc analysis, weight loss >10% was also associated with a reduction in CVD by 20%.[30,34]

Metabolic bariatric surgery

A systematic review assessed long-term outcomes in 84,890 people with T2DM, of whom 24,247 underwent MBS (11 studies – nine retrospective cohort, one prospective cohort, one small RCT [n = 150]) with follow-up durations between five and 15 years. Significant decreases were observed in microvascular complications incidence (hazard ratio [HR]=0.57), macrovascular complications incidence (HR=0.59), and mortality (HR=0.53).[26]

A recently published network meta-analysis has undertaken an indirect comparison between MBS and blood glucose-lowering therapies and reported an advantage in glycaemic control and weight management for MBS. However, the lack of direct head-to-head comparative trials between MBS and the incretin-based therapies is a critical research gap.[35]

Anti-obesity pharmacotherapy

Pharmacotherapeutic options for the management of obesity were limited in the pre-incretin-based era. The increasing range of novel

anti-obesity medications include GLP-1 receptor agonists (such as higher strength liraglutide 3.0 mg and semaglutide 2.4 mg), dual GLP-1 and GIP receptor agonists (such as tirzepatide), and triple GLP-1, GIP, and glucagon receptor agonists (such as retatrutide). However, they are expensive and not generally available, especially in resource-limited settings.

Incretin-based therapies have demonstrated benefits in the management of people with T2DM, as reviewed in Chapter 3. This section reviews the incretin-based therapies targeting weight management and their use in people with T2DM.

Semaglutide

Semaglutide has been shown to effectively reduce weight and improve CVD, renal, and heart failure outcomes in overweight and obese people with T2DM.

The weight loss efficacy of higher doses of once-weekly subcutaneous GLP-1 receptor agonist, semaglutide 2.4 mg, has been established in the STEP-1 trial in people without diabetes with a BMI ≥30 or ≥27 kg/m^2 with one or more weight-related coexisting condition where placebo-subtracted weight loss of 12.4% was observed over 68 weeks.[36]

The STEP-2 trial assessed once-weekly subcutaneous semaglutide 2.4 mg versus 1.0 mg (approved dose for diabetes management) and placebo in adults with overweight or obesity and T2DM. Semaglutide 2.4 mg achieved a placebo-subtracted weight loss of 6.2% and a placebo-subtracted improvement in HbA1c of 1.4% (15 mmol/mol) over 68 weeks while semaglutide 1.0 mg achieved a placebo-subtracted weight loss of 3.8% and a placebo-subtracted improvement in HbA1c of 1.1% (12 mmol/mol) over 68 weeks.[37]

The PIONEER 6 trial randomised 3,183 individuals with T2DM to once-daily oral semaglutide (14 mg) or placebo for a median of 15.9 months. There was a significant reduction in body weight (–4.2 kg versus –0.8 kg) and HbA1c (–1.0% versus –0.3% [-11 mmol/mol versus -3 mmol/mol]) in the oral semaglutide compared to placebo group. The primary outcome (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was not significantly different in the oral semaglutide group versus the placebo group, demonstrating non-inferiority but not superiority to placebo.[38]

Among people with T2DM and obesity-related heart failure with preserved ejection fraction, semaglutide 2.4 mg once-weekly resulted in a 6.4% greater placebo-subtracted weight loss at one year and was associated with significantly larger reductions in heart failure-related symptoms and physical limitations.[39]

Tirzepatide

In SURPASS-2, 1,879 adults with T2DM (HbA1c 8.3% [67 mmol/mol], weight 93.7 kg) were randomised to receive tirzepatide (GLP-1/GIP dual agonist) 5 mg, 10 mg, 15 mg, or semaglutide 1.0 mg subcutaneously weekly over 40 weeks. The change from baseline in HbA1c was -2.01% (-17 mmol/mol), -2.24% (24.5 mmol/mol), -2.30% (25.1 mmol/mol), and -1.86% (20.3 mmol/mol) and body weight loss was -7.6 kg, -9.3 kg, -11.2 kg, and -5.7 kg, respectively. An HbA1c <6.5% (48 mmol/mol) was achieved in 69%, 77%, 80%, and 64% and diabetes remission (HbA1c <5.7% [<39 mmol/mol]) was achieved in 27%, 40%, 46%, and 19%, respectively.[40]

The SURMOUNT-2, a 72-week phase 3 trial of tirzepatide in adults with obesity and T2DM, demonstrated significant weight reductions with tirzepatide 10 mg and 15 mg, with mean body weight decreases of 12.8% and 14.7%, respectively, compared to a 3.2% reduction in the placebo group. This study confirmed the robust effect of tirzepatide on weight loss in a population with diabetes, with 79%–83% of tirzepatide-treated participants achieving a body weight reduction of 5% or higher.[41]

Similar to semaglutide studies, in the SURMONT-4 trial, in participants with obesity/overweight, withdrawing tirzepatide led to substantial regain of lost weight while those who continued treatment maintained and augmented the initial weight reduction.[42]

The SURPASS-CVOT study is currently examining the cardiovascular safety and efficacy of tirzepatide compared with the GLP-1 receptor agonist dulaglutide in T2D.[43]

Retatrutide

Retatrutide is a novel GLP-1/GIP/glucagon receptor triple agonist which is in the early stages of clinical trials. In a phase 2, double-blind, randomised, placebo-controlled trial, 338 adults with a BMI ≥30 or ≥27 with at least one weight-related complication, excluding diabetes, were randomised to retatrutide 1 mg,

2 mg, 4 mg, 12 mg, or placebo administered subcutaneously once-weekly for 48 weeks. There was a dose-dependent weight reduction of 8.7%, 16.3%, 21.7% and 24.2% respectively with increasing dose compared with 2.1% weight loss in the placebo group. At week 48, 72% of the participants with intermediate hyperglycaemia at baseline had a HbA1c <5.7% (<39 mmol/mol) in the retatrutide groups compared to 22% in the placebo group.[44] In a subsequent study, adults with T2DM received once-weekly doses of retatrutide, dulaglutide, or placebo over 24 weeks, with a 36-week follow-up. Retatrutide 12 mg significantly improved HbA1c levels by 2% (17 mmol/mol) and achieved a 16.9% decrease in body weight compared with a 0.01% (~0.1 mmol/mol) reduction in HbA1c and a 3% reduction in body weight in the placebo group.[45]

Effects of other blood glucose-lowering therapies on weight

With the limited availability and affordability of BGL medications with established weight loss potential in many countries throughout the world, particularly incretin-based therapies, a key strategy for *Basic Care* is to preferentially use BGL therapies with minimal negative impact on weight. In these settings, nutrition education at diagnosis and throughout the care process is particularly important for mitigating weight gain.

The effects of BGL therapies on body weight vary both between and within drug classes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are associated with weight loss and their global availability is improving. Metformin results in a small weight loss; dipeptidyl peptidase 4 (DPP4) inhibitors and α-glucosidase inhibitors are considered weight-neutral; and glitazones are associated with weight gain.[46]

As a class, sulfonylurea monotherapy is associated with a weight gain of approximately 2.0 kg.[46] However, weight change has been reported to be limited in other longer-term studies. In the ADVANCE study, mean body weight with gliclazide during the RCT follow-up period was 0.7 kg greater in the intensive control group than in the standard control group,[47] but only 0.1 kg over five years in the post-trial.[48] The RECORD trial showed that weight was not increased in those randomised to dual therapy with metformin and a sulfonylurea.[49] The TOSCA study showed that dual metformin and sulfonylurea therapy was associated with an initial small weight gain in the first year, returning to baseline weight over five years.[50]

Globally, sulfonylureas remain an important option, either as monotherapy or more commonly as combination therapy. While concerns remain about the risk of hypoglycaemia and weight gain with some sulfonylureas, newer agents (such as glimepiride and gliclazide) are associated with better safety profiles and continue to be promoted in guidelines, especially in combination with other BGL therapies.[51,52]

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Chapter 6

Cardio-Renal Protection in Type 2 Diabetes

RECOMMENDATIONS

	Optimal Care	Basic Care
Atherosclerotic Cardiovascular Disease (ASCVD)		
Screening/risk assessment	• History of ASCVD • High-risk assessment - Age plus 2 risk factors - CVD risk score	
Management	• Glycaemic control • Risk factor control • Blood pressure/lipid control • Consider aspirin • SGLT2i or GLP-1RA • Consider SGLT2i and GLP-1RA	• Glycaemic control • Risk factor control • Blood pressure/lipid control • Consider aspirin • SGLT2i*
Heart Failure (HF)		
Screening/risk assessment	• Symptoms • Hospitalisation for HF • ECG • Echocardiography • Risk score • Biomarkers - BNP / NT-proBNP	• Symptoms • Hospitalisation for HF • ECG • Risk score
Management	• Glycaemic control • Risk factor control • Blood pressure/lipid control • ACEi or ARB • Beta-blockers • Metformin+SGLT2i • Consider adding a non-steroidal MRA • Consider adding GLP-1RA/tirzepatide in obese individuals	• Glycaemic control • Risk factor control • Blood pressure/lipid control • ACEi or ARB • Beta-blockers • Metformin+SGLT2i* • Consider adding a steroidal MRA
Chronic Kidney Disease (CKD)		
Screening/risk assessment	• eGFR • UACR	
Management	• Glycaemic control • Risk factor control • Blood pressure/lipid control • ACEi or ARB • SGLT2i • Consider adding semaglutide	• Glycaemic control • Risk factor control • Blood pressure/lipid control • ACEi or ARB • SGLT2i*

* SGLT2 inhibitors are increasingly available in several low- and middle-income countries at generally affordable cost.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BNP/NT-proBNP, b-type natriuretic peptide/N- terminal pro-b-type natriuretic peptide; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio.

KEY POINTS

- Diabetes complications result from a complex interplay of hyperglycaemia, cardiometabolic risk factors (e.g., elevated blood pressure and lipids), obesity, and unhealthy lifestyle behaviours.
- Cardio-renal complications, including atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD), are major drivers of premature mortality and morbidity in type 2 diabetes mellitus (T2DM).
- Cardiovascular disease (CVD) is highly prevalent in T2DM, around 30% overall, with significant rates of coronary artery disease, silent myocardial infarctions, and HF; CKD affects around 40% of individuals, with marked ethnic differences.
- Early and regular screening for CVD (using risk scores, symptom assessment, electrocardiogram, echocardiography, and biomarkers) and CKD (estimated glomerular filtration rate [eGFR] and urine albumin-to-creatinine ratio) is critical for timely intervention.
- A multi-pillar management approach is essential, focusing on glycaemic control, risk factor modification (blood pressure and lipid management, smoking cessation, weight control), and use of proven cardio-renal protective therapies.
- Newer blood glucose lowering agents, especially SGLT2 inhibitors and GLP-1 receptor agonists, have demonstrated robust benefits in reducing adverse cardio-renal outcomes.
- SGLT2 inhibitors consistently reduce risks of kidney disease progression, HF hospitalisations, and cardiovascular death across diverse groups with T2DM.
- GLP-1 receptor agonists reduce major adverse cardiovascular events, all-cause mortality, and composite kidney outcomes.
- Other glucose lowering therapies (metformin, sulfonylureas, DPP4 inhibitors, insulin) generally have neutral cardio-renal effects while thiazolidinediones increase HF risk.
- Non-steroidal mineralocorticoid receptor antagonists (e.g., finerenone) further expand options for reducing cardio-renal risk in T2DM.
- Global challenges, especially in low resource settings, limit availability and access to comprehensive screening and optimal medications to reduce cardio-renal risk.
- A structured, multi-pillar treatment approach that integrates both traditional and novel therapies is recommended to improve cardio-renal outcomes in people with T2DM.

BACKGROUND

Diabetes complications are the result of a complex interplay of hyperglycaemia, cardiometabolic risk factors such as elevated blood pressure and lipids, obesity, and an unhealthy lifestyle (diet, physical inactivity, smoking). In addition, some complications increase the risk of other complications, with chronic kidney disease (CKD) associated with an increased risk of all-cause and cardiovascular (CVD) mortality, CVD events, and hospitalisation with heart failure (HF).[1]

This Chapter focuses on cardio-renal protection, a major driver of premature mortality and significant morbidity in people with type 2 diabetes mellitus (T2DM) (Figure 6.1).

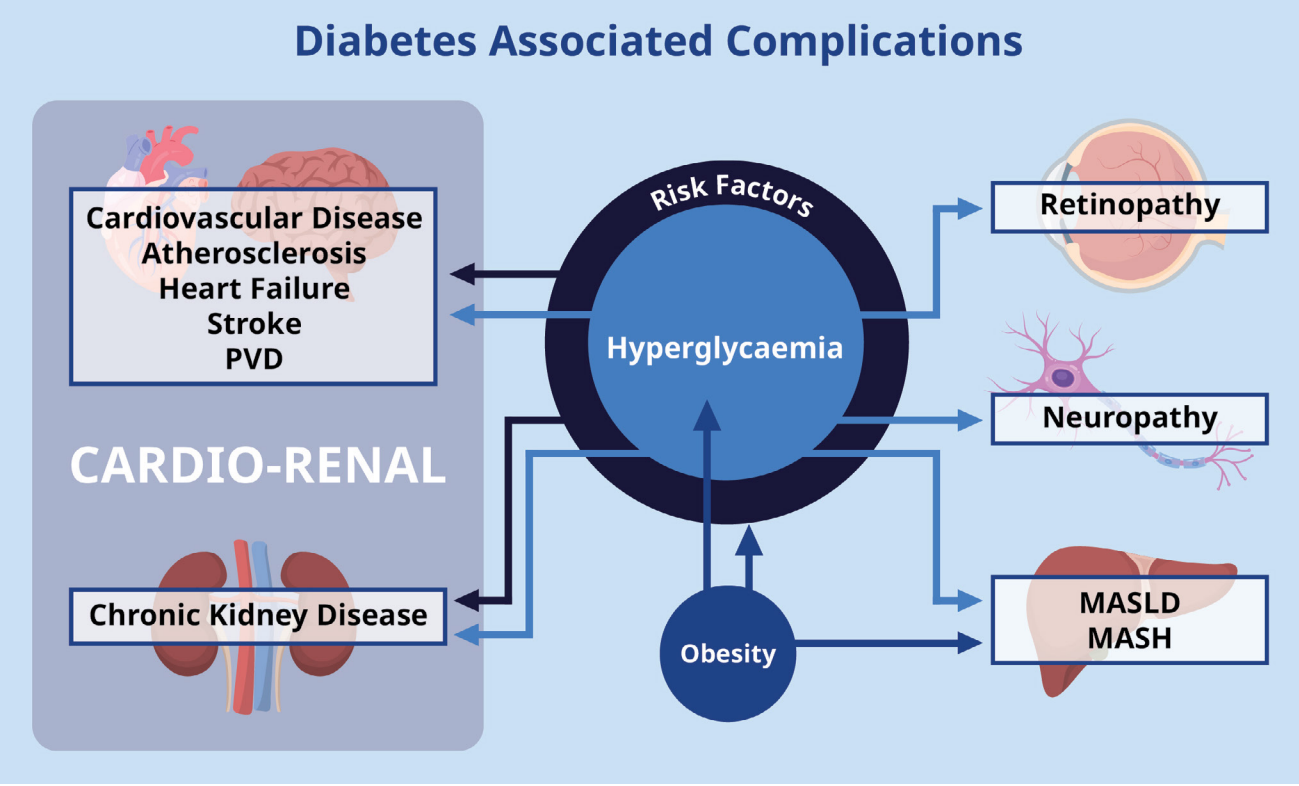
Minimising cardio-renal complications requires effective and regular screening to detect CVD and CKD, and early comprehensive intervention, including consideration of newer blood glucose-lowering (BGL) medications with established cardio-renal protection (sodium-glucose cotransporter-2 [SGLT2] inhibitors and glucagon-like peptide-1 [GLP-1] receptor agonists)[1] in the context of the key pillars in diabetes management (Figure 6.2).

GLOBAL CONSIDERATIONS

In low resource settings, particularly in low- and middle-income countries, access, availability, and affordability of comprehensive Optimal Care for screening and management of cardio-renal risk is often limited. This includes healthcare services, qualified healthcare professionals, diagnostic tests, and availability and affordability of medications. For example, in 125 surveyed countries, fewer than one in four had facilities available for routine measurements of serum creatinine or proteinuria and there was considerable interregional and intraregional variability.[2]

A broad range of medications is available on the World Health Organization (WHO) Essential Medicines List (EML) for managing cardio-renal risk, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, diuretics, and spironolactone.[3] While this does not guarantee local availability, the WHO EML serves as a platform for lobbying local policy makers to have these medications on the country's national EML. As described in Chapter 3 on non-insulin glucose-lowering medications, while access to these medications is limited globally,

Figure 6.1 Diabetes-associated complications



MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; PVD, peripheral vascular disease.

Figure 6.2 Key pillars of diabetes management

the range is increasing in many countries, including generic and affordable SGLT2 inhibitors. However, if Optimal Care cannot be achieved, implementing programmes to achieve Basic Care standards have the potential to significantly reduce cardio-renal risk and improve outcomes for people with T2DM.

EVIDENCE SUMMARY

Prevalence of CVD and CKD in people with T2DM

T2DM increases the risk of developing atherosclerotic cardiovascular disease (ASCVD), HF, CKD, and risk of premature death compared with those without T2DM.[4] A recent systematic review of over four million individuals with T2DM reported an overall CVD prevalence of 32.2%; 29.1% with coronary artery disease (CAD), 14.9% HF, 14.6% angina, 10.0% myocardial infarction (MI), and 7.6% stroke.[5] CVD was the cause of death in 9.9%, representing 50.3% of all deaths.[5]

In a real-world study in primary care of 123,261 individuals (9,616 with T2DM), 43.7% presented with ASCVD and/or CKD and/or HF: 34.8% ASCVD, 4.0% HF, and 14.6% CKD.[6] Asymptomatic CVD is common in T2DM with approximately one in three individuals experiencing undetected ischaemic episodes.[7] The UKPDS study reported a prevalence of around 20% of "silent" MI in people with T2DM.[8]

Heart failure is an important but under-recognised risk factor for adverse outcomes in people with T2DM and has often been overlooked compared with prevention of ASCVD. HF represents a substantial global burden with significant unmet needs in terms of morbidity and mortality. A meta-analysis of 43 studies established diabetes as a significant adverse factor linked to long-term survival and hospitalisation risk in both acute and chronic HF.[9] In a 2016 cross-sectional study, 26.4% of US nursing home residents aged 65 or older with T2DM had HF.[10] HF is not only common in T2DM but is preventable and treatable.

CKD affects approximately 40% of individuals with T2DM overall but prevalence varies with age, ethnic background, duration of diabetes, and presence of cardiometabolic risk factors.[11] CKD in individuals with T2DM has remained consistently high at approximately 40% from 2007 to 2012.[12] There are significant ethnic disparities with higher rates among Black and Mexican-American populations. Alarmingly, one in four persons under age 65 with T2DM has CKD, underscoring the need to improve early detection and management.[12]

The intricate relationship between T2DM, CVD, and CKD is highlighted in a cross-sectional multicentre study of individuals with T2DM from the United Arab Emirates and Kuwait, in whom CKD prevalence was 44.3%, followed by CVD (17.3%) and CAD (15%), with a discernible male predilection. Co-prevalence of CVD and CKD was common (11.7%), and a longer duration of T2DM correlated with heightened risks of CVD, CAD, and peripheral artery disease.[13]

Individuals with T2DM without known cardio-renal disease have an 80% lifetime risk of developing CVD or renal events: a 54% risk of CKD; 41% risk of CVD death; 29% risk of HF; 20% risk of stroke; 19% risk of MI; and 9% risk of peripheral vascular disease (PVD). Achieving ideal CVD health could potentially reduce risks by 37% if evidence-based interventions for reducing CVD associated with T2DM were more widely used.[14]

Screening for CVD and CKD in people with T2DM

The availability of effective therapeutic options to prevent and reduce adverse cardio-renal outcomes underscores the importance of screening and early detection for both CVD and CKD in people with T2DM. The following is an overview of approaches for assessing cardio-renal risk. While access will vary across countries and health systems, it is important for each health service to develop local criteria for assessing and defining cardio-renal risk and to implement management strategies.

CVD screening and risk assessment

(i) ASCVD – established event and/or high-risk

a. Established ASCVD traditionally includes those who have had an MI, stroke, or a revascularisation procedure. Some definitions also include a transient ischaemic attack, angina, amputation, PVD.
b. High CVD risk can be assessed using a formal CVD risk score or by clinical characteristics (e.g., age plus 2 additional risk factors such as smoking, elevated blood pressure, dyslipidaemia).[15]

Screening should include routine questions for symptoms of ASCVD. Risk assessment in people with T2DM should be considered from age 40 years.

(ii) Heart failure

a. Symptoms of HF, hospitalisation for HF
b. Electrocardiogram (ECG / EKG)
c. Echocardiography with measurement of ejection fraction
d. Biomarkers – natriuretic peptides (b-type natriuretic peptide [BNP] and N-terminal pro-b-type natriuretic peptide [NT-proBNP]). BNP or NT-proBNP are biomarkers which are surrogates for intracardiac volumes and filling pressures. Screening protocols using these biomarkers and cut-off values are not universally agreed, require further validation, and are currently not widely available in routine clinical practice.[16-20]

Screening should include routine questions for symptoms of HF. There is no consensus on routine screening for HF but some suggest formal assessment for HF should commence at least from five years post-T2DM diagnosis.[21]

CKD screening and risk assessment

Renal function should be assessed by measuring the following:

1. Estimated glomerular filtration rate (eGFR)
2. Urine albumin-to-creatinine ratio (UACR)

The primary biomarkers for CKD are eGFR and UACR.[22] Normal albuminuria is defined as less than 30 mg/g of creatinine (3 mg/mmol), 30–300 mg/g (3–30 mg/mmol) as moderately increased albuminuria, and greater than 300 mg/g (30 mg/mmol) as severely increased albuminuria. An eGFR <60 mL/min/1.73 m^2 signifies impaired renal function.

Figure 6.3, shown on the next page, illustrates the Kidney Disease – Improving Global Outcomes (KDIGO) classification of CKD based on eGFR and UACR and the associated level of risk. Higher categories of CKD, characterised by lower GFR and greater albuminuria, independently increase risk for adverse outcomes which include CKD progression, CVD, all-cause and CVD mortality, HF, kidney failure, and acute kidney injury.[23]

Annual screening is recommended for CKD starting at diagnosis of T2DM because evidence of CKD is often present already at diagnosis.

Management of CVD and CKD in people with T2DM

The key pillars for reducing cardio-renal risk follow the same principles for diabetes complications in general (Figure 6.2), adapted according to local availability and affordability of specific therapies in developing and implementing a personalised treatment plan.

Pillars of management to improve cardio-renal outcomes in people with T2DM

1. Glycaemic control

The importance of early and intensive glycaemic control is considered in Chapter 3 on non-insulin glucose-lowering medications; meta-analyses of randomised controlled trials (RCTs) have confirmed that intensive glucose control reduces the risk of CVD, retinopathy, and nephropathy.[24,25]

2. Risk factor control

This is an essential and routine pillar of diabetes care and cardio-renal risk protection irrespective of other interventions and is of

Figure 6.3 KDIGO nomenclature for chronic kidney disease[23]

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, Glomerular filtration rate (GFR) category (G1-G5) and Albuminuria category (A1-A3), abbreviated as CGA.

KDIGO: Prognosis of CKD by GFR and albuminuria categories

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

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

CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease – Improving Global Outcomes.

added relevance when access and availability to newer therapies are limited. Modifiable risk factors include blood pressure control, lipid control, smoking cessation, and management of obesity or overweight.

A comprehensive review of the complete spectrum of risk factor control is outside the scope of these clinical recommendations but can be found elsewhere.[15,23,26] The following is a summary of key points relevant to blood pressure and lipid control.

(i) Blood pressure control[26]

- Hypertension is common among people with T2DM, is a major risk factor for ASCVD, HF, and CKD, and its treatment reduces cardio-renal complications.
- An elevated blood pressure is defined as a systolic blood pressure (SBP) 120–129 mmHg and a diastolic blood pressure (DBP) <80 mmHg and hypertension as a SBP ≥130 mmHg or a DBP ≥80 mmHg.
- Blood pressure should be measured at every routine clinical visit.
- The treatment goal is a blood pressure <130/80 mmHg, if it can be safely attained.
- ACE inhibitors or ARBs are recommended first-line therapy for hypertension in people with T2DM with or at risk of cardio-renal complications.
- Multiple-drug therapy is often required to achieve blood pressure targets.
- Combinations of ACE inhibitors and ARBs and combinations of ACE inhibitors or ARBs with direct renin inhibitors should not be used.
- An ACE inhibitor or ARB is recommended first-line treatment for hypertension in people with diabetes and elevated UACR.

The benefits of tighter blood pressure control were confirmed in a recent study in people with T2DM which reported a significantly lower incidence of major CVD events (composite of non-fatal stroke, non-fatal MI, treatment or hospitalisation for HF, or death from CVD) with intensive treatment targeting a SBP of <120 mmHg compared with standard treatment targeting a SBP of <140 mmHg.[27]

(ii) Lipids[26]

- Lipid should be measured at T2DM diagnosis and annually.
- Target low-density lipoprotein (LDL) cholesterol goals are <1.8 mmol/L (70 mg/dL) for primary prevention and <1.4mmol/L (55 mg/dL) for secondary prevention.
- Statins are first-choice pharmacotherapy

for primary and secondary prevention with other therapies considered if LDL cholesterol goal is not met on statins or if intolerant to statins.
- KDIGO recommends statins in adults with T2DM aged 18–49 years with CKD if not treated with chronic dialysis or kidney transplantation.[23]
- Hypertriglyceridemia should be addressed as required.

3. Other standard therapies

(i) ACE inhibitors or ARBs
KDIGO recommends starting an ACE inhibitor or ARB for people with CKD and T2DM and moderately-to-severely increased albuminuria (G1–G4, A2 and A3 – Figure 6.3) but avoiding any combination of ACE inhibitors, ARB, and direct renin inhibitor therapy.[23]

(ii) Beta-blockers
Beta-blockers are effective in reducing all-cause death and hospitalisation for HF in people with HF with reduced ejection fraction (HFrEF) with diabetes.[15]

4. Blood glucose-lowering therapies

(i) SGLT2 inhibitors and GLP-1 receptor agonists
There is now compelling evidence of specific cardio-renal protection with SGLT2 inhibitors and GLP-1 receptor agonists. Consequently, these agents should be considered as mainstream therapies for people with T2DM with or at increased cardio-renal risk and their use has become a key pillar of managing cardio-renal risk.[28]

SGLT2 inhibitors
SGLT2 inhibitors have clearly demonstrated benefits across the spectrum of cardio-renal outcomes. The weight of current evidence favours these agents in people with T2DM at high risk or with established HF or CKD.

In a meta-analysis of six studies of 46,969 individuals with T2DM, including 66% with ASCVD, SGLT2 inhibitors were associated with a 10% reduced risk of major adverse CVD events, 32% reduced risk of hospitalisation for HF, and 38% reduction in adverse kidney outcomes. The largest benefit across the SGLT2 inhibitor class was risk reduction for hospitalisation for HF and adverse kidney outcomes.[29]

A meta-analysis of 13 studies with 90,409 participants (82.7% with T2DM) compared SGLT2 inhibitors with placebo. SGLT2 inhibitors reduced the risk of kidney disease progression by 37% and reduced the risk of CVD death or hospitalisation for HF by 23%. The risk reduction was similar in individuals with and without diabetes and irrespective of mean baseline eGFR.[30]

A meta-analysis of 48 studies involving 58,165 people with T2DM demonstrated that SGLT2 inhibitors were associated with significant reductions in UACR and reduced the risk of microalbuminuria by 31% and macroalbuminuria by 51% compared with placebo or active comparators.[31] The EMPA KIDNEY study showed that empagliflozin slowed the progression of impaired glomerular filtration in people with or without T2DM, and with or without albuminuria.[32]

A meta-analysis of four heart failure studies (n = 15,684 participants, 42%–100% with T2DM), four trials in people with T2DM at high ASCVD (n = 42,568), and three trials in CKD (n = 19,289 participants, 68%–100% T2DM) reported significantly better outcomes with SGLT2 inhibitors compared with placebo: 23% reduced risk of hospitalisation for HF or CVD death, 14% reduced CVD death, 36% less kidney disease progression, and a 12% reduction in all-cause mortality.[33]

In five trials of 21,947 people with HF, SGLT2 inhibitors reduced the risk of composite CVD death or hospitalisation for HF by 23%, CVD death by 13%, first hospitalisation for HF by 28%, and all-cause mortality by 8%. These outcomes for each endpoint were consistently observed in HF with mildly reduced or preserved ejection fraction and results were similar in those with and without diabetes.[34]

GLP-1 receptor agonists
A recent meta-analysis of 11 trials involving 67,769 people with T2DM examined the cardio-renal effects of GLP-1 receptor agonists versus placebo. Composite renal outcome was reduced by 18%, kidney failure by 16%, major adverse cardiovascular events (MACE) by 13%, and all-cause mortality by 12%. Overall hospitalisation for HF was reduced by 13% but no baseline information was available on HF status or ejection fraction. Risk of serious adverse events was similar but treatment discontinuation due to adverse events was 51% higher with GLP-1 receptor agonists.[35]

A meta-analysis of 13 cardiovascular outcome trials (CVOTs; 83,258 people with and without diabetes) examined the effects of GLP-1

receptor agonists versus placebo. GLP-1 receptor agonists significantly reduced MACE by 14%, all-cause mortality by 13%, CV mortality by 13%, fatal stroke by 26%, non-fatal stroke by 13%, coronary revascularisation by 14%, and composite kidney outcome by 24%. These effects were independent of sex, CVD history, body mass index (BMI), and eGFR. GLP-1 receptor agonists did not significantly reduce fatal or non-fatal MI, hospitalisation for unstable angina, or HF hospitalisation.[36]

Until recently, the renal effects of GLP-1 receptor agonists have been derived from secondary and post-hoc kidney outcomes analysis in clinical trials of GLP-1 receptor agonists for CVD and glycaemic control studies. The FLOW study is the first dedicated study comparing a GLP-1 receptor agonist (semaglutide 1.0 mg once weekly) and placebo in people with T2DM and CKD. The study was ceased early after a prespecified interim analysis demonstrated a 24% reduction in the composite primary outcome with semaglutide. Benefits were observed in the composite of the kidney-specific components of the primary outcome (21% reduction) and CVD death (29% reduction). The results of all confirmatory secondary outcomes also favoured semaglutide.[37]

To date, no clinical trial has specifically evaluated the efficacy of GLP-1 receptor agonists on CVD outcomes in people with T2DM and heart failure. The STEP-HFpEF DM Trial randomised people with T2DM and HF with preserved ejection fraction and a BMI ≥30 to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The primary HF endpoint was change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score. Semaglutide resulted in larger reductions in heart failure-related symptoms and physical limitations.[38]

The cardiovascular outcome SUSTAIN-6 study noted an increase in retinopathy.[39] A dedicated RCT of semaglutide versus placebo (FOCUS-NCT03811561) to assess the impact on retinopathy in people with T2DM is due to report in 2026.[40]

Combination SGLT2 inhibitors and GLP-1 receptor agonists
No clinical trial has studied combinations of SGLT2 inhibitors and GLP-1 receptor agonists on cardio-renal outcomes in people with T2DM and CKD. However, some indirect data are available.

A meta-analysis of 13 real-world observational studies examined combinations of SGLT2 inhibitors and GLP-1 receptor agonists in people with T2DM. The combination was associated with a 51% significantly lower all-cause mortality compared with individual therapies and significant reductions in weight, SBP, and HbA1c. However, the study had a number of limitations, with the authors concluding that the certainty of evidence was deemed to be low-to-very low by the GRADE criteria.[41]

In a prespecified analysis, the FLOW trial examined the overall benefits of semaglutide on kidney and CVD outcomes in people with T2DM and CKD in relation to baseline users (n = 550) and non-users (n = 2,983) of SGLT2 inhibitors and reported that outcomes were not influenced by the concomitant use of SGLT2 inhibitors. However, the power of the analysis was limited by the low use of SGLT2 inhibitors at trial entry and that more participants initiated SGLT2 inhibitors in the placebo group during the trial.[42]

(ii) Tirzepatide
Tirzepatide is a long-acting agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, which results in considerable weight loss. To date, clinical trial data are lacking with respect to its effects on cardio-renal outcomes. The SURPASS-CVOT study is currently examining the cardiovascular safety and efficacy of tirzepatide compared with the GLP-1 receptor agonist dulaglutide in with T2DM[43]

The SUMMIT trial randomised people with HF and preserved ejection fraction (48% with T2DM) and BMI ≥ 30 to receive tirzepatide (up to 15 mg subcutaneously once per week) or placebo. After a median follow-up 104 weeks, CVD death or a worsening HF event was reduced by 38% (worsening HF events by 46%) and health status was improved in the tirzepatide group compared with placebo group.[44]

(iii) Effects of other blood glucose-lowering therapies on cardio-renal outcomes
The following is a brief summary of the cardio-renal effects of other BGL therapies. Overall cardio-renal effects have been neutral (except for increased risk of HF with thiazolidinediones), suggesting that these agents can be used when required to improve glycaemic control.

Metformin
The cardio-renal effects of metformin have not been studied in a dedicated CVOT. While the UKPDS showed beneficial effects of metformin on long-term diabetes outcomes, the primary focus of the RCT component of the UKPDS was

on comparing intensive with less intensive diabetes control. The UKPDS included a nested RCT of 753 overweight or obese people with T2DM, comparing conventional glucose targets with a policy of intensive glucose lowering with metformin.[45] Metformin reduced MI by 39%, coronary death by 50%, and stroke by 41% over a median period of 10.7 years. Post-trial follow-up after 24 years showed that early intensive glycaemic control with metformin therapy compared with conventional glycaemic control resulted in 20% risk reduction in all-cause mortality and a 31% reduction in MI.[46]

Sulfonylureas
CVD outcomes with sulfonylureas has been studied in two RCTs. The ADVANCE study examined gliclazide in the context of intensified glycaemic control and did not show any CVD benefits or harms.[47] Similarly, the post-trial follow-up ADVANCE-ON study observed no differences in risk of death from any cause or major macrovascular events.[48]

The dedicated CAROLINA CVOT compared CVD outcomes in people with T2DM randomised to the DPP4 inhibitor, linagliptin, and the sulfonylurea, glimepiride, in addition to usual care. The primary outcome of time to first occurrence of CVD death, non-fatal MI, or non-fatal stroke over a follow-up period of 6.3 years was not different between the two groups but hypoglycaemia was more common in the sulfonylurea group.[49]

In the UKPDS in individuals with newly diagnosed T2DM, the sulfonylureas chlorpropamide and glibenclamide/glyburide had no statistically significant effects on CV outcomes and equally did not suggest adverse CVD effects of sulfonylureas.[50]

Alpha glucosidase inhibitors
There is no dedicated CVOT with an alpha glucosidase inhibitor (AGI) in people with T2DM. The ACE study examined the effect of the AGI acarbose on CVD outcomes in people with CAD and impaired glucose tolerance and failed to show a difference in outcomes between acarbose and placebo.[51]

Thiazolidinediones
The RECORD study assessed CV outcomes in people with T2DM after addition of rosiglitazone to either metformin or sulfonylurea compared with the combination of the two. Rosiglitazone did not increase the risk of overall CVD morbidity or mortality although there was a possible increase in MI compared with standard glucose-lowering therapies.[52]

The PROACTIVE CVOT assessed the CVD effects of pioglitazone versus placebo in individuals with T2DM and ASCVD and failed to show a statistically significant effect on the primary composite outcome.[53]

The thiazolidinediones pioglitazone and rosiglitazone are associated with increased risk of HF.

DPP4 inhibitors
Four CVOTs in people with T2DM with or at high risk of ASCVD have assessed the CVD effects of DPP4 inhibitors versus placebo and demonstrated non-inferiority but not superiority of DPP4 inhibition in the primary CVD endpoint.[54-57] The SAVOR-TIMI 53 study showed that saxagliptin significantly increased the risk of hospitalisation for HF versus placebo.[58]

Insulin
Two basal insulins have been formally evaluated in dedicated CVOTs and did not show a difference in CVD outcomes. The ORIGIN study of insulin glargine included individuals at high CVD risk with impaired fasting glucose, impaired glucose tolerance, or T2DM. After a median follow-up of 6.2 years, the incidence of CV outcomes did not differ between the insulin glargine and standard care groups.[59]

The DEVOTE trial randomised individuals with T2DM with ASCVD or with a high CVD risk to once daily insulin degludec versus insulin glargine. There was no significant difference in the primary composite of CVD death, non-fatal MI, or non-fatal stroke between the two groups after a median 1.8 years follow-up.[60]

Mineralocorticoid receptor antagonists

a. Steroidal mineralocorticoid receptor antagonists (MRAs) spironolactone or eplerenone reduce death and HF hospitalisation in people with HFrEF, with consistent results in people with or without diabetes. Caution is required when using MRAs in people with impaired renal function and in those with serum potassium concentration >5.0 mmol/L.[15] The efficacy of these agents in people with HF and mildly reduced or preserved ejection fraction has not been established.
b. *Non-steroidal MRA – finerenone*
The placebo-controlled FIDELIO-DKD[61] and

FIGARO-DKD[62] trials demonstrated that finerenone reduced risk of kidney failure and CVD outcomes (CVD death, non-fatal MI, non-fatal stroke, or hospitalisation for HF) in people with CKD and T2DM who were on maximum doses of ACE inhibitors or ARBs.[63]

Finerenone has also been shown to further improve renal function in people with CKD and T2DM already receiving SGLT2 inhibitors at baseline[64] and cardio-renal outcomes in people with CKD and T2DM irrespective of SGLT2 inhibitor use.[65]

A recent outcome study reported that in people with HF and mildly reduced or preserved ejection fraction (41% of whom had T2DM), finerenone resulted in a significantly lower rate of a composite of total worsening HF events and death from CVD compared with placebo.[66]

Summary

The emergence of newer therapies has resulted in a significant paradigm shift in the management of cardio-renal risk through a structured, multi-pillar treatment approach to improve outcomes. In addition to the traditional pillars of improving glycaemic control and interventions for established risk factors, the cardio-renal benefits of SGLT2 inhibitors, GLP-1 receptor agonists, and non-steroidal mineralocorticoid receptor antagonists are supported by robust clinical trial evidence.[67] These therapies have expanded standard CKD treatment with renin-angiotensin system (RAS) blockers.[68]

Current guidelines[15,26] include decision algorithms which highlight established and new pillars for managing cardio-renal risk and enhance risk reduction for people with T2DM with at least one of ASCVD, HF, CKD, or those at high risk for ASCVD.[26,69]

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Chapter 7

Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in Type 2 Diabetes

RECOMMENDATIONS

	Optimal Care	Basic Care
Screening and risk assessment	• Suspect MASLD in all people with T2DM, especially if overweight or obese; LFTs are abnormal • Screen for MASLD-related fibrosis - FIB-4 score - Imaging if FIB-4 result elevated - VCTE - MRE	• Suspect MASLD in all people with T2DM, especially if overweight or obese; LFTs are abnormal • Screen for MASLD-related fibrosis - FIB-4 score - Imaging if FIB-4 result elevated (if available)
Management of people with T2DM and at-risk MASLD	• Implement Pillars of Diabetes Care (Chapter 6) • At-risk MASLD determined by FIB-4 and imaging • Promote healthy lifestyle change and at least 5% weight loss if overweight or obese • Specific MASLD therapy - Resmetirom (where approved) - GLP-1RAs (including semaglutide, liraglutide, and tirzepatide) • Consider metabolic bariatric surgery	• Implement Pillars of Diabetes Care (Chapter 6) • At-risk MASLD determined by FIB-4 alone or with imaging if available • Promote healthy lifestyle change and at least 5% weight loss if overweight or obese • Specific MASLD therapy - Pioglitazone (if available and not contraindicated) - SGLT2i for weight loss and cardio-renal protection

Note: These recommendations also apply to people with intermediate hyperglycaemia.

FIB-4, fibrosis-4 index; GLP-1RA, glucagon-like peptide-1 receptor agonist; LFT, liver function test(s); MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; SGLT2i, sodium-glucose cotransporter-2 inhibitor; T2DM, type 2 diabetes mellitus; VCTE, vibration-controlled transient elastography.

KEY POINTS

- Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is steatotic liver disease without harmful alcohol intake.
- MASLD is the most common chronic liver disease and is closely linked with type 2 diabetes mellitus (T2DM), intermediate hyperglycaemia, and obesity.
- MASLD increases risk of adverse liver and cardio-renal outcomes.
- All people with T2DM are at-risk of MASLD. The main objective is to identify and manage those with "at-risk MASLD" to prevent progression to cirrhosis and its complications.
- Identifying and managing MASLD in resource-poor settings is challenging due to the limited availability of required blood and imaging tests, access to preferred glucose-lowering medications, and the scarcity of specialised services.
- The global prevalence of MASLD in people with T2DM is 65% and metabolic dysfunction-associated steatohepatitis (MASH) is 32%. Thirty-six per cent of people have fibrosis and 15% advanced fibrosis. MASLD is common in obesity.
- Individuals with T2DM and suspected MASLD should be assessed for risk of developing advanced liver disease with a blood-based risk score (Fibrosis-4 index [FIB-4]) and followed up with vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) imaging to detect fibrosis, if available.
- Liver biopsy is not required for managing most people with MASLD.
- MASLD-specific interventions include lifestyle modification and weight loss (≥5%–10%).
- Resmetirom is the only approved (in the USA) MASH-targeted therapy. It is an oral, liver-directed, thyroid hormone beta-1 receptor agonist and is indicated for non-cirrhotic MASH and moderate-to-advanced liver fibrosis.
- No blood glucose-lowering (BGL) medication for T2DM has an indication as a MASLD-targeted therapy.
- Some glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, liraglutide, tirzepatide) and pioglitazone improve histological features of MASH. Semaglutide has recently been demonstrated to improve liver fibrosis.
- Pioglitazone is not available in many countries and its side effect profile should be considered in deciding whether or not to prescribe it.
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors improve liver steatosis without affecting liver fibrosis linked to weight loss.
- Insulin is the preferred treatment of hyperglycaemia in T2DM with decompensated cirrhosis.
- Statin therapy is safe in T2DM and MASLD, including compensated cirrhosis.
- Metabolic bariatric surgery is an option to treat MASLD/MASH in those with severe obesity and has been associated with resolution of MASLD and MASH but not advanced fibrosis.

BACKGROUND

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factors (including type 2 diabetes mellitus [T2DM] and intermediate hyperglycaemia) and the absence of harmful alcohol intake. The change in nomenclature from "non-alcoholic" to "metabolic dysfunction" reflects an evolving understanding of these conditions and their metabolic links.[1]

MASLD is the most common chronic liver disease and is closely linked with T2DM, intermediate hyperglycaemia, and obesity. In addition to adverse liver outcomes, MASLD is associated with an increased risk of adverse cardio-renal outcomes.

Other forms of SLD include alcohol-related liver disease (ALD) (alcohol intake >50 g/day for females and >60 g/day for males) and MASLD with moderate increased alcohol intake (MetALD) (alcohol intake 20–50 g/day for females and 30–60 g/day for males).[1]

The spectrum of MASLD includes:

- **Metabolic dysfunction-associated steatotic (fatty) liver (MASL)**
- **Metabolic dysfunction-associated steatohepatitis (MASH)**
- **Fibrosis**
- **Cirrhosis**
- **MASH-related hepatocellular carcinoma (HCC)**

The intricate association between MASLD/MASH in individuals with T2DM and intermediate hyperglycaemia and adverse liver and systematic impacts emphasises the need for proactive intervention and tailored personalised management strategies.

A definitive diagnosis of hepatic steatosis requires either imaging or histology and is not practical or necessary in a routine clinical setting. Adverse outcomes of MASLD relate to MASH and fibrosis. Consequently, the objective is to have a high index of suspicion for MASLD in all people with T2DM and to specifically identify and intervene in those with "at-risk MASLD" to prevent progression to cirrhosis and its complications.

GLOBAL CONSIDERATIONS

MASLD is an important, common, and increasingly recognised serious comorbidity in people with T2DM and intermediate hyperglycaemia. Identifying and managing MASLD in resource-poor settings present several challenges. The blood and imaging tests required for screening for at-risk individuals with MASLD may not be available. Preferred glucose-lowering medications for managing people with MASLD may not be available, accessible, and affordable. The only MASLD-targeted treatment is only currently approved in the United States. Specialised services are scarce. Despite these limitations, much can still be done through primary care and diabetes services in resource-limited settings to improve the management and outcomes for people with T2DM and MASLD.

EVIDENCE SUMMARY

The prevalence of MASLD, MASH, and fibrosis in T2DM

An estimated 30% of the global general population has MASLD with regional differences ranging from 25% in Western Europe to 44% in Latin America.[2]

The global prevalence of MASLD in people with T2DM is 56%, two-fold higher than in the general population, with studies from Europe reporting the highest prevalence at 68%. The reported prevalence of MASH is 37%, and 17% who had a liver biopsy had advanced fibrosis. Individuals with T2DM not only have a greater prevalence of MASLD but also an increased risk of developing MASH and advanced fibrosis compared with the general population.[2]

A more recent analysis of nearly two million individuals with T2DM reported prevalence rates of MASLD of 65% and MASH of 32%, with 36% of those with MASLD having fibrosis (stage F2–F4) and 15% advanced fibrosis (stage F3–F4).[3] However, it should be noted that many of the included studies were from clinics and hospital settings and were not random samples.

In a study involving 360 people with T2DM who underwent liver biopsies when alanine aminotransferase (ALT) levels were persistently >20 IU/L in females or >30 IU/L in males in the absence of other liver disease, the prevalence of MASH, advanced fibrosis, and cirrhosis was 58%, 38%, and 10%, respectively.[4]

Of note and relevance to diabetes, in overweight populations the prevalence of MASLD was 70%, MASL 42%, MASH 34%, fibrosis stages 2–4 20%, and 7% had advanced fibrosis stages 3–4. Prevalences were similar in the obese population.[5] Fibrosis progression is subject to a myriad of influences, including comorbidities, genetic factors, and environmental conditions.

The increased risk of major adverse liver outcomes is linked to the particular manifestation of MASLD. A Swedish registry-based cohort study of 230,992 people with T2DM without a history of liver disease reported a low incidence of adverse outcomes, with 3,215 (1.4%) developing major adverse liver outcomes over 10 years.[6] In a national matched prospective cohort study of 10,568 individuals with biopsy-confirmed MASLD with a median follow-up of 14.2 years, 4,338 with MASLD died. Compared with controls, individuals with MASLD had significantly increased overall mortality (16.9 versus 28.6/1000 person-years). Significant excess mortality risk was 8.3/1000 person-years for simple steatosis, 13.4/1000 person-years for non-fibrotic MASH, 18.4/1000 person-years for non-cirrhotic fibrosis, and 53.6/1000 person-years for cirrhosis.[7]

T2DM is associated with poorer outcomes in individuals with biopsy-proven MASH and compensated cirrhosis, including an increased risk of death and HCC. Compared with metabolically healthy individuals, people with T2DM had the highest risk of having MASLD (odds ratio [OR] = 10.88) followed by intermediate hyperglycaemia (OR = 4.19). During a median follow-up of 26.7 years, people with MASLD had significantly higher age-adjusted mortality than non-MASLD (32.7% versus 28.7%) with the highest age-standardised cumulative mortality in those with T2DM (41.3%), followed by intermediate hyperglycaemia (35.1%), compared with metabolically healthy individuals (21.9%).[8]

While the natural history of MASLD is relatively well-defined, there is substantial individual variability in disease trajectories. The risk of future liver-related events starts to increase at the fibrosis stage. However, it takes decades for MASLD to progress to cirrhosis and hepatic decompensation.[1]

Screening and diagnosis of MASLD at-risk of advanced liver disease in people with T2DM

The association between MASLD stage and adverse outcomes underlines the need for nuanced clinical approaches.[1] The primary goal in the management of MASLD in people with T2DM is to identify individuals at-risk of MASLD-related fibrosis, particularly those with abdominal obesity and additional metabolic risk factors or abnormal liver function tests. This has become an important aspect of comprehensive care for T2DM but remains challenging in resource-limited health systems.

Screening and diagnosis of individuals with MASLD who are at-risk of developing advanced liver disease usually involves a two-step approach of an initial blood-based score followed by imaging.

Blood-based score

The Fibrosis-4 index (FIB-4) is the most widely used available tool. It uses a combination of blood test values and anthropometric information to screen for risk of liver fibrosis. FIB-4 is calculated as age x aspartate transaminase (AST)/(platelet count x $\sqrt{}$ ALT) (age in years, ALT and AST in U/L, and platelet count in 109/L).[9] A FIB-4 score <1.3 identifies individuals who are not likely to have advanced fibrosis and who require ongoing periodic re-evaluation (one to three years) while a FIB-4 value >2.67 is associated with high-risk and ideally should be referred to a hepatologist.[10] The ability of FIB-4 to detect fibrosis is limited in the intermediate score range (1.30–2.67). A lower cut-off value of 2.0 is recommended in people aged over 65 years and the test does not perform well in individuals younger than 35 years, and also less well in people with diabetes.[11] Automated FIB-4 score calculation followed by reminder messages in the electronic health system has been shown to increase referral of individuals with increased fibrosis scores to hepatologists from 3% to 33%.[12]

Persistently or intermittently elevated ALT levels >30 U/L may indicate chronic liver injury, whereas AST levels lack sensitivity and specificity in identifying MASLD with advanced fibrosis.

Imaging

Individuals assessed as moderate or high-risk of advanced disease on FIB-4 should undergo further assessment with imaging.

Vibration-controlled transient elastography (VCTE) is commonly used to estimate liver stiffness measurement (LSM) as an assessment of degree of fibrosis and controlled attenuation parameter (CAP) as an assessment of steatosis.[13]

Other ultrasound-based methods like acoustic radio force impulse (if available) may be preferred due to cost considerations. Some ultrasound techniques may not be reliably used to examine adults with class 2 obesity.[1]

Magnetic resonance elastography (MRE) can also be used to assess liver stiffness and is more sensitive than VCTE in detecting fibrosis stage ≥2 but requires specialised equipment to generate mechanical waves and dedicated acquisition techniques, which are only available at a few sites.[10]

Tests of specific collagen-related blood constituents (e.g., the Enhanced Liver Fibrosis test, ELF) may be an alternative to imaging to identify advanced liver fibrosis in the future.[1]

Liver biopsy is not required for clinical management in most cases of people with MASLD.

Management

The evolving landscape of MASLD management in T2DM requires personalised approaches based on the Key Pillars of Diabetes Management (See Chapter 6) and considering MASH-targeted therapy if available, accessible, and affordable.

MASLD-specific interventions

Lifestyle modification and weight loss

Overweight and obese MASLD people with T2DM and intermediate hyperglycaemia should be recommended dietary and physical activity lifestyle changes that promote weight loss to reduce liver steatosis and improve cardiometabolic profile, while discouraging alcohol consumption.[1]

The degree of weight loss has a significant impact on different MASLD manifestations. Sustained diet-induced weight loss of ≥5% reduces liver fat, 7%–10% weight loss improves liver inflammation, and ≥10% weight loss improves fibrosis.[1, 14] For example, weight loss of at least 7% by lifestyle modification with a Mediterranean diet was associated with MASH resolution after 52 weeks, and weight loss of more than 10% with improvement in liver fibrosis. However, histological changes with lifestyle intervention are achieved in less than 20% of people.[15]

Pharmacotherapy

1. MASH-targeted therapy – resmetirom

Resmetirom is the first specific medication for the treatment of MASLD and received accelerated FDA approval in March 2024. It is an orally active, liver-directed, thyroid hormone beta-1 receptor agonist and is indicated for adults with non-cirrhotic MASH and moderate-to-advanced liver fibrosis in conjunction with diet and exercise. In a phase 3 randomised controlled trial (RCT), resmetirom 80 mg resulted in resolution of MASH without worsening of fibrosis in 25.9% of individuals compared with 9.7% in the placebo group, and fibrosis improvement by at least one stage with no worsening of MASLD activity score in 24.2% compared with 14.2% in the placebo group. Low-density lipoprotein concentrations were also significantly decreased.[16]

The usual daily dose is 80 mg in individuals with a body weight <100 kg and 100 mg with body weight ≥100 kg. Dose reduction should be considered with moderate CYP2C8 inhibitors such as clopidogrel. Resmetirom is generally well-tolerated with the most common side effects being gastrointestinal (diarrhoea, nausea, and vomiting) and pruritus.[1, 14] However, it is not widely available.

There is currently no effective MASH-targeted pharmacotherapy available for people with MASH and cirrhosis.

2. Blood glucose-lowering medications

Blood glucose-lowering (BGL) medications for T2DM have been reviewed in Chapters 3 and 4. BGL medications may impact MASLD directly or through improved glycaemic control and/or weight loss. No currently available BGL or weight management medication is approved as a MASLD-targeted therapy. The following is a brief review of the specific effects of BGL medications on MASLD.

Metformin
Metformin has not been shown to improve steatohepatitis in paired-biopsy studies. However, it is safe and should be continued in individuals with cirrhosis unless discontinuation is required due to hepatic decompensation or renal failure.

Sulfonylureas
There are no RCTs with liver histological endpoints which have examined the effects of sulfonylureas as a MASLD-targeted therapy. There is an increased risk of hypoglycaemia in cirrhotic liver disease.

Insulin
Insulin reduces hepatic steatosis but its effect on steatohepatitis remains unknown.[17] Insulin treatment for uncontrolled T2DM in the presence of MASLD can decrease liver steatosis by addressing lipotoxicity and glucotoxicity. However, it may potentially increase hepatic triacylglycerol content and contribute to hepatic fat accumulation.[18] Insulin is the preferred treatment of hyperglycaemia in adults with T2DM with decompensated cirrhosis.

Thiazolidinediones (pioglitazone)
Pioglitazone has been demonstrated in several phase 2 RCTs to improve histological features of MASH but has no clear effect on fibrosis regression.[19-21] However, there has not been a large phase 3 multicentre trial with pioglitazone which has further assessed these findings. Pioglitazone is not available in many countries and its side effect profile should be considered in deciding whether or not to prescribe it.

SGLT2 inhibitors
Short-term SGLT2 inhibitor RCTs have shown reversal of liver steatosis and a reduction in plasma aminotransferase levels but no improvement in markers of liver fibrosis.[22, 23] These changes seem to be primarily linked to weight loss rather than specific targeted MASLD effects. SGLT2 inhibitors are safe in people with T2DM and MASLD and have other well-documented cardio-renal benefits.

GLP-1 receptor agonists
Single GLP-1 receptor agonists (liraglutide and semaglutide),[18] dual GLP-1 receptor agonists (tirzepatide[24, 25] and survodutide[26]), and triple GLP-1 receptor agonists (retatrutide)[27] have shown positive effects not only on weight loss and hyperglycaemia but also on the reduction of liver steatosis, with some showing benefits on histological parameters in people with biopsy-proven non-cirrhotic MASH.[25, 27]

Recently, the positive results of the ESSENCE study were released. The ESSENCE study is a phase 3 RCT evaluating the effect of subcutaneous semaglutide 2.4 mg in people with biopsy-proven MASH and fibrosis stage 2 or 3, which included 56% of participants with T2DM.[28] After 72 weeks in the first 800 individuals (56% T2DM), endpoints were significantly better with semaglutide compared with placebo. Primary endpoints showed 62.9% of people treated with semaglutide 2.4 mg achieved resolution of steatohepatitis with no worsening of liver fibrosis compared to 34.1% taking placebo, and 37.0% treated with semaglutide achieved improvements in liver fibrosis with no worsening of steatohepatitis compared to 22.5% taking placebo. Secondary endpoints showed 32.8% of participants treated with semaglutide achieved both resolution of steatohepatitis and improvements in liver fibrosis (compared to 16.2% taking placebo).[29] This is the first phase 3 GLP-1 receptor agonist-related study to show significant definitive improvement in liver fibrosis in MASLD.

GLP-1 receptor agonists have not been shown to be beneficial in cirrhosis, with a placebo-controlled RCT in adults with biopsy-confirmed MASH-related compensated cirrhosis and body mass index ≥27 kg/m^2 failing to show an improvement with semaglutide 2.4 mg weekly in fibrosis or achievement of MASH resolution, but there were no safety concerns.[30]

Cohort studies have reported that GLP-1 receptor agonist use in people with T2DM are associated with lower risk of progression to cirrhosis and lower mortality compared with using DPP4 inhibitors but the protective association was not seen in people with existing cirrhosis.[31] Another cohort study which matched people with T2DM with and without cirrhosis reported that GLP-1 receptor agonist use was associated with lower risk of death and major liver outcomes.[32]

Overall, given the established cardio-renal benefits of SGLT2 inhibitors and GLP-1 receptor agonists and the weight reduction effects, especially of GLP-1 receptor agonists, these agents are preferred in people with T2DM and MASLD, if available, accessible, and affordable, and taking into account each individual's characteristics and comorbidities.

3. Statins

Statin therapy is safe in adults with T2DM and MASLD, including in those with compensated cirrhosis. Statins should be initiated or continued for cardiovascular risk reduction as clinically indicated. Recent data have reported that regular use of statins was associated with a 15% lower hazard ratio of new-onset liver disease and a 28% lower hazard ratio for liver-related deaths (cirrhosis and HCC) compared with no statin use.[33] Data on statin safety and efficacy in individuals with decompensated cirrhosis are limited and therefore statin therapy should be used with caution and closely monitored.

4. Metabolic bariatric surgery

Metabolic bariatric surgery (MBS) is an option to treat MASLD/MASH in those with severe obesity given the positive effect on T2DM and cardiovascular disease and has been associated with resolution of MASLD and MASH.[34, 35] However, advanced fibrosis can persist for many years and is associated with lesser weight loss and metabolic improvement.[36] In adults with T2DM and compensated cirrhosis from MASLD, MBS should be used with caution and is currently not recommended in decompensated cirrhosis.

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