



Advances in the management of type 2 diabetes in adults

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ABSTRACT

Type 2 diabetes is a chronic and progressive cardiometabolic disorder that affects more than 10% of adults worldwide and is a major cause of morbidity, mortality, disability, and high costs. Over the past decade, the pattern of management of diabetes has shifted from a predominantly glucose centric approach, focused on lowering levels of haemoglobin A_{1c} (HbA_{1c}), to a directed complications centric approach, aimed at preventing short term and long term complications of diabetes, and a pathogenesis centric approach, which looks at the underlying metabolic dysfunction of excess adiposity that both causes and complicates the management of diabetes. In this review, we discuss the latest advances in patient centred care for type 2 diabetes, focusing on drug and non-drug approaches to reducing the risks of complications of diabetes in adults. We also discuss the effects of social determinants of health on the management of diabetes, particularly as they affect the treatment of hyperglycaemia in type 2 diabetes.

Introduction

Diabetes, a chronic and progressive cardiometabolic disorder, is a major cause of morbidity, disability, and mortality worldwide. Comprehensive person centred management of diabetes requires attention to glycaemic control and risk factors for cardiovascular disease (hyperlipidaemia, hypertension, and tobacco use), weight management, early detection and treatment of microvascular, macrovascular, and metabolic complications of diabetes and mental health concerns, mitigation of burden of treatment, addressing social determinants of health, and improving quality of life.¹ The past decade has seen multiple developments in each aspect of the management of diabetes. This review focuses specifically on recent advances in the management of hyperglycaemia in diabetes, including drug and non-drug treatments. People with diabetes, caregivers, clinicians, health systems, payers, and policy makers need to appreciate the complexity and cost associated with optimal care of diabetes to meaningfully improve the health and well being of people living with diabetes.

Epidemiology

The current prevalence of diabetes among adults is 10.5% worldwide (536.6 million adults), with marked variation across regions and countries, and is estimated to reach 12.2% (783.2 million adults) by 2045.² Diabetes is more prevalent in

high income (11.1%) and middle income (10.8%) countries than in low income countries (5.5%). The prevalence of diabetes is rising everywhere, most rapidly in middle income countries where the prevalence is expected to reach 13.1% by 2045,² probably because of changing diet and lifestyle factors, rising rates of obesity, inadequate resources for early diagnosis and prevention, and potentially greater genetic or epigenetic susceptibility arising from inadequate fetal and childhood nutrition. Data for low and middle income countries are likely to be underestimated because of barriers to screening and timely diagnosis.

More than 90% of people with diabetes have type 2 diabetes,³ characterised by insulin resistance and progressive beta cell failure, and commonly associated with other cardiometabolic disorders, including obesity, hypertension, cardiovascular disease, and hepatic steatosis. Diabetes contributed to 6.7 million deaths in 2021 alone,⁴ highlighting the urgency of preventing diabetes and optimising its management to improve health outcomes and quality of life for all people at risk of or with the disease.¹

Sources and selection criteria

We searched PubMed for articles published in English. We prioritised randomised controlled trials, clinical guidelines, consensus statements, and systematic reviews. Search terms were: ((type 2 diabetes mellitus AND management (medical subject headings (MeSH) terms)) AND (type 2 diabetes mellitus (MeSH terms))) AND (care management, patient (MeSH terms)). Filters applied were: clinical trial, guideline, meta-analysis, practice guideline, randomised controlled trial, and systematic review, from 1 January 2013 to 1 January 2023. The reference lists of these articles were screened for relevant publications.

Goals and targets of management of type 2 diabetes

The primary objectives of the management of diabetes are to reduce the incidence and burden of complications and to improve quality of life (figure 1). Historically, these objectives were pursued through control of hyperglycaemia. In this glucose centric approach, clinical practice guidelines recommend targeting haemoglobin A_{1c} (HbA_{1c}) concentrations at <7% (53 mmol/mol) or <6.5% (47.5 mmol/mol) and, more recently, continuous glucose monitoring time in range >70% for most non-pregnant adults with type 2 diabetes, with lower or higher glycaemic thresholds individualised for each person.⁵⁻⁷ These recommendations for levels of HbA_{1c} come from data from randomised controlled trials showing a reduction in microvascular complications with more

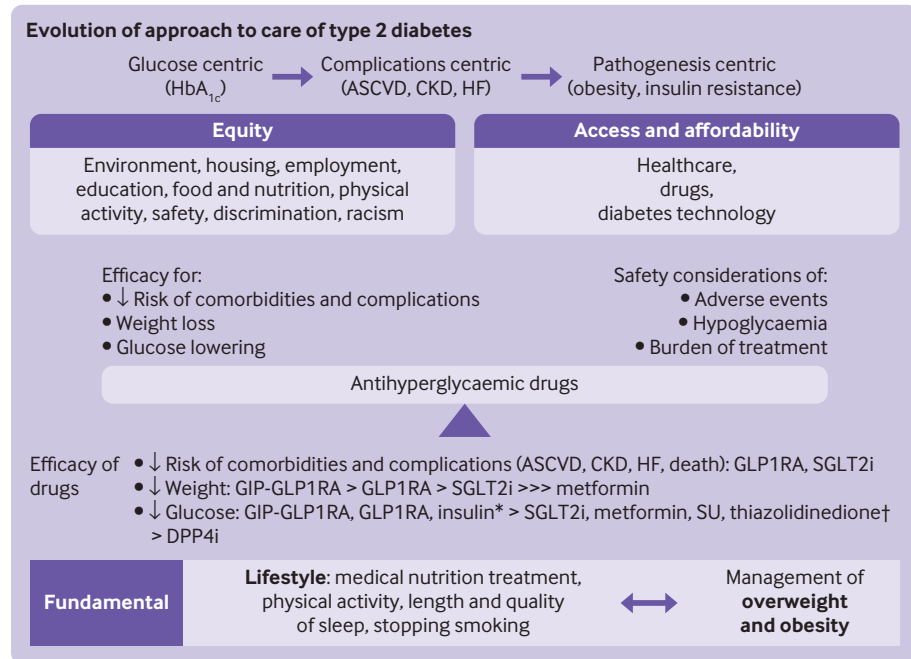


Figure 1 | Shifting pattern of management of type 2 diabetes. HbA_{1c}=haemoglobin A_{1c}; ASCVD=atherosclerotic cardiovascular disease; CKD=chronic kidney disease; HF=heart failure; GIP=glucose dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium glucose cotransporter 2 inhibitor; SU=sulfonylurea; DPP4i=dipeptidyl peptidase 4 inhibitor. *Insulin is preferred for acute management of severe hyperglycaemia; †Thiazolidinediones improve insulin resistance

intensive glycaemic control,^{8–12} although data for the association between time in range and risk of complications of chronic diabetes are limited but emerging.¹³ Implementation of glycaemic targets based on continuous glucose monitoring has also been limited by gaps in insurance coverage and accessibility, although continuous glucose monitoring is increasingly recommended for and used by people with type 2 diabetes.^{14 15}

Randomised controlled trials of older antihyperglycaemic treatments, such as sulfonylureas and insulins, however, have not shown a consistent association between intensive glycaemic control and reduction in macrovascular complications or mortality.¹⁶ Nevertheless, longer term follow-up of intensively treated adults provides some evidence of a lower risk of macrovascular events and cardiovascular death.^{8 17} Conversely, intensive glycaemic control in individuals with frailty, advanced age, and multimorbidity was associated with an increased risk of severe hypoglycaemia and death.^{18–20} Therefore, future research is needed to examine the effect of intensive glycaemic control when achieved with newer glucose lowering drugs, which have a lower risk of hypoglycaemia and additional cardio-reno-metabolic benefits. Taken together, these data highlight the importance of individualised glycaemic management and the need to shift the emphasis away from the imperfect surrogate of levels of HbA_{1c} towards reducing hard outcomes of the adverse health effects of diabetes, while lessening the burden of treatment.^{21 22}

Over the past decade, multiple randomised controlled trials have shown a reduction in cardiovascular disease, kidney disease, heart failure, and mortality with the use of glucagon-like peptide 1 receptor agonists (GLP1RAs) and sodium glucose cotransporter 2 inhibitors (SGLT2is), independent of a reduction in levels of HbA_{1c}.²³ These findings signalled a new complications centric era of the management of diabetes, focused directly on preventing or reducing macrovascular, microvascular, and other emerging complications of diabetes, such as heart failure. Many,^{6 24 25} although not all,²⁶ clinical practice guidelines recommend treatment with GLP1RAs or SGLT2is, or both, for patients with cardiovascular or kidney disease, or both, or with risk factors for atherosclerotic cardiovascular disease, independent of glycaemic control, although all continue to stress the concurrent importance of achieving HbA_{1c} targets.

More recently, the pattern of management of diabetes has begun to shift further, with a renewed focus on looking at the causes of type 2 diabetes and its metabolic comorbidities and long term complications. This pathogenesis centric approach places the management of obesity at the centre of the prevention and treatment of the disease.²⁷ Even a relatively small amount (5–7%) of weight loss reduced the risk of incident diabetes and improved glycaemic control in people with type 2 diabetes.^{28–31} Greater amounts of weight loss have been reported to have greater beneficial

effects on glycaemic control (including remission of diabetes), metabolic dysfunction, and quality of life.^{29 30 32–37} Weight loss achieved with metabolic surgery reduced the risks of microvascular and macrovascular complications of diabetes and reduced mortality.^{38–41}

By contrast, intensive lifestyle treatments in the Look AHEAD (Action for Health in Diabetes) randomised controlled trial of 5145 adults with type 2 diabetes and overweight/obesity did not reduce the risk of cardiovascular events compared to usual care.³⁰ The likelihood of detecting differences between the intensive lifestyle and conventional treatment groups might have been reduced because the cardiovascular event rate in the Look AHEAD population was much lower than anticipated (0.7% per year *v* estimated 3.1% per year).⁴² A post hoc analysis suggested that those who lost at least 10% of their body weight in the first year had a significantly lower risk of the primary outcome, which was a composite of the first occurrence of death from cardiovascular causes, non-fatal acute myocardial infarction, stroke, and hospital admission for angina (adjusted hazard ratio 0.79, 95% confidence interval 0.64 to 0.98, $P=0.034$).³⁵ How weight loss achieved with drug treatment, particularly agents such as semaglutide and tirzepatide, compares with metabolic surgery for glycaemic control, microvascular and macrovascular complications, and mortality, should be examined.

Lifestyle treatments: medical nutrition treatment, physical activity, and sleep

Successful management of type 2 diabetes must include consistent attention to behaviours that sustain a healthy lifestyle and are foundational for achieving glycaemic control, preventing complications, supporting quality of life, and preserving optimal health. Medical nutrition treatment for diabetes emphasises a balanced selection of nutrient dense foods while minimising or eliminating added sugar, refined grains, and highly processed foods.^{6 7 43} Recommendations for optimal carbohydrate intake and composition vary, with the strongest evidence supporting an overall reduction in intake of carbohydrates. This principle can be applied to multiple dietary patterns, including a Mediterranean diet high in monounsaturated and polyunsaturated fats, low carbohydrate, vegetarian, or a plant based diets, and the Dietary Approaches to Stop Hypertension diet, with a focus on non-starchy vegetables, fruits, and legumes, and some dairy in those who are lactose tolerant.^{6 43} Only the Mediterranean diet has been shown to reduce cardiovascular disease and mortality.⁴⁴ Also, evidence indicates the beneficial effects of involvement of community health workers to support education in self-management of diabetes and overall care,

especially in rural or underserved communities, or both.⁴⁵ Because hypertension and cardiovascular disease are major causes of mortality in individuals with diabetes, more attention needs to be paid to overall sodium intake and limiting the content of saturated fat and trans fat in the diet.⁶

Stopping smoking and abstinence from tobacco products is also imperative for cardiovascular health in adults with diabetes, and robust evidence supports the benefit of stopping smoking despite the potential for weight gain.^{6 46} Although nicotine replacement products and electronic cigarettes might facilitate stopping smoking, nicotine itself can impair glucose tolerance and adversely affect the cardiovascular system through increased sympathetic activation.⁴⁷

Baseline levels of physical activity should be assessed to set reasonable and realistic behaviour oriented goals. Increasing the duration of physical activity and reducing sedentary time have been reported to improve cardiorespiratory fitness and HbA_{1c} levels.⁴⁸ Recommendations can be made to increase leisure time physical activity (walking, taking the stairs, and household chores), decrease sedentary time, and introduce physical activity on most days.^{6 49} Physical activities include both aerobic and resistance training, as well as flexibility and balance training.⁵⁰

The length and quality of sleep are increasingly recognised as essential components of the management of diabetes and individuals should be screened for sleep related disorders.^{6 43} Referral for diagnosis and treatment of obstructive sleep apnoea and other sleep disorders should be considered if indicated. Screening for psychosocial factors and social determinants of health that might affect an individual's diabetes care and quality of life should also be performed, with engagement of or referral to relevant clinical team members for further evaluation and care, as appropriate.⁴³

Lifestyle interventions in individuals with obesity or who are overweight are most successful when efforts are intensive and frequent follow-up is available, either in person or virtually.^{6 49} Weight loss can be achieved in various ways, and is most effective when strategies are combined: caloric restriction, increased caloric expenditure, elimination or substitution of drugs that promote weight gain, use of weight reducing drugs and, in select individuals, metabolic or bariatric surgery. One dietary strategy that has received considerable attention in recent years is time restricted eating,⁵¹ although data in adults with type 2 diabetes are limited to one randomised controlled trial^{52 53} and a larger trial is ongoing ($n=344$; Using Early Time Restricted Feeding and Timed Light Therapy to Improve Glycemic Control in Adults With Type 2 Diabetes, NCT04155619). Weight management is discussed in more detail below.

Drug treatment of type 2 diabetes

Initial management of type 2 diabetes has traditionally included metformin in most adults because of its glucose lowering effect, neutral effects on weight, minimal risk of hypoglycaemia, safety profile, low cost, and ease of administration. Now, in the light of evidence from trials of cardiovascular and kidney outcomes, decisions on treatment of diabetes with drugs should be made based on cardiac comorbidities (established atherosclerotic cardiovascular disease and heart failure), risk factors for atherosclerotic cardiovascular disease and kidney disease, engaging adults in shared decision making, and prioritising the use of drugs shown to reduce the risk of cardiovascular or kidney adverse outcomes, or both, in adults with specific comorbidities.^{7 24–26}

Adults with atherosclerotic cardiovascular disease or indicators of high risk

In people with established atherosclerotic cardiovascular disease or risk factors for atherosclerotic cardiovascular disease, a GLP1RA or SGLT2i with known cardiovascular benefit should be started, regardless of levels of HbA_{1c} or background glucose lowering treatments.²⁴ Drugs that have been shown to cause significant reductions in major adverse cardiovascular events in cardiovascular outcomes trials compared with placebo include the GLP1RAs dulaglutide (hazard ratio 0.88, 95% confidence interval 0.79 to 0.99), liraglutide (0.87, 0.78 to 0.97), and subcutaneous semaglutide (0.74, 0.58 to 0.95), and the SGLT2is canagliflozin (0.86, 0.75 to 0.97) and empagliflozin (0.85, 0.75 to 0.97).^{54–58} None of the trials of cardiovascular outcomes involved head-to-head comparisons of GLP1RAs versus SGLT2is.⁵⁹

Individual components of the composite major adverse cardiovascular events outcome as well as secondary outcomes in the cardiovascular outcomes trials vary between GLP1RAs and SGLT2is. A reduction in stroke was seen in meta-analyses of randomised controlled trials of GLP1RAs compared with placebo (hazard ratio 0.83, 95% confidence interval 0.76 to 0.92) but not with SGLT2is compared with placebo (0.95, 0.85 to 1.05).⁵⁹ The mechanisms and benefits of GLP1RAs and SGLT2is seem to be complementary, and evidence is emerging to support combination treatment, which might provide more benefit than each used alone.^{60–62} Currently, guidelines from the American Diabetes Association/European Association for the Study of Diabetes recommend the addition of the alternative class when more glucose lowering is needed.^{24 25}

Adults with heart failure

GLP1RAs have not shown benefit for heart failure outcomes in individual randomised controlled trials of cardiovascular outcomes,^{55 56 58} although meta-analyses of these studies suggested a potential benefit.^{59 63 64} SGLT2is, by contrast, have

consistently shown significant benefit for heart failure outcomes.^{54 57 65} Also, dapagliflozin and empagliflozin were beneficial in people with reduced or preserved ejection fraction without type 2 diabetes, and have an indication for improving heart failure outcomes.^{66–69} Accordingly, in people with heart failure, an SGLT2i with known benefit should be started to reduce the risk of major adverse cardiovascular events and worsening heart failure.^{24 26}

Adults with chronic kidney disease

GLP1RAs have shown benefit for secondary kidney related outcomes in large individual randomised controlled trials^{55 56 70} and meta-analyses^{59 63 64} of cardiovascular outcomes, but dedicated kidney outcome trials are ongoing.⁷¹ Several SGLT2is, including canagliflozin, dapagliflozin, and empagliflozin, have shown benefit in adults with chronic kidney disease with or without type 2 diabetes and in dedicated kidney outcome trials, and have an indication for improving chronic kidney disease outcomes.^{24 72} Therefore, SGLT2is with primary evidence are preferred for individuals with an estimated glomerular filtration rate <60 mL/min/1.73 m² or albuminuria, or both, to reduce the progression of chronic kidney disease. If SGLT2is are not tolerated or cannot be used, GLP1RAs with demonstrated renal benefit are a reasonable alternative.^{24 26 73} Current prescribing information allows SGLT2is to be started in adults with an estimated glomerular filtration rate of ≥20 mL/min/1.73 m² for kidney benefit, although the glucose lowering effects are substantially reduced at an estimated glomerular filtration rate <45 mL/min/1.73 m².⁷⁴ A small reduction in the estimated glomerular filtration rate can be seen after starting treatment with SGLT2is because of reversal or correction of the previous hyperfiltration state in adults with diabetes, but it does not predict further reductions in estimated glomerular filtration rate or require discontinuation of treatment.

Role of metformin

Although metformin was a commonly used background drug in most large trials of cardiovascular and kidney outcomes,⁷⁵ several post hoc analyses have demonstrated benefit with GLP1RAs or SGLT2is regardless of background use of metformin.^{76–82} Current guidelines from the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinology no longer recommend metformin as the preferred first line agent for all individuals with type 2 diabetes, and instead suggest consideration of cardiac and kidney comorbidities when selecting first line treatment.^{6 24 25} Cost is a major consideration in selecting the most appropriate treatment, however, probably contributing to differences in these recommendations from guidelines used in other countries. In the US, insurers have not caught

up with the guidelines, and require that metformin is used before other agents. Guidance from the National Institute for Health and Care Excellence (NICE) still recommends metformin as the first line treatment for people with cardiac or kidney comorbidities, or both, with introduction of an SGLT2i in people who cannot tolerate metformin or need intensification of treatment.²⁶ Despite robust outcome data, GLP1RAs are not recommended by NICE until failure of triple oral drug treatment and only in people with a high body mass index or in whom insulin treatment cannot be used.²⁶ Insurance formulary restrictions on prescribing GLP1RAs and SGLT2is, including the requirement of step treatment starting with metformin, still persist but should be reconsidered to better align with scientific evidence.

Other situations when a drug other than metformin can be considered as first line treatment include severe or symptomatic hyperglycaemia (HbA_{1c} >10%, ketosis, or weight loss), creatinine clearance or estimated glomerular filtration rate <30 mL/min/1.73 m², or when the person cannot tolerate metformin despite slow up titration of the dose or a trial of the extended release formulation, or both. Sulfonylureas and thiazolidinediones are now less commonly recommended because of their adverse effect profiles. Sulfonylureas can lead to weight gain and are associated with a high risk of hypoglycaemia, and thiazolidinediones can also cause weight gain, as well as fluid retention and osteoporosis. People treated with thiazolidinediones must be monitored

for the development of heart failure; thiazolidinediones are not recommended for those with symptoms of heart failure and are contraindicated in class 3 or 4 heart failure. Because generic forms of sulfonylureas and thiazolidinediones are available, however, these drug classes are options when cost is a barrier to accessing other agents or the individual's clinical situation requires these drugs. Pioglitazone, a thiazolidinedione, has beneficial effects in hepatic steatosis and stroke, and can be considered in these contexts.^{6,83}

Effect on weight and weight related comorbidities

Clinicians should also consider the effect of the glucose lowering regimen on weight and weight related comorbidities, including overweight or obesity and non-alcoholic fatty liver disease or non-alcoholic steatohepatitis. Weight loss is greatest with the dual glucose dependent insulinotropic polypeptide (GIP)-GLP1RA, tirzepatide, and subcutaneous semaglutide, followed by dulaglutide and liraglutide.²⁷ Moderate weight loss is seen with the other GLP1RAs and SGLT2is. Drugs with neutral effects on weight include the dipeptidyl peptidase 4 inhibitors (DPP4is) and metformin, whereas the sulfonylureas, thiazolidinediones, and insulin all increase the risk of weight gain (table 1).^{24 27 84} Recent single centre and population based cross sectional studies in the US estimated that >70% of people with type 2 diabetes have non-alcoholic fatty liver disease and more than half of those with type 2 diabetes and non-alcoholic

Table 1 | Choosing drug class for type 2 diabetes

Drug class	Glucose efficacy	Effect on weight	Risk of hypoglycaemia	Route of administration	Cost	Ideal candidates for use
Metformin	High	Neutral	No	Oral	Low	▶ Newly diagnosed, especially in the absence of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease
SGLT2i	Intermediate to high	Loss (intermediate)	No	Oral	High	▶ Established or high risk of atherosclerotic cardiovascular disease ▶ Heart failure ▶ Chronic kidney disease
GLP1RA	High	Loss (intermediate to very high)	No	Subcutaneous (oral semaglutide)	High	▶ Established or high risk of atherosclerotic cardiovascular disease ▶ Chronic kidney disease (after SGLT2is) ▶ Non-alcoholic steatohepatitis or non-alcoholic fatty liver disease ▶ Overweight or obesity
GIP-GLP1RA	High	Loss (very high)	No	Subcutaneous	High	▶ Overweight or obesity
DPP4i	Intermediate	Neutral	No	Oral	High	▶ Older adults or others that require easy administration and high tolerability
Sulfonylurea	High	Gain	Yes	Oral	Low	▶ Those with cost or access barriers, especially in the absence of atherosclerotic cardiovascular disease, heart failure, chronic kidney disease, or overweight or obesity
Thiazolidinedione	High	Gain	No	Oral	Low	▶ Those with cost or access barriers, especially in the absence of heart failure, chronic kidney disease, or overweight or obesity ▶ Non-alcoholic steatohepatitis or non-alcoholic fatty liver disease ▶ History of stroke/TIA

GIP=glucose dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium-glucose cotransporter 2 inhibitor; DPP4i=dipeptidyl peptidase 4 inhibitor.

fatty liver disease have steatohepatitis.^{85–88} Insulin resistance, impaired lipid and glucose metabolism, and altered insulin secretion play a part in non-alcoholic fatty liver disease and progression of type 2 diabetes, and might indicate why the two diseases are so closely linked.⁸⁹ Although limited evidence exists so far, current guidelines recommend the use of a GLP1RA or pioglitazone for the treatment of diabetes in people with non-alcoholic steatohepatitis.^{90,91} Weight management, which is essential for the treatment of hepatic steatosis, is discussed below.

Glucose lowering efficacy

In addition to choosing a drug that targets cardiovascular, kidney, and metabolic outcomes, clinicians should also develop a treatment approach that has sufficient efficacy to achieve glycaemic targets.²⁴ Although some guidelines (most notably, the Australian Diabetes Society) cite a lack of evidence to support substantial differences in glucose lowering between antihyperglycaemic drug classes when used as monotherapy,⁹² prior meta-analyses, including a meta-analysis of 453 trials assessing nine drug classes, and the recently completed Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) pragmatic randomised clinical trial comparing insulin glargine U-100, the sulfonylurea glimepiride, the GLP1RA liraglutide, and the DPP4i sitagliptin in 5047 individuals with moderately uncontrolled type 2 diabetes found insulin and GLP1RA to be significantly more effective at lowering HbA_{1c} than the other examined drugs.⁹³⁹⁴ The American Diabetes Association Standards of Care there categorise drug classes as having very high, high, or intermediate glucose lowering efficacy (table 1).²⁴ The greatest reductions in levels of HbA_{1c} are seen with the dual GIP-GLP1RAs, GLP1RAs, and insulin. In the GLP1RA class, subcutaneous semaglutide and dulaglutide had the highest efficacy for glucose lowering. The recently approved dual GIP-GLP1RA, tirzepatide, seems to have the greatest efficacy for reducing levels of glucose. SGLT2is and DPP4is have less robust HbA_{1c} lowering effects and are classified as intermediate to high (SGLT2is) and intermediate (DPP4is).^{24,25,93}

GRADE, a large scale, comparative effectiveness study of four drugs in combination with metformin, found that insulin glargine and liraglutide achieved and maintained HbA_{1c} targets more effectively than glimepiride and sitagliptin. The study did not, however, include newer agents, such as the SGLT2is, or once weekly GLP1RAs.⁹⁵ The GRADE study also highlighted the challenges of maintaining glucose targets over time, with 71% of study participants progressing to HbA_{1c} $\geq 7\%$ within four years, regardless of the treatment option.⁹⁴ A meta-analysis of 229 randomised controlled trials comprising 121 914 participants suggested that glucose lowering efficacy was highest with GLP1RA and weakest with

DPP4i, with other agents in between.⁹⁶ By contrast, a meta-analysis of 140 randomised trials and 26 observational studies showed that each new class of non-insulin drugs added to metformin monotherapy lowers levels of HbA_{1c} by about 0.7–1%.⁹⁵ A shift towards earlier use of combination treatment, in contrast with a stepwise approach, to reach glucose targets and provide better glycaemic durability has been reported.^{24,97} For people with marked hyperglycaemia (eg, HbA_{1c} $>10\%$ or with symptoms), clinicians should start insulin, or a combination of insulin with GLP1RAs.⁹⁸ When improved glycaemic control is achieved, many people with type 2 diabetes can be safely transitioned to non-insulin treatments with close monitoring to prevent hypoglycemia and hyperglycemia.

Safety considerations

Other considerations in the selection of treatment for diabetes are the risks of hypoglycaemia, other adverse effects and safety considerations, as well as cost and administration requirements that often result in barriers to adherence. Therefore, individuals with diabetes, care partners, and clinicians need to engage in shared decision making to identify treatment strategies that are aligned with the individual's goals of care, treatment preferences, the clinical and psychosocial context, and risks and benefits associated with each treatment option. Tables 1 and 2 summarise this information. Some key and controversial safety considerations are discussed below.

Acute pancreatitis

Acute pancreatitis has been reported in individuals who received GLP1RAs, DPP4is, and the GIP-GLP1RA, tirzepatide. After early post-marketing reports, the US Food and Drug Administration warned of a potential link between acute pancreatitis and GLP1RAs and DPP4is.⁹⁹ Multiple preclinical, observational, and randomised controlled studies were inconsistent, with some showing positive associations and others showing no association.¹⁰⁰ Ultimately, the FDA concluded that a causal relation could not be established and insufficient evidence existed to modify treatment. Systematic reviews and meta-analyses of randomised controlled trials (eg, long term cardiovascular outcomes trials) concluded that treatment with GLP1RAs or DPP4is was not associated with an increased risk of pancreatitis or pancreatic cancer.^{101–103}

Nonetheless, current prescribing information, FDA guidance, and treatment guidelines recommend cautious use of these drug classes in people with a history of pancreatitis, in part because these people were excluded from most trials.²⁴ If these drug classes are used, individuals should be monitored for signs and symptoms of pancreatitis and, if pancreatitis develops, treatment should be discontinued and not restarted.^{24,99} We also suggest caution

Table 2 | Safety and mitigation considerations for each drug class for type 2 diabetes

Drug class	Safety considerations	Strategies for successful initiation and use	Key education points
Metformin	<p>Common adverse effects are gastrointestinal (diarrhoea, stomach upset), metallic taste, vitamin B12 deficiency (with long term use)</p> <p>Use caution:</p> <ul style="list-style-type: none"> ▶ estimated glomerular filtration rate 30-45 mL/min/1.73 m² ▶ increased risk of lactic acidosis <p>Do not use:</p> <ul style="list-style-type: none"> ▶ estimated glomerular filtration rate <30 mL/min/1.73 m² 	<ul style="list-style-type: none"> ▶ Start at low dose and titrate slowly to lessen gastrointestinal adverse events ▶ Consider extended release to lessen gastrointestinal adverse events ▶ Monitor vitamin B12 at regular intervals after five years of use ▶ Monitor kidney function and adjust dose accordingly based on prescribing information. 	<ul style="list-style-type: none"> ▶ Gastrointestinal adverse events are usually transient and lessen over time ▶ Take with food ▶ Do not crush or chew extended release products
SGLT2i	<p>Common adverse effects are genital mycotic infections and urinary tract infections (less common)</p> <p>Use caution:</p> <ul style="list-style-type: none"> ▶ recurrent yeast infections or urinary tract infections ▶ volume depletion ▶ diabetic ketoacidosis ▶ amputations ▶ <u>necrotising fasciitis of perineum (exceedingly rare)</u> 	<ul style="list-style-type: none"> ▶ Use lowest dose for cardiorenal effects ▶ Recognise less glucose lowering effect if estimated glomerular filtration rate <45 mL/min/1.73 m² ▶ Consider delaying start of treatment during severe hyperglycaemia ▶ Assess volume status, blood pressure, and adjust other drugs (eg, diuretics) if needed ▶ Hold during acute illness and before surgery (at least 72 hours) ▶ Identify those at high risk for adverse events and evaluate benefits and risks (eg, high amputation risk, recurrent yeast or urinary tract infections, diabetic ketoacidosis) ▶ Do not stop SGLT2i after initial drop in estimated glomerular filtration rate unless related to volume depletion. Initial drop is considered correction of previous hyperfiltration rates, not predictor of further estimated glomerular filtration rate trajectories ▶ Adjust background treatments as needed to avoid hypoglycaemia ▶ Monitor kidney function and adjust dose accordingly based on prescribing information ▶ Cross communicate with other healthcare providers 	<ul style="list-style-type: none"> ▶ <u>You might notice an increase in urine output</u> ▶ Stay well hydrated, stand up slowly, and note any dizziness ▶ Recognise signs and symptoms of genital mycotic infections, maintain good personal hygiene, call healthcare provider if yeast infection occurs because it can likely be treated without discontinuing SGLT2i ▶ Follow sick day plan when sick; do not stop taking your insulin ▶ Do not start a low or non-carbohydrate diet without consulting your healthcare provider ▶ Call your healthcare provider if you experience symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, tiredness, trouble breathing)
GLP1RA	<p>Common adverse effects are gastrointestinal (nausea, vomiting, diarrhoea, constipation)</p> <p>Use caution:</p> <ul style="list-style-type: none"> ▶ pancreatitis ▶ diabetic retinopathy ▶ gastroparesis ▶ gallbladder and biliary disease <p>Do not use:</p> <ul style="list-style-type: none"> ▶ thyroid C cell carcinoma (black box warning; contraindicated in personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2) 	<ul style="list-style-type: none"> ▶ Start at low dose and titrate slowly to lessen gastrointestinal adverse events (for most agents) ▶ Consider slower dose titration if gastrointestinal adverse events persist ▶ Provide practical education on administration, storage, missed doses ▶ Use demonstration delivery pen devices and ask the patient to demonstrate administration technique with the teach back method ▶ Set expectations (eg, time to full effect, dose titration, timing of adverse effects, and how to lessen) ▶ Adjust background treatments as needed to avoid hypoglycaemia ▶ Follow-up within first few weeks to assess and reinforce ▶ Don't assume the patient is resistant to injections ▶ Proactive screening for diabetic retinopathy is recommended 	<ul style="list-style-type: none"> ▶ Gastrointestinal adverse events are usually mild to moderate, transient, and resolve in most individuals ▶ Eat smaller meals, eat slowly, stop eating once full, avoid eating when not hungry, avoid high fat or spicy food, and limit alcohol¹⁸⁹⁻¹⁹¹
GIP-GLP1RA	Same as GLP1RA	Same as GLP1RA	Same as GLP1RA
DPP4i	<p>Very well tolerated; few common adverse effects</p> <p>Use caution:</p> <ul style="list-style-type: none"> ▶ pancreatitis ▶ gallbladder and biliary disease ▶ joint pain 	<ul style="list-style-type: none"> ▶ Monitor kidney function and adjust dose accordingly based on prescribing information 	<ul style="list-style-type: none"> ▶ Take once daily by mouth with or without food
Sulfonylurea	<p>Common adverse effects are weight gain and hypoglycaemia</p>	<ul style="list-style-type: none"> ▶ Avoid in kidney dysfunction and older adults (especially glibenclamide and glyburide) ▶ Set expectations about adverse effects 	<ul style="list-style-type: none"> ▶ Prevention, detection, and treatment of hypoglycaemia ▶ Eat meals consistently to avoid hypoglycaemia
Thiazolidinedione	<p>Common adverse effects are oedema and weight gain</p> <p>Use caution:</p> <ul style="list-style-type: none"> ▶ heart failure ▶ risk of bone fractures ▶ bladder cancer 	<ul style="list-style-type: none"> ▶ Consider using lower dose, especially when used in combination with insulin to avoid side effects ▶ Set expectations about adverse effects 	<ul style="list-style-type: none"> ▶ Take once daily by mouth with or without food

GIP=glucose-dependent insulinotropic polypeptide; GLP1RA=glucagon-like peptide 1 receptor agonist; SGLT2i=sodium-glucose cotransporter 2 inhibitor; DPP4i=dipeptidyl peptidase 4 inhibitor.

in starting these drugs in people with a previous history of pancreatitis, particularly when the cause of pancreatitis is unknown or persists. Monitoring of lipase levels in randomised controlled trials showed asymptomatic fluctuations in both groups (intervention and placebo). Hence no evidence exists to suggest ongoing monitoring during treatment.

Gallbladder or biliary disease

GLP1RAs, DPP4is, and GIP-GLP1RAs are also associated with an increased risk of gallbladder and biliary disease, including cholelithiasis and cholecystitis.^{104–107} Although the absolute risk of biliary or gallbladder disease with GLP1RA therapy seems to be small, with a recent meta-analysis of 76 randomised controlled trials involving 103 371 participants reporting an additional 27 incidences per 10 000 patients per year,¹⁰⁴ this finding might under-represent the true risk, because many studies did not report biliary related events. The risk seems to be higher with higher doses of drugs, longer duration of use, and when used for weight loss rather than glycaemic control. We therefore advise caution with the use of GLP1RAs, DPP4is, and GIP-GLP1RAs in people at high risk of biliary complications.

Diabetic retinopathy

A significant increase in retinopathy complications (3% v 1.8%, $P=0.02$), including vitreous haemorrhage, blindness, or need for photocoagulation treatment or an intravitreal agent, was seen in people receiving semaglutide during the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long term Outcomes With Semaglutide in Subjects With Type 2 Diabetes) randomised controlled trial with 3297 participants with type 2 diabetes.⁵⁶ Of those with retinopathy complications, 83.5% had a history of retinopathy at baseline. In a meta-analysis of four cardiovascular outcomes trials of dulaglutide, liraglutide, oral semaglutide, and subcutaneous semaglutide, use of GLP1RAs was associated with an increased risk of rapidly worsening retinopathy (odds ratio 1.23, 95% confidence interval 1.05 to 1.44).¹⁰⁸ In another meta-analysis, GLP1RAs were not independently associated with an increased risk of retinopathy, but an association between retinopathy and the magnitude of the reduction in levels of HbA_{1c} was found.¹⁰⁹ Rapid glucose lowering has previously been associated with worsening diabetic retinopathy,¹¹⁰ and the GLP1RA cardiovascular outcomes trials were not powered to detect differences in retinopathy complications. Thus whether worsening retinopathy is caused by the drug itself, a change or rate of change in glucose levels, or a combination of both is unclear. We advise caution when GLP1RAs are used, particularly semaglutide, in people with diabetic retinopathy, and individuals should be monitored closely for progression of retinopathy.¹¹¹

Whether other GLP1RAs similarly increase the risk of progressive diabetic retinopathy is not known. Consultation with an ophthalmologist should be considered before starting GLP1RAs in people with pre-existing retinopathy.¹¹¹ A large randomised controlled trial (A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS), NCT03811561) evaluating the long term effects of subcutaneous semaglutide on eye disease in 1500 people with type 2 diabetes is ongoing and should provide more evidence.

Amputations

An increased risk of lower limb amputations was first reported in the cardiovascular outcomes trial for canagliflozin that included 10 142 participants with type 2 diabetes and high cardiovascular risk (6.3 v 3.4 participants per 1000 patient years; hazard ratio 1.97, 95% confidence interval 1.41 to 2.75)⁵⁷ and led to a warning added to the prescribing information for canagliflozin in 2017.¹¹² The FDA removed the warning in 2020 based on more clinical trial data that found that the risk was less than previously described.¹¹³ Subsequent real world cohort studies, randomised controlled studies, and meta-analyses have reported conflicting results, with some suggesting an increased risk with all SGLT2is and others finding no increased risk.^{114–121} Therefore, reasonable steps to take are to consider factors that increase the risk of amputations before starting an SGLT2i, closely monitor people for lower limb ulcers or infections, and discontinue the SGLT2i if these occur. Subgroup and exploratory analyses of the SGLT2i cardiovascular outcomes trials, however, suggest cardiovascular benefit in patients with peripheral arterial disease,^{122–124} so clinicians should use shared decision making when assessing the benefits and risks of SGLT2is in those at high risk.

Diabetic ketoacidosis

SGLT2is are associated with an increased risk of diabetic ketoacidosis, particularly in people with type 1 diabetes and in the perioperative population.^{125 126} Rates in adults with type 2 diabetes are low and range from 0.16 to 0.76 events per 1000 patient years.¹²⁷ In type 2 diabetes, the risk is increased in people who are insulin deficient, in older people, with prolonged use of SGLT2is, or in those with a combination of these factors.¹²⁸ Guidance on risk management of diabetic ketoacidosis is mainly from individuals with type 1 diabetes, with little guidance specific to type 2 diabetes, and recommendations are mostly extrapolated from the type 1 diabetes context.^{126 129} People with diabetes should be informed of the importance of adherence to insulin treatment, avoiding very low carbohydrate diets (such as ketotic diets), and excessive intake of alcohol. Education on management of sick days should also be given, and insulin

doses should be monitored carefully; basal insulin should not be discontinued completely during illness or planned activity, particularly in those receiving intensive insulin treatment.

Clinicians and people with diabetes should be aware of predisposing factors and the clinical presentation of diabetic ketoacidosis, which often occurs with lower serum glucose levels (so-called euglycaemic diabetic ketoacidosis), sometimes at glucose concentrations of ≤ 200 mg/dL (11.1 mmol/L). The SGLT2i should be discontinued and treatment started promptly if diabetic ketoacidosis is suspected. SGLT2is should also be discontinued 3-4 days before scheduled surgery, during prolonged fasting or low carbohydrate intake, or during critical illness to lessen the risk of diabetic ketoacidosis.²⁴ Some have suggested that absence of ketosis (< 0.6 mmol/L blood ketones, negative urine ketones) should be confirmed in people with type 1 diabetes before the start of treatment if SGLT2is are being used off label in this population,¹²⁶ but no evidence exists in support of this practice for people with type 2 diabetes.

Starting and titrating insulin treatment

Many people with type 2 diabetes will eventually require insulin because of the progressive nature of the disease. For most people, a GLP1RA should be considered as the first injectable agent before basal insulin, based on the strong evidence of similar efficacy, beneficial effect on weight, and less hypoglycaemia.¹³⁰⁻¹³¹ If more treatment is needed after a GLP1RA, basal insulin should be started first and titrated to a maximum effective dose in a safe and timely way.⁷⁻⁹⁸ Several steps are necessary to support optimisation of insulin treatment, including clear communication of expectations, adequacy of glucose monitoring (including continuous glucose monitoring for people with basal insulin or intensive insulin treatment, and remote telemonitoring), a feasible dose titration plan, clearly defined glycaemic targets, and education on proper administration of insulin and storage.¹³¹⁻¹³⁴ Whether the individual can self-titrate the dose or if more support is needed should be assessed. People who can self-titrate can be instructed to continue uptitrating the dose until fasting glucose levels are consistently between 80 and 130 mg/dL (4.4 to 7.2 mmol/L; or an individualised glycaemic target), an anticipated maximum basal dose is reached (eg, 0.5 units/kg/day), or have unexplained hypoglycaemia. Providing these endpoints is key to reducing the risk of being treated with an inappropriately high dose of basal insulin in an attempt to compensate for inadequate postprandial glycaemic control (ie, overbasalisation) while facilitating continued titration to an effective dose.¹³⁵ If the individual cannot self-titrate, consider providing weekly follow-up healthcare remotely (ie, telehealth) for timely dose titrations.

If the basal insulin dose has been sufficiently titrated but levels of HbA_{1c} remain above the person's individualised target or concern for overbasalisation exists, targeting postprandial glucose excursions is warranted. Initially, consider adding a GLP1RA or GIP-GLPRA if not already being used. The next step is to add prandial insulin as a separate injection or by switching to a fixed ratio combination. Basal bolus insulin treatment requires more injections, more glucose testing, more education, and carries a higher risk of hypoglycaemia and weight gain.⁹⁸ Metformin or complication centric drugs (GLP1RAs and SGLT2is), or both, should be continued. Sulfonylureas should be discontinued because of the risk of hypoglycaemia with concurrent insulin treatment.

Weight management in type 2 diabetes

Among adults with diabetes in the US, almost 28% are overweight (body mass index 25.0-29.9), 46% have obesity (body mass index 30.0-39.9), and 16% have severe obesity (body mass index ≥ 40.0).¹³⁶ Increasingly recognised as a chronic disease, obesity (termed adiposity based chronic disease)¹³⁷⁻¹³⁸ is characterised by excessive, maldistributed, and dysfunctional adipose tissue, and is associated with increased risks of hyperglycaemia (ie, prediabetes and type 2 diabetes), cardiovascular disease, hyperlipidaemia, hypertension, chronic kidney disease, cancer, urinary incontinence, non-alcoholic fatty liver disease, osteoarthritis, infertility, obstructive sleep apnoea, and gastro-oesophageal reflux disease.¹³⁷

Obesity is closely related to the pathogenesis and pathophysiology of type 2 diabetes and it also affects the management and outcomes of diabetes.¹³⁷⁻¹³⁹ Strong evidence indicates that weight loss, particularly if $> 10\%$ of body weight, can prevent, improve, and even reverse type 2 diabetes.¹⁴⁰ The Diabetes Prevention Programme showed that people with prediabetes who were randomised to receive an intensive lifestyle intervention had a 16% reduction in the risk of progressing from prediabetes to diabetes for every kilogram of weight loss.³⁷ In the Look AHEAD study of people with type 2 diabetes and overweight or obesity, improvement in fasting glucose and HbA_{1c} levels was found with weight loss as little as ≥ 2 kg, and improvements were directly proportional to the amount of weight lost.³¹ After initial weight loss from lifestyle interventions or pharmacotherapy, compensatory physiological responses often make efforts at further weight loss more difficult, less successful, or difficult to maintain, a biological phenomenon referred to as obesity protecting obesity.¹⁴¹ Hence clinicians should provide a supportive approach, recognising personal biases, and avoiding stigma and judgment to facilitate weight management efforts.¹⁴¹

Despite years of commercial availability, obesity drugs are rarely used, with fewer than 5-10% of people with diabetes and obesity receiving obesity drugs in the US.¹⁴² This finding could be driven by the relatively low efficacy of historically available drugs for weight loss, with most drugs causing <7% body weight loss.¹⁴¹ Recent developments with incretin treatments have closed this gap, however, with up to 20% weight loss reported with tirzepatide.¹⁰⁷ Several studies in people with obesity, with or without type 2 diabetes, treated with semaglutide or tirzepatide have reported reductions in body weight of at least 5-10% in up to 80-90% of people, and reductions of 15-20% in up to 40-50% of people.^{106 107 143 144} Efforts to lose weight in people with type 2 diabetