Type 2 diabetes

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Type 2 diabetes accounts for nearly 90% of the approximately 537 million cases of diabetes worldwide. The number affected is increasing rapidly with alarming trends in children and young adults (up to age 40 years). Early detection and proactive management are crucial for prevention and mitigation of microvascular and macrovascular complications and mortality burden. Access to novel therapies improves person-centred outcomes beyond glycaemic control. Precision medicine, including multiomics and pharmacogenomics, hold promise to enhance understanding of disease heterogeneity, leading to targeted therapies. Technology might improve outcomes, but its potential is yet to be realised. Despite advances, substantial barriers to changing the course of the epidemic remain. This Seminar offers a clinically focused review of the recent developments in type 2 diabetes care including controversies and future directions.

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See Online for appendix

Epidemiology and global trends in type 2 diabetes

Defined solely on the basis of persistently elevated blood glucose concentration, type 2 diabetes is increasingly recognised as a complex, cardiorenal-metabolic disease entity driven by a chronic positive energy balance.[1] Multiple metabolic and homoeostatic disturbances develop over the course of the disease and are sustained over time. Perturbations in glucose and lipid metabolism have profound detrimental effects on vascular integrity and supply, leading to organ dysfunction and premature death.

The rising global incidence of type 2 diabetes is associated with a rise in obesity trends. Rapid economic development and urbanisation coupled with sedentary lifestyles and unhealthy eating patterns are believed to be the main environmental factors fuelling this increase.[2]

About 537 million adults worldwide have diabetes, most of whom have type 2 diabetes, and this number is expected to rise to 783 million by 2045.[3] Globally, the proportion of people living with undiagnosed diabetes is around 45%, but this figure ranges from 54% in Africa to 24% in North America and the Caribbean regions.[3] Additionally, about 352 million people have impaired fasting glucose or impaired glucose tolerance,[4] which can progress to type 2 diabetes at a rate of 5–10% of people within this population per year.[5]

More than 80% of people with type 2 diabetes live in low-income and middle-income countries.[2] Although Africa has the lowest prevalence (5·3%) relative to other global regions, this continent is projected to have the highest increase over the next 25 years.[2]

Although the number of new cases of type 2 diabetes increases rapidly after age 55 years, the rates of early-onset type 2 diabetes (aged ≤40 years) are increasing and present new public health and societal challenges.[6] Generally, type 2 diabetes is more common among marginalised groups in any society. Genetic and epigenetic changes associated with persistent hyperglycaemia perpetuate disparities in the distribution and burden of the disease. Environmental factors contribute further to widening the gap. Natural and man-made disasters also negatively affect diabetes care.[7,8]

The prevalence of type 2 diabetes is correlated with lifestyle choices, but for most people with type 2 diabetes, choices in lifestyle are non-existent. Affordability, availability, and accessibility profoundly affect not only meal patterns and fitness routines, but also food preparation methods and portions consumed while eating. A person's next meal might not be guaranteed,[9] and the so-called appropriate meal choice might be difficult to source. Consequently, management goals for type 2 diabetes will need to adapt to the changing demography and better understanding of pathophysiology. Detailed genotyping and phenotyping, individualised targets, weight management, and maintaining a good quality of life, including mental wellbeing, might represent new goals of care.[10] However, a united, international response truly focused on improving global health inequalities in the delivery of diabetes care is needed to accomplish all these management goals (appendix p 7).[11]

Pathophysiology

The pathophysiology of type 2 diabetes is characterised by insulin resistance and initial hyperinsulinaemia, followed by progressive decline in the capacity of pancreatic β cells to produce insulin. The variable mix of β-cell dysfunction and insulin resistance ultimately underlies the complexity of type 2 diabetes. Although at diagnosis 40–80% of β-cell function is already lost,[12,13] with good glycaemic control or remission substantial functional β-cell mass can be restored.[14] Reactivation or recovery of existing β-cells or redifferentiation and regeneration from other pancreatic cell lines might underpin this restoration.[15] Consequently,

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase for manuscripts published in English only in peer-reviewed journals between Jan 1, 2000, and Dec 31, 2021. We used the search terms "type 2 diabetes" or "type 2 diabetes mellitus". We largely selected publications from 2019 onwards, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by our broad search strategy and selected those we judged relevant. Our reference list was modified on the basis of comments from coauthors and reviewers focusing on high-quality publications.

a β-cell-centric model, recognising abnormal β-cell function as a primary defect of type 2 diabetes, has been proposed.[16] In 2009, DeFronzo proposed that incretin dysregulation, lipolysis, hyperglucagonaemia, increased glucose reabsorption in kidney, and central appetite dysregulation have key roles in the pathophysiology of type 2 diabetes in addition to the traditional triumvirate of muscle, liver, and β-cell interplay.[17] This interplay was later extended to include defects in 11 interlocking pathways, with β-cell dysfunction as the common denominator connecting the pathways.[16]

In this Seminar, we combine all the pathophysiological factors contributing to hyperglycaemia: the deleterious dozen (figure 1). This model incorporates dysbiosis in gut microbiota, inflammation, immune dysregulation, and islet amyloid polypeptide (amylin) deposition in the pancreas.[18] It has implications for management of type 2 diabetes, with reprofiling of existing drugs to target the underlying pathophysiological defects and the development of new drugs (figure 1).

Screening and diagnosis

Universal screening for diabetes is not recommended as there is little evidence that this approach is cost-effective or improves health outcomes.[19,20] Consensus guidelines advocate screening individuals at high risk, including people who are overweight or obese, ethnic groups susceptible to type 2 diabetes at a younger age, or people with a strong family history of type 2 diabetes and previous gestational diabetes (figure 2).

When suspected, the diagnosis of type 2 diabetes can be made by analysis of plasma glucose concentrations or glycated haemoglobin (HbA_{1c}; table 1). Although type 2 diabetes is the most prevalent type of diabetes, distinguishing it from other forms of diabetes, including type 1 diabetes, monogenic diabetes or maturity-onset diabetes of the young, or latent autoimmune diabetes in adults (LADA), is not always straightforward (figure 2). Taking time to review the history and clinical context is extremely important for diagnosis and appropriate management. For example, LADA and diabetes arising from pancreatic disease (type 3) are occasionally mistaken for type 2 diabetes, as these conditions usually present after 30 years of age. The presence of diabetes-associated autoantibodies including glutamic acid decarboxylase (GAD), normal BMI, and rapid progression to insulin requirement (usually after 6 months of diagnosis) can aid in diagnosis of LADA.[23] Ketosis-prone diabetes shares similar pathophysiology to type 2 diabetes but can present like type 1 diabetes; for

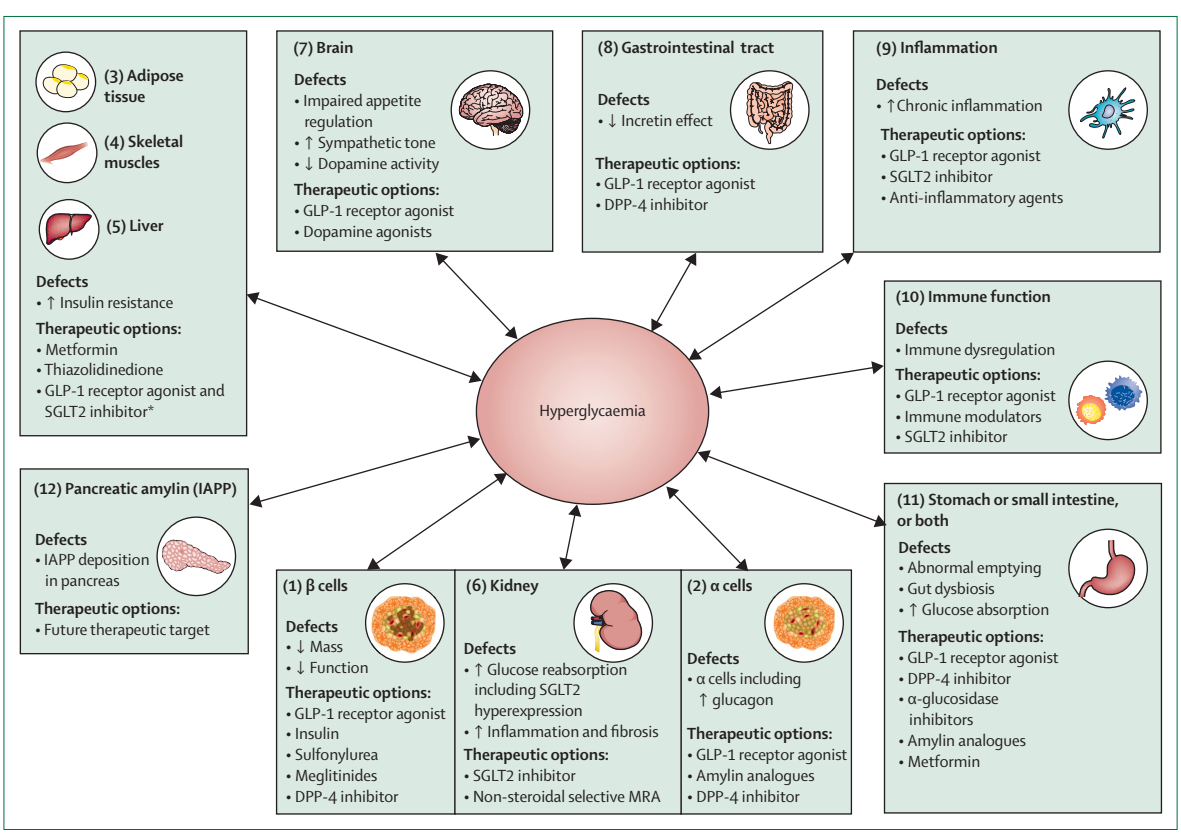
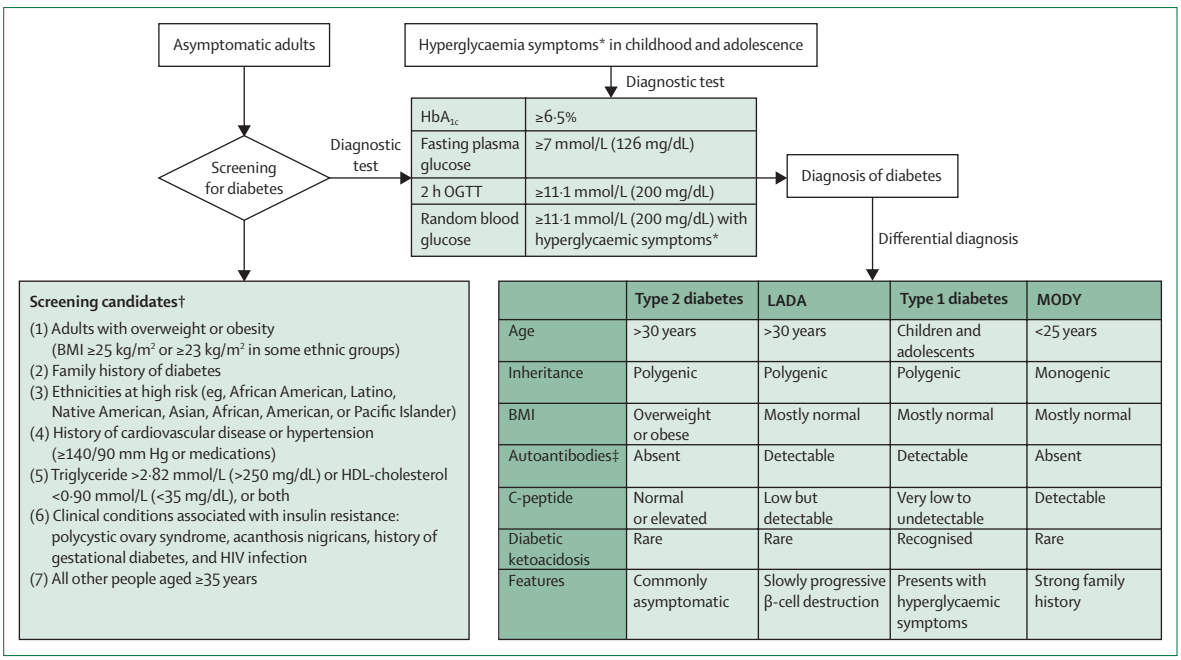


Figure 1: **The deleterious dozen: 12 pathophysiological defects contributing to β-cell failure in type 2 diabetes with therapeutic options for individual pathways**

↑=increase. ↓=decrease. DPP-4=dipeptidyl peptidase 4. GLP-1=glucagon-like peptide-1. IAPP=islet amyloid polypeptide. MRA=mineralocorticoid receptor antagonist. SGLT2=sodium-glucose cotransporter 2. *Not the primary mechanism of action.



	Type 2 diabetes	LADA	Type 1 diabetes	MODY
Age	>30 years	>30 years	Children and adolescents	<25 years
Inheritance	Polygenic	Polygenic	Polygenic	Monogenic
BMI	Overweight or obese	Mostly normal	Mostly normal	Mostly normal
Autoantibodies‡	Absent	Detectable	Detectable	Absent
C-peptide	Normal or elevated	Low but detectable	Very low to undetectable	Detectable
Diabetic ketoacidosis	Rare	Rare	Recognised	Rare
Features	Commonly asymptomatic	Slowly progressive β-cell destruction	Presents with hyperglycaemic symptoms	Strong family history

Figure 2: **Screening process for diabetes, its diagnostic criteria, and differential diagnosis**
HDL=high-density lipoprotein. LADA=latent autoimmune diabetes in adults. MODY=maturity-onset diabetes of the young. OGTT=oral glucose tolerance test. *Polyuria, polydipsia, polyphagia, or weight loss. †Modified from *Standards of Medical Care in Diabetes—2022*.[21] ‡Glutamic acid decarboxylase, islet tyrosine phosphatase 2, and zinc transporter-8.

example, with increased risk of diabetic ketoacidosis.[24] Unlike LADA, this condition is not associated with GAD antibodies and occurs most commonly in men with overweight.[25] This type is often seen in African populations who require insulin during acute illnesses and hospital admissions. However, ketosis-prone diabetes can be managed with diet or oral glucose-lowering therapies under most circumstances.[25] If diagnostic uncertainty persists, the condition should not be labelled as either type 1 diabetes or type 2 diabetes until diagnosis is confirmed, while safely managing glycaemic control.

Subtypes of type 2 diabetes

In clinical practice, the diagnosis of type 2 diabetes is focused on specific phenotypic characteristics, such as BMI, or is made once other types of diabetes have been excluded. Use of precision medicine models, including biogenetics, might aid in diagnosis and management of subtypes of type 2 diabetes.

A Swedish model analysed data from a cohort of more than 20 000 people from Scania County with newly diagnosed diabetes. The model identified five subtypes using clinical variables on the basis of the understanding that diabetes develops when insulin secretion does not meet the demands of insulin resistance.[26] The variables included age of onset, BMI, HbA_{1c}, GAD antibody, β-cell function (homoeostasis model assessment [HOMA] for β-cell function; HOMA2-B), and insulin resistance (HOMA2-IR). The novel subtypes have different clinical characteristics, disease progression rates, and clinical outcomes (panel). The frequency of different subtypes varies across populations. Mild obesity-related diabetes and mild age-related diabetes have been identified as the main cluster in European populations and severe insulin-deficient diabetes (SIDD) has been identified as the predominant cluster in Asian populations, which tend to develop diabetes at a younger age and lower BMI than do Europeans.[26–28] Some subtypes, especially those

	HbA_{1c}*(%)	Fasting plasma glucose (mmol/L)	2 h glucose in oral glucose tolerance test (mmol/L)	Random blood glucose (mmol/L)
Diabetes	≥6·5	≥7	≥11·1	≥11·1 with symptoms
Prediabetes, range	6–6·4 (5·7–6·4†)	6·1–6·9 (impaired fasting glucose; 5·6–6·9†)	7·8–11 (impaired glucose tolerance)	..
No diabetes	<6 (<5·7†)	≤6	<7·8	..

HbA_{1c}=glycated haemoglobin. *In individuals without symptoms, HbA_{1c} should be repeated. HbA_{1c} alone should not be used for diagnosis in children or young adults (<18 years old), pregnant women, people with short duration of symptoms (<2 months), or in people with certain haematological disorders (eg, anaemia or haemoglobinopathies) causing rapid red blood cell turnover. †Stated in some guidelines, including American Diabetes Association.[22]

Table 1: **Diagnosis of diabetes**

Panel: **Characteristics of diabetes subtypes**

Type 1 diabetes or latent autoimmune diabetes in adults

Severe autoimmune diabetes (known as SAID)

- Positive glutamic acid decarboxylase (GAD) antibody
- Early onset
- Low BMI
- Low insulin secretion
- High glycated haemoglobin (HbA_{1c})
- Early requirement for insulin
- High prevalence of retinopathy

Type 2 diabetes

Severe insulin-deficient diabetes (known as SIDD)

- Negative GAD antibody but other features like SAID
- Low insulin secretion
- High HbA_{1c}
- Early requirement for insulin
- High prevalence of retinopathy and nephropathy

Severe insulin-resistant diabetes (known as SIRD)

- Obesity
- Insulin resistance
- Late onset
- Increased risk of kidney disease and fatty liver

Mild obesity-related diabetes (known as MOD)

- Obesity
- Lack of insulin resistance
- Early onset

Mild age-related diabetes (known as MARD)

- Late onset
- Low risk of complications

predominant in Asian populations like SIDD, are associated with high risk of complications.[26]

Other approaches to phenotyping and characterising subtypes of type 2 diabetes have also been proposed,[29,30] but further research is need to help clarify the best methods to identify different subtypes of type 2 diabetes.

Long-term complications of type 2 diabetes

Type 2 diabetes is associated with increased risk of both microvascular (ie, retinopathy, neuropathy, and nephropathy) and macrovascular (ie, ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) complications. Long duration of diabetes, suboptimal glycaemic control, increased glycaemic variability, male sex, underlying comorbidities, and pre-existing complications such as albuminuria or subclinical atherosclerosis are all associated with increased risk of microvascular and macrovascular complications in people with type 2 diabetes.[31–33] These complications of diabetes can impose substantial socioeconomic burden and affect quality of life.[34] The UK Prospective Diabetes Study (UKPDS)[35] and several subsequent studies[36,37] have shown that achieving intensive glycaemic control, especially early intervention, could have a clinically significant impact in reducing the risk of future complications. By contrast, intensification of glucose-lowering therapy at a later stage in people with long duration of type 2 diabetes might not be beneficial[38–40] and, in fact, might result in worse outcomes.[39] Benefits of glucose-lowering therapies persisted for years after the conclusion of the initial trial period in UKPDS, despite loss of earlier glycaemic between-group differences, an occurrence termed the legacy effect.[36]

Because of the multifactorial nature of type 2 diabetes, other modifiable risk factors, like hypertension and dyslipidaemia, should be addressed with a holistic approach, and not just glycaemic control, to reduce risk of long-term complications. The Steno-2 study[41] showed that multifactorial risk reduction targeting glycaemic, blood pressure, and lipid control in those with pre-existing microalbuminuria reduced both microvascular and macrovascular complications.

Prevention and delay of type 2 diabetes

Proactive management at an early stage in individuals at high risk is key to delaying or preventing type 2 diabetes. Considerable evidence shows that type 2 diabetes can be prevented, or its onset delayed, through lifestyle interventions (calorie-restricted diets and exercise) particularly targeting weight loss or by use of pharmacotherapy, including metformin, pioglitazone, and liraglutide.[42–45] Community-based cluster phenotyping might aid in identifying individuals at increased risk for type 2 diabetes and allow for efficient prevention strategies.[46]

Unfortunately, long-term effectiveness and adherence to all these interventions remain challenging,[47,48] particularly in low-income and middle-income countries.[49] There is an increasing emphasis in advanced health-care systems on the implementation of effective strategies for preventing type 2 diabetes through promotion of healthier lifestyle and working with food manufacturers and retailers to encourage healthy eating at national levels.[50] Risk assessment and then management of people at high risk (fasting plasma glucose of 5·5–6·9 mmol/L or HbA_{1c} of 6·0–6·4%) are the two key components of this strategy. Individuals who are overweight, with a BMI of 25 kg/m² or more (≥23 kg/m² in some ethnic groups), are encouraged to lose weight through diet, exercise, and pharmacotherapies. Use of modern technology, including use of wearable devices, might aid in delivering prevention programmes.[51,52] A systematic review assessed the effectiveness of different technology-driven programmes to prevent type 2 diabetes.[53] Digital features in these programmes comprised of diet and weight tracking, activity monitors, online coaching, social media, reminders, and gamification. The review found that these technology-driven programmes to be effective in both the short-term (≤6 months) and long-term (≥12 months).

Gestational diabetes is an established risk factor for developing type 2 diabetes. A meta-analysis has shown that future risk of type 2 diabetes is almost ten times

higher in women with previous gestational diabetes than in the healthy control group,[54] highlighting the need for effective prevention strategies during pregnancy and post partum. Lifestyle interventions and metformin have been trialled with variable success,[55–57] and the blended approaches including lifestyle and medications might be more useful to the needs and time restrictions of pregnant women. However, challenges remain for the successful implementation of prevention strategies, including person engagement, use of new technologies, assessment of weight loss interventions, development of risk models, and embracing of omics to help with individualised care plans to accelerate understanding of gestational diabetes.[58]

Glycaemic management

The consensus guidelines by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend a target HbA_{1c} of 7% or less for most adults with sufficient life expectancy for long-term benefits, particularly microvascular benefits.[59,60] Lower targets should only be aimed at otherwise stable people with type 2 diabetes if these targets can be achieved safely without hypoglycaemia or adverse effects of the therapies. The ADA and the EASD consensus[59,60] stress the need for a person-centred holistic approach to achieving glycaemic targets including weight reduction, control of cardiovascular risk factors, and cardiorenal protection. This shift from a glucocentric model to a more holistic approach aims to empower people living with diabetes. The consensus also stresses the need for diabetes self-management education. Such programmes are considered an integral part of routine care for type 2 diabetes.[61]

The 2022 ADA and EASD consensus report[59,60] emphasises the need for management of multiple comorbidities to reduce the burden of complications and improve quality of life as important goals of care. In addition, remission of type 2 diabetes should be a treatment goal for those newly diagnosed or with a short duration of type 2 diabetes.

Lifestyle management

Lifestyle management is considered first-line treatment in the management of type 2 diabetes. Several studies have confirmed that intensive lifestyle intervention, especially when accompanied by clinically significant weight loss, improves glycaemic control.[62,63]

Obesity is linked to multiple comorbidities including type 2 diabetes. More than 80% of people with type 2 diabetes are classified as overweight or obese.[64] Consequently, targeting weight loss is an effective means of reducing the metabolic burden of type 2 diabetes. Sustained weight loss of 5–10% can delay progression from a prediabetes state to diabetes.[42] Studies have shown that weight loss of at least 5% is required for beneficial effects on glycaemic control, and greater weight loss of 15% or more can induce diabetes remission in a large proportion of people with type 2 diabetes (HbA_{1c} to <6·5% for at least 3 months without any glucose-lowering therapies).[65,66] A key component of short-term diabetes remission is achieving adequate weight loss through use of restricted calorie intake in the form of either a low energy diet (800–1200 calories per day) or very low energy diets (<800 calories per day).[65,67] However, long-term adherence to such diets is challenging and many people regain weight.[68]

A balanced diet is a core component of lifestyle management in type 2 diabetes. Medical nutrition therapy delivered by dietitians is associated with improved glycaemic control across diverse ethnic groups.[69] Nutritional recommendations should be individualised, ongoing, and delivered by expert health-care providers. Self-management education should be specific to a person's needs and culturally sensitive.[70,71]

Low carbohydrate and low-glycaemic index diets, comprising mainly of non-starchy vegetables, wholegrains, and pulses, are advocated for prevention and management of type 2 diabetes.[70] Evidence exploring the effect of low-glycaemic index diets, such as Mediterranean diets, shows that this diet is associated with improvements in HbA_{1c} and bodyweight.[72–74] Calorie restriction is important for reduction in bodyweight and metabolic risk factors.[75]

Interest is increasing in exploring the effect of ketogenic diets and intermittent fasting on health outcomes of people with type 2 diabetes. Ketogenic diets consist of 90% of total daily calorie intake from fat and only 10% from proteins and carbohydrates,[76] whereas intermittent fasting is an eating pattern characterised by periods of negligible energy intake alternating with periods of ad-libitum feeding.[77] A meta-analysis showed that the ketogenic diets were associated with improvement in glycaemic control in the short-term only.[78] A decline in compliance was proposed as the primary reason for this. Similarly, a review of RCTs comparing intermittent fasting to continuous energy-restricted diet for people with type 2 diabetes did not find any difference in glycaemic control between the two groups.[79] There were also safety concerns including hypoglycaemia and hyperglycaemia with intermittent fasting. In summary, the full potential of these dietary approaches for type 2 diabetes is yet to be explored, and it is important to take a person-centred approach that is beneficial and sustainable for that individual.

Exercise should be part of routine management of type 2 diabetes due to the diverse cardiometabolic benefits beyond glycaemic control. These include improved insulin sensitivity and reduced visceral fat content.[80,81] A prospective intervention study showed that habitually active individuals who decreased their physical activity for 2 weeks accrued abdominal and liver fat and developed adverse metabolic features including insulin resistance and dyslipidaemia.[82] By contrast, randomised controlled

trials (RCTs) for diabetes prevention[42,83,84] have shown that moderate-to-vigorous physical activity (eg, brisk walking or swimming) has proven effective in the management of hyperglycaemia and cardiometabolic risk.

Regular engagement in exercise (both aerobic and resistance) elicits adaptations that can lead to improvements in clinical outcomes like diabetes prevention, reductions in abdominal and visceral fat, and mental wellbeing and a substantially lower cardiovascular and overall mortality risk.[85,86] The benefits of exercise are especially prominent for people currently doing less than 30 min of purposeful activity including work-related or recreational activity per week.[87] Breaking up prolonged sitting time with short regular bouts of slow walking and simple resistance exercises (eg, calf raises and squats) has been shown to improve glucose metabolism.[85] Smart watches or physical activity trackers with step counters are effective in supporting behaviour change through enabling goal setting and feedback.[88]

The most successful glycaemic outcomes were seen with exercise programmes that were multifactorial, including programmes that were structured, flexible, individually tailored, supervised with behavioural support, culturally appropriate, and made use of digital technology.[88–91] Exercise should be combined with dietary support for maximum benefits.[92]

Drug therapies

In many guidelines, metformin is considered first-line glucose-lowering therapy for management of type 2 diabetes.[59,60,93] Reasons for this recommendation include widespread availability, low cost, ease of administration, good tolerability, low risk of hypoglycaemia, weight neutrality, combination formulations, and importantly decades of experience with clinical effectiveness.[94] However, sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, with or without metformin, are appropriate initial therapy for individuals with established or who are at high risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[59,60,93]

Sulfonylurea and meglitinides have good glucose-lowering efficacy and are less expensive but they have unfavourable effects such as hypoglycaemia and weight gain. These agents might be recommended when cost and availability matters. Of note, glyburide or glipizide, which have high affinity for mitochondrial K_{ATP} channels, have shown increased risk of major adverse cardiovascular events (MACE) compared with gliclazide or glimepiride, which have lower affinity for K_{ATP}.[95]

Thiazolidinediones have durable glucose-lowering properties and improve insulin resistance with low risk of hypoglycaemia. The PROactive Study[96] exploring use of pioglitazone for secondary prevention of macrovascular events in people with type 2 diabetes showed reduction in composite macrovascular outcomes compared with placebo. However, adverse effects of pioglitazone, such as fluid retention, weight gain, heart failure, and decreased bone mineral density, should be considered when prescribing.

Since the mid-2000s, dipeptidyl peptidase 4 (DPP-4) inhibitors have been widely used because of their safety including low risk of hypoglycaemia, good tolerability, wide availability, and convenient dosing. However, their glucose-lowering efficacy is only modest and exerts neutral effect on weight.

Both SGLT2 inhibitors and GLP-1 receptor agonists have shown cardiorenal benefits in trials with weight loss and low risk of hypoglycaemia. International guidelines now recommend early use of these agents even before metformin in patients with established or at high risk of cardiovascular and renal diseases irrespective of baseline HbA_{1c}.[97,98] SGLT2 inhibitors are also now included in the WHO list of essential medications along with metformin, sulfonylureas, and insulin.[99] Noteworthy adverse effects of these agents include genital infection (SGLT2 inhibitors), gastrointestinal side-effects (GLP-1 receptor agonists), and increase in heart rate (GLP-1 receptor agonists).

Treatment intensification beyond metformin should be guided by presence of established or high-risk of cardiorenal comorbidities, including heart failure and chronic kidney disease, weight issues, and risk of hypoglycaemia.[59,60] The GRADE trial[100] assessed the relative effectiveness of the four common second-line glucose-lowering therapies after metformin, namely glimepiride, sitagliptin, liraglutide, and basal insulin glargine. The results show that after a mean follow-up of 5 years, all four medications, when added to metformin, reduced HbA_{1c} concentrations. However, glargine and liraglutide were significantly more effective in achieving and maintaining target HbA_{1c} concentrations of <7%. We have scarce evidence for combined use of both SGLT2 inhibitors and GLP-1 receptor agonists with early results showing additive glycaemic and metabolic benefits.[101–103] As these medications target different pathways in the deleterious dozen, preference should possibly be given to combinations of these agents to produce additive or synergistic effects that ultimately reduce risk of microvascular and macrovascular complications and improve cardiometabolic and renal outcomes.[104] However, dedicated RCTs are required to confirm these beneficial effects. In the VERIFY trial,[105] an initial combination therapy of metformin and vildagliptin provided greater and more durable long-term benefits than metformin monotherapy in people with newly diagnosed type 2 diabetes. Use of fixed-dose combinations can also facilitate improved medication-taking behaviour.[106]

Tirzepatide, a novel dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) analogue, has been approved by the US Food and Drug Authority (FDA) and European Medicines Agency for management of type 2 diabetes. Across the

SURPASS phase 3 programme[107–111] versus placebo and active comparators, including semaglutide, tirzepatide has shown superior dose-dependent reductions in HbA_{1c} (2–2·5%) and weight (11–13%), which is expected to further change the landscape of type 2 diabetes management.

Insulin therapy (both basal and bolus) remains an important part of glycaemic management of type 2 diabetes, especially in people who are struggling to meet glycaemic targets. The main advantage of insulin over other glucose-lowering therapies is that it lowers glucose in a dose-dependent manner to almost any glycaemic target; however, it comes with the disadvantage of weight gain, risk of hypoglycaemia, and frequent glucose monitoring.[60] Use of basal insulin is the preferred approach to initiating insulin therapy in people with type 2 diabetes. These can be combined with GLP-1 receptor agonists to reduce the risk of hypoglycaemia and weight gain.[59,60] Fixed-ratio combinations of GLP-1 receptor agonists and basal insulin give the option of convenience with fewer injections, increased efficacy, and reduced risk of side-effects.[59,60] A comprehensive approach to insulin therapy is provided in the ADA and EASD report for management of hyperglycaemia.[59,60] Details of the oral and injectable glucose-lowering therapies including commonly prescribed basal and bolus insulins are provided in tables 2 and 3.

Large cardiovascular and renal outcomes trials

The FDA requires all glucose-lowering therapies in development to undergo RCTs for cardiovascular outcomes to confirm their cardiovascular safety and to exclude risk of MACE. Cardiovascular outcome trials of DPP-4 inhibitors, such as alogliptin, sitagliptin, and linagliptin, have shown a neutral effect on MACE outcomes, with the exception of saxagliptin, which increased the risk of hospital admission for heart failure.[112] Among the nine cardiovascular outcome trials of GLP-1 receptor agonists, six trials of liraglutide (Novo Nordisk, Bagsvaerd, Denmark), both injectable and oral semaglutide (Novo Nordisk), albiglutide (GlaxoSmithKline, Brentford, UK), dulaglutide (Eli Lilly, Indianapolis, IN, USA), and efpeglenatide (Hanmi Pharmaceutical, Seoul, South Korea) have shown superiority in MACE.[113] In the cardiovascular outcome trials with SGLT2 inhibitors, empagliflozin, canagliflozin, dapagliflozin, and sotagliflozin have shown superiority in MACE, but ertugliflozin has not.[114] A forest plot showing the composite MACE outcomes for GLP-1 receptor agonists and SGLT2 inhibitors and further details about the individual trials of these novel agents are in the appendix (pp 2–5, 8–11).

GLP-1 receptor agonists, particularly dulaglutide and semaglutide, showed better results in stroke prevention than other glucose-lowering therapies.[115] GLP-1 receptor agonists have antioxidant and neuroprotective effects through upregulating vascular endothelial growth factor production[116] and reducing pro-inflammatory cytokine production,[117] suggesting that some GLP-1 receptor agonists have vasculoprotective properties, which might be the main mechanism of their beneficial effect on stroke prevention. A cardiovascular outcome trial of tirzepatide is also ongoing (SURPASS-CVOT; NCT04255433).

SGLT2 inhibitor therapy is effective in reducing hospitalisation for heart failure and progression of chronic kidney disease in patients with type 2 diabetes.[118] Some large trials showed a reduction in hospitalisation for heart failure and renal complications by more than 30% with SGLT2 inhibitor therapy (appendix p 6). The reduction in these outcomes occurred within 6 months, and these reductions were also seen in people without type 2 diabetes, which suggests that the cardiovascular and renal benefits driven by SGLT2 inhibitors might be induced through its haemodynamic effects rather than glucose-lowering effects.[119]

Because of the beneficial effects of GLP-1 receptor agonists and SGLT2 inhibitor therapies beyond glycaemic management,[120,121] guidelines now recommend early addition of these agents in people with established cardiorenal disease or at high risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[59,60,122]

Management beyond glycaemic control

Obesity management

Type 2 diabetes and obesity are interconnected, heterogeneous diseases that share many pathophysiological mechanisms including ectopic adiposity, insulin resistance, inflammation, and β-cell dysfunction.[66] However, much remains unknown about the relationship between obesity and type 2 diabetes, including the fundamental pathophysiological mechanism to explain how overnutrition and chronic adipose tissue accumulation predispose to insulin resistance, β-cell dysfunction, and ultimately type 2 diabetes. Not everyone classed as overweight or obese will develop type 2 diabetes;[123] similarly, people with a so-called healthy weight can be diagnosed with type 2 diabetes, suggesting that other factors have a role in pathogenesis. There is also little evidence that weight loss, per se, improves patient-relevant outcomes or premature death from cardiovascular disease in people with type 2 diabetes.[62,124]

Recent advances add to our understanding of the biological mechanisms underpinning this relationship and might provide important insight into future clinical applications. Hereditability of obesity and type 2 diabetes is reportedly in the range of 30–70%, suggesting substantial genetic influence in disease susceptibility.[125,126] Awareness of inherited risk through polygenic scoring could allow earlier identification of individuals at high risk, and provide targeted management.[127]

With better understanding of biological mechanisms, pharmacotherapies targeting pathways common to both obesity and type 2 diabetes are improving in efficacy. Liraglutide 3·0 mg once daily[128] and semaglutide 2·4 mg

	Medications	Primary mechanism of action	Advantages	Common side-effects or disadvantages	Additional notes
Biguanide	Metformin	Decrease hepatic glucose production and output, insulin sensitiser	Long-term safety and efficacy data, no hypoglycaemia, weight neutral or loss, low cost, and can be combined safely with most other glucose-lowering therapies	Gastrointestinal symptoms, lactic acidosis (rare), and vitamin B12 deficiency	Contraindicated if eGFR is <30 mL/min per 1·73m^2; gastrointestinal side-effects can be reduced with gradual dose titration or using slow-release formulation
Sulfonylurea	Glibenclamide (also known as glyburide), glipizide, gliclazide, and glimepiride	Stimulate release of insulin from β cells of pancreas (insulin secretagogues)	Extensive experience, widely available, low cost, and effective glucose-lowering properties	Risk of hypoglycaemia, weight gain, and no cardiovascular benefits	Gliclazide and glipizide are associated with less risk of hypoglycaemia than are older generation of sulfonylureas like glibenclamide; glyburide or glipizide that has high affinity for mitochondrial K_{ATP} channel showed increased risk of cardiovascular events compared with gliclazide or glimepiride with low affinity
Thiazolidinedione (PPAR-γ agonist)	Pioglitazone, lobeglitazone, and rosiglitazone	Insulin sensitiser	No hypoglycaemia, low cost, widely available, and effective in fatty liver disease	Weight gain, fluid retention, heart failure, and increased risk of fractures	Rosiglitazone is rarely used now due to increased risk of adverse cardiovascular outcomes
Meglitinide	Repaglinide, nateglinide, and mitiglinide	Short-acting insulin secretagogues	Shorter duration of action, less hypoglycaemia than sulfonylureas, and flexible dosing	Hypoglycaemia and weight gain	Because of quick onset, can be used as an option in people who need meal-related blood glucose control like fasting patients or shift workers
α-glucosidase inhibitor	Acarbose, voglibose, and miglitol	Delays digestion and absorption of glucose from the gastrointestinal tract	Low hypoglycaemia, decrease post-prandial rise in blood glucose, low cost, and cardiovascular safety	Gastrointestinal side-effects like diarrhoea and flatulence	Non-systemic mechanism of action
DPP-4 inhibitor (gliptin)	Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, gemigliptin, teneligliptin, anagliptin, and evogliptin	Increase insulin secretion and decrease glucagon secretion	No hypoglycaemia, weight neutral, good tolerability, and simple dose scheduling	Angioedema, acute pancreatitis, and increased risk of heart failure with saxagliptin	No dose adjustment is needed in people with renal impairment for linagliptin, gemigliptin, teneligliptin, and evogliptin
SGLT2 inhibitor (gliflozin)	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and sotagliflozin	Increase urinary excretion of glucose via kidneys	No hypoglycaemia, weight reduction, heart failure benefits, CKD benefits including albuminuria, reduce blood pressure, and decrease major adverse cardiovascular events in cardiovascular outcome trials	Genital tract infection, risk of dehydration, euglycaemic ketoacidosis, Fournier's gangrene, and fracture and amputation (canagliflozin in CANVAS trial)	Dapagliflozin and empagliflozin have proven heart failure and CKD benefits even in people without type 2 diabetes; dapagliflozin is approved for use in CKD with eGFR ≥15 mL/min per 1·73 m^2; canagliflozin approved for use in CKD with eGFR ≥30 mL/min per 1·73 m^2
GLP-1 receptor agonist	Exenatide lixisenatide, albiglutide, liraglutide, semaglutide, dulaglutide, efpeglenatide, and tirzepatide	Increase insulin secretion and reduce glucagon secretion, reduce gastric emptying, and promote satiety mainly by binding to receptors in the hypothalamus and hindbrain	No hypoglycaemia, weight reduction, and cardiovascular benefits (except lixisenatide)	Gastrointestinal side-effects, acute pancreatitis, and contraindicated if medullary carcinoma of thyroid	Lixisenatide is short acting; albiglutide is withdrawn; semaglutide, dulaglutide, efpeglenatide, and tirzepatide are weekly injections; semaglutide is available in oral formulation; higher doses of liraglutide 3 mg daily and semaglutide 2·4 mg weekly are approved for obesity management; tirzepatide has been approved for the treatment of adults with type 2 diabetes (May, 2022) and is the first commercially licensed dual GLP-1 and GIP agonist
Fixed-dose combination of GLP-1 receptor agonist and long-acting insulin	Lixisenatide plus insulin glargine, liraglutide plus insulin degludec	Combined benefit of GLP-1 receptor agonist and basal insulin therapy	Less weight gain than insulin therapy alone	High cost, less flexibility in dosing, and risk of hypoglycaemia	Can be considered a good alternate in people who prefer fewer injections than separate injections

CKD=chronic kidney disease. DPP-4=dipeptidyl peptidase-4. eGFR=estimated glomerular filtration rate. GIP=glucose-dependent insulinotropic polypeptide. GLP-1=glucagon-like peptide-1. K_{ATP}, ATP-sensitive potassium channel. PPAR-γ=peroxisome proliferator-activated receptor-γ. SGLT2=sodium-glucose cotransporter-2.

***Table 2*: Non-insulin, glucose-lowering therapies (oral and injectable) routinely used in the management of type 2 diabetes**

once weekly[129] have been approved by both FDA and National Institute for Health and Care Excellence for chronic weight management in people with obesity. Tirzepatide[130] has shown significant weight loss efficacy with all doses at 72 weeks in people with obesity but without type 2 diabetes (–15·0% with 5 mg weekly doses, –19·5% with 10 mg doses, and –20·9% with 15 mg doses compared with –3·1% for placebo). Metabolic surgery is the most effective means of achieving the amount of sustained weight loss required to affect

	Names of insulin in the class	Peak onset (h)	Duration of action (h)	Timing with relation to meals	Additional notes
Ultra rapid acting (bolus insulins)	Faster acting insulin aspart (Fiasp; Novo Nordisk, Bagsvaerd, Denmark) and ultra-rapid lispro insulin (Lyumjev; Eli Lilly, Indianapolis, IN, USA)	1–2	4–6	Can be taken at the start of meal or within 20 min of starting a meal	Allows flexibility in relation to meals
Rapid acting (bolus insulins)	Aspart, lispro (U100, U200), and glulisine	1–3	2–5	5–15 min before meal	These insulin formulations are used to provide cover for post-prandial rise in blood glucose
Short acting	Human regular (U100, U500)	1–5	5–9	15–30 min before meal	Also used as subcutaneous infusions in diabetic ketoacidosis or hyperglycaemic hyperosmolar state management
Intermediate acting (basal insulin)	Human Neutral Protamine Hagedorn	2–12	12–24	Usually used as basal insulin once or twice daily	Cloudy insulin preparation, most other formulations are clear
Long acting (basal insulins)	Degludec (U100, U200), detemir, and glargine (U100, U300) including biosimilar insulins	Mostly peakless insulins, except detemir (6–14)	16–42	Usually once or twice daily	An advantage is they are usually once daily injections; weekly insulin preparations (Icodec and basal insulin Fc) are in the pipeline
Premixed	Varying proportions of short-acting or rapid-acting and intermediate-acting insulins (25:75, 30:70, and 50:50 formulations are commercially available)	1–4	12–24	10–30 min before meals depending upon formulation	Mostly preferred for people who have a fixed lifestyle with meals twice daily

Insulins work by increasing uptake of glucose in the target organs, mainly skeletal muscles. Dose of the insulins can be adjusted to the glycaemic target and all carry the risk of hypoglycaemia and weight gain. U=concentration of insulin formulation in units (eg, U100 means 100 units per mL of insulin solution).

Table 3: **Insulin formulations commonly used in treatment of type 2 diabetes**

long-term outcomes. It is an invasive procedure and associated with complications including nutritional deficiencies and post-prandial hypoglycaemia. The procedure is an important addition to pharmacotherapy and lifestyle intervention options and is the right approach in some patients.[131]

Physical dysfunction and frailty in people with type 2 diabetes

Type 2 diabetes increases biological ageing and leads to early-onset frailty, consequently leading to impaired physical function and reduced quality of life.[132] Data from the Chronotype of Patients with Type 2 Diabetes and Effect on Glycaemic Control cross-sectional study[133] showed that nearly a third of people with type 2 diabetes have some impairment of physical function. Risk of frailty and decline in physical function are strongly associated with obesity, poor glycaemic control, longer duration of diabetes, and comorbidities like hypertension.[134] Assessment of frailty and physical function in management of type 2 diabetes is rarely undertaken in clinical practice and there is a need to develop reliable point-of-care tools for assessment of these variables.

Sarcopenic obesity, characterised by low functional capacity of muscles in the presence of adiposity despite large muscle mass,[135] is a feature of type 2 diabetes and one of the main reasons for decline in physical function. The pathogenesis of sarcopenic obesity includes ageing, physical inactivity, malnutrition, low-grade inflammation, insulin resistance, and hormonal changes,[135] which are also common risk factors for type 2 diabetes. Interventions like multicomponent exercise, which improve muscle function, could be used to improve this condition and quality of life in people with type 2 diabetes.[136,137]

The precise effect of different glucose-lowering therapies on physical function and frailty is unknown. Novel agents, SGLT2 inhibitors, and GLP-1 receptor agonists not only induce weight loss but exert pleiotropic metabolic effects, which could mean an improvement in physical function. However, 20–50% of total weight loss achieved by the use of these agents consists of lean body mass,[138] which could adversely affect some of the potential benefits realised. Hence, there is a need for dedicated trials to explore the exact effect of these therapies, including combination therapies on physical function.[132] The implications of glucose-lowering therapies should also be considered when prescribing for a frail, older population, including risk of hypoglycaemia, glycaemic targets, and complexity of regimen.[139]

Sleep behaviours

Type 2 diabetes is associated with poor sleep hygiene, including insomnia.[140] Poor sleep quality, such as short sleep duration, sleep fragmentation, and variability, is associated with increased risk of type 2 diabetes and obesity.[141–143] Both duration and timing of sleep (chronotypes) can have a major impact on the risk of type 2 diabetes,[144] with evening chronotypes (ie, go to bed late and get up late) at a higher risk of type 2 diabetes than are morning chronotypes (ie, early to bed and early to rise).[145] This effect is primarily driven by clustering of unhealthy behaviours—probably sedentary lifestyle, higher BMI, and hypertension. Poor sleep patterns are also associated with impaired quality of life.[146,147] Non-pharmacological therapies, such as structured sleep education programmes, behavioural therapy, and exercise, can improve sleep hygiene in people with type 2 diabetes.[147–151]

Obstructive sleep apnoea frequently coexists in people with type 2 diabetes and contributes to poor sleep quality.[152] It is recognised as a risk factor for type 2 diabetes and obesity,[153,154] and nearly 50% of people with type 2 diabetes have obstructive sleep apnoea.[155] Consequently, it is important to screen for obstructive sleep apnoea with validated questionnaires.[156] Use of continuous positive airway pressure has been found to improve insulin resistance in people without diabetes and might lead to a trend in decrease in insulin resistance in people with diabetes.[157] As weight loss improves obstructive sleep apnoea, the use of glucose-lowering therapies associated with weight loss is also expected to improve it. SGLT2 inhibitors have been shown to reduce the incidence of obstructive sleep apnoea.[158,159] However, as weight loss with SGLT2 inhibitors is only modest, other factors, including decrease in cardiac preload and beneficial effects on respiratory dynamics, might also be responsible.[159] Similarly, liraglutide therapy showed significant improvement in the apnoea–hypopnea index.[160]

Mental wellbeing and depression

Like many chronic medical conditions, type 2 diabetes is strongly linked to depression. Almost one in four people with type 2 diabetes experience depression at some point.[161] This increased risk is related to female sex, socioeconomic status, complications, and metabolic control including obesity.[162,163] If left untreated, depression can have a major detrimental impact on both physical and mental wellbeing, including cognitive function and self-management of diabetes.[164–166] Moreover, people with type 2 diabetes and depression are at increased risk of cardiovascular mortality and morbidity.[167] Timely recognition and therapy, either in the form of psychotherapy, group therapy, lifestyle intervention, or pharmacotherapy, are crucial to reducing the growing burden of depression in people with type 2 diabetes.[168,169] There is evidence that use of GLP-1 receptor agonist therapy is associated with slowing of cognitive decline in people with type 2 diabetes.[170,171] Further studies are, however, needed to understand these relationships.

Emerging populations in diabetes management

Early-onset type 2 diabetes

The incidence and prevalence of type 2 diabetes in young people (aged 40 years or younger) is rising globally. Rates vary widely depending upon the age, sex, and ethnicity of the study population and geography, resulting in an incidence range of 0–330 cases per 100 000 person-years and a prevalence rate of 0–5300 cases per 100 000 children and adolescents.[172] Early-onset type 2 diabetes represents a more aggressive metabolic phenotype,[173] and is associated with increased insulin resistance, early β-cell failure, and earlier onset of complications.[174,175] One study showed that nearly 60% of individuals with early-onset type 2 diabetes have at least one complication by early adulthood.[176] Furthermore, complication rates are high in people from minority ethnic groups and individuals with lower income.[177] Few treatment options are explored for young people with type 2 diabetes because of limited long-term safety data.[174] Novel treatment approaches and innovative study designs are needed to address these concerns as currently only few trials have assessed the safety and efficacy of glucose-lowering therapies in people younger than 40 years of age.[174,178,179] ADA and EASD[59,60] both now recommend early combination therapy in young people (aged <40 years) with type 2 diabetes.

Ethnicity, diversity, cultural, and religious considerations

The risk and burden of vascular complications in type 2 diabetes is underestimated in women.[180,181] UK studies have consistently shown that women are less likely to meet quality targets for risk factor control than are men.[181–183] Women are also under-represented in cardiovascular outcome trials assessing the safety of glucose-lowering therapies.[184] Similarly, health research often does not understand and address the needs of minority ethnic groups,[185] even though these groups present with higher metabolic risk even at lower BMI with earlier-onset of type 2 diabetes and rapid progression to diabetes-related complications.[186,187] Thus an aggressive approach to not only early diagnosis and management is needed in people from minority ethnic groups but it is equally important to ensure their inclusion in clinical research through robust designs.

Cultural and religious views must be taken into consideration when making management decisions (eg, allowing flexibility during Ramadan). Ensuring safe fasting can be challenging for several reasons: increased risk of hypoglycaemia during the fasting hours, hyperglycaemia after the fast, alterations in physical activity, changes in sleeping patterns, and socioeconomic and cultural differences.[188] To reduce risk of complications during Ramadan, treatment goals for Ramadan should

be mutually agreed and use of novel glucose-lowering therapies considered well in advance during the pre-Ramadan counselling.[189]

COVID-19 pandemic and the effect on people with type 2 diabetes

The COVID-19 pandemic has adversely affected global health-care systems, causing disruptions in health-care delivery services and reduced frequency of contact with health-care providers.[190] It has also altered the social environment toward unhealthy lifestyles such as decrease in physical activity and increase in unhealthy food consumption,[191] which have influenced cardiometabolic factors in a negative way.[192]

People with type 2 diabetes, especially with obesity and cardiorenal comorbidities, are at high risk of severe infection, high morbidity, and mortality.[193] Several pathophysiological mechanisms underlie this relationship,[194] including effects on glucose dysregulation, inflammation, and activation of the renin–angiotensin–aldosterone system.[194,195] Hyperglycaemia also affects immune function; conversely, a dysregulated immunological status is linked to diabetic complications, potentially explaining the poor prognosis of patients with diabetes and COVID-19 (appendix p 12).[196,197]

In terms of the prescription of glucose-lowering therapies during the pandemic, a large observational study, found no specific associations between the use of specific glucose-lowering therapies and COVID-19-related mortality.[198] Although use of SGLT2 inhibitors is usually discouraged in severely ill people, in the DARE-19 trial,[199] dapagliflozin therapy was well tolerated in hospitalised patients with COVID-19. Taken together, there is no clear indication to change glucose-lowering therapies in patients with COVID-19.

Metabolic dysfunction-associated fatty liver disease (MAFLD)

MAFLD is a phenotype of cardiometabolic syndrome and is fundamentally linked to cardiovascular and hepatic outcomes.[200] The term MAFLD stresses a causal relationship between impaired glucose metabolism and the initiation and progression of fatty liver disease.[200–202] Therefore, it is reasonable to explore the potential therapeutic efficacy of SGLT2 inhibitors and GLP-1 receptor agonists, as they reduce bodyweight in addition to improving glycaemic control.[203] Preliminary evidence from clinical trials shows that these therapies can reduce intrahepatic triacylglycerol accumulation and prevent progression of hepatic fibrosis.[204,205] Because neither SGLT2 nor GLP-1 receptors are expressed in the liver, these agents have indirect mechanisms interfering with the pathophysiology of MAFLD, including:[206,207] (1) contribution of weight loss and associated improvements in insulin sensitivity; (2) adipokine-mediated and cytokine-mediated anti-inflammatory, antifibrotic, and antioxidant effects; (3) alterations in hepatic substrate supply (glucose and free fatty acids) and ketone body metabolism; and (4) changes in microbiota (mainly GLP-1 receptor agonist). Tirzepatide has also shown significant reductions in liver fat content compared with insulin degludec in people with type 2 diabetes and a fatty liver index of at least 60 in the SURPASS-3 study.[109]

Substantial evidence also supports the beneficial effects of thiazolidinediones for the alleviation or mitigation of fatty liver disorders. In an RCT involving people with biopsy-proven non-alcoholic steatohepatitis (NASH or MAFLD), pioglitazone 45 mg daily for 6 months significantly improved insulin sensitivity, hepatic steatosis, ballooning necrosis, and inflammation.[208] Another RCT showed that more than half of patients with NASH and glucose dysregulation had a significant reduction in fatty liver activity score and histological improvement with 18-month pioglitazone treatment.[209] However, only a few licensed medications are approved for MAFLD.[210]

Challenges and future directions of type 2 diabetes management

Clinical inertia

Clinical or therapeutic inertia is defined as health-care providers not initiating, intensifying, or deintensifying therapy when indicated. Despite encouragement to consider early addition of novel agents in people with elevated risk of cardiorenal disease, irrespective of glycaemic control, the uptake of these agents remains generally low, especially at the primary or community care level.[211] A global survey of 1677 health-care providers showed that 67% of the respondents were aware of the published cardiovascular outcome trial data for novel glucose-lowering therapies, and 81·6% agreed that early intensification is associated with clinical benefits; however, 46·1% would reserve these therapies for late stage only.[212] Similarly, risk of overtreatment with conventional older agents, particularly sulfonylureas, which increase risk of hypoglycaemia, remains a concern.[213]

Clinical inertia is a multifactorial problem with issues at the level of the prescribers, patients, and health-care systems, including reduced frequency of clinical consultations, higher costs, and medications availability issues.[214] The solution is also multifactorial, involving multidisciplinary care approaches through patient-focused interventions. A 2021 meta-analysis showed that the most effective approaches to mitigating clinical inertia are those involving non-physician providers such as nurses and pharmacists in partnership with health-care providers, supported by appropriate guidelines and collaborative work.[215]

Use of technology in management of type 2 diabetes

Technology offers benefits extending beyond glucose management, including remote monitoring and patient empowerment. There is a growing interest in use of telehealth, including virtual consultations,[216] which has the potential to improve health services and patient

satisfaction. Use of wearable technology, like physical activity monitors and calorie counting apps, can provide insight into the lifestyle behaviours.[217,218]

Use of continuous glucose monitoring systems, including flash glucose monitoring (FGM) and automated insulin delivery devices, is mostly restricted to type 1 diabetes. However, because of the emerging evidence, this technology will probably expand to type 2 diabetes. A study in people with type 2 diabetes using insulin showed that use of FGM was associated with significant reduction in HbA_{1c} along with improvement in treatment satisfaction and perceived frequency of hypoglycaemia.[219] The REPLACE study[220] assessed the use of FGM as a replacement for self-monitoring of blood glucose in people with type 2 diabetes and showed a significant reduction in HbA_{1c} for young participants (<65 years of age) with improved treatment satisfaction. There is an increasing advocacy for use of FGM in people with type 2 diabetes requiring intensive insulin therapy.[221]

The use of continuous subcutaneous insulin infusion or insulin pump therapy is not yet advocated in people with type 2 diabetes and only little evidence is available.[222,223] Combining continuous glucose monitoring systems with continuous subcutaneous insulin infusion, also known as closed-loop systems or an artificial pancreas, has been proposed as a viable long-term solution for people with type 1 diabetes.[224] Again, there are scarce data available for these interventions in people with type 2 diabetes because of different pathophysiological mechanisms and availability of alternate non-insulin therapies.

Precision medicine and future therapeutic options

As a multifactorial heterogeneous disease, the development of type 2 diabetes involves a confluence of susceptible genetic and predisposing environmental factors. With advances in genome-wide association studies (GWAS), around 400 genetic variants associated with type 2 diabetes have been identified.[225,226] Many of these variants also have strong genetic correlation with cardiometabolic traits such as obesity, hypertriglyceridaemia, coronary artery disease, unhealthy sleeping behaviours, and depression.[227] However, many are low-frequency, rare variants and their contribution to overall disease risk and burden is not fully understood.

GWAS could aid in developing precision medicine models in type 2 diabetes, in which an individual's own genetic data could aid in prevention, diagnosis, and development of targeted therapies. Using GWAS, a large UK biobank study has identified 202 independent genetic variants associated with higher waist-to-hip ratio.[228] The study found that hip-specific polygenic scores were specifically associated with lower gluteofemoral and waist-specific polygenic scores with higher abdominal fat. However, to implement precision medicine in type 2 diabetes, not only a better understanding of genomics is required, but it will be imperative to integrate other types of omics, including epigenomics, proteomics, metabolomics, and pharmacogenomics, into the precision medicine model of type 2 diabetes.[229] Also, large scale studies are needed to show the full potential and clinical benefit of such approaches. The future role of precision medicine in diabetes management is also acknowledged by the ADA, and the Precision Medicine in Diabetes Initiative was launched by the ADA in 2018, in partnership with the EASD.[10]

Targeting the key therapeutic pathways and organs, such as the brain, kidneys, and particularly the gastrointestinal system, which has an important role in glucose regulation, could be possible.[230] Artificial intelligence might also aid in precise repurposing or reprofiling of therapies in management of type 2 diabetes, by matching patients to their optimal drug combinations with techniques like large-scale prediction models.

Several agents that mimic the action of gut hormones and thus regulate appetite and weight are in development. In this regard, dual agonists, including combinations of GLP-1 receptor agonist and GIP or triple agonist such as GLP-1 receptor agonist–GIP–glucagon, and long-acting amylin derivatives are all in different development phases with promising early results and are likely to have key roles in the near future. In healthy volunteers, a GLP-1–GIP–glucagon triple agonist (SAR441255; Sanofi, Bridgewater, NJ, USA) improved glycaemic control with good tolerability.[231] The results show that integrating glucagon receptor agonism might be able to induce greater weight loss and better glycaemic control. In a 2021 RCT, treatment with cagrilintide, a once-weekly amylin analogue, led to significant reductions in bodyweight in people with overweight and obesity.[232] Based on these findings, various combinations such as GLP-1–GIP (NCT04153929), GLP-1–amylin derivative (NCT04982575, NCT05394519, and NCT04940078), or GLP-1–GIP–glucagon receptor agonist (NCT03744182) are under clinical trials for obesity management and glucose control.

Oral and novel insulins (also called smart insulins), which have shown promising results in the trials, are also expected to become available in the near future.[233] An RCT comparing a weekly insulin preparation (icodec) to glargine in people with type 2 diabetes showed similar efficacy and safety, including risk of hypoglycaemia between the two preparations.[234] Similarly, basal insulin Fc is another novel, once-weekly insulin in development that combines Fc, a fusion protein, with human immunoglobulin G,[235] and in early trials showed lower risk of hypoglycaemia than insulin degludec with similar glycaemic efficacy.[236]

Contributors

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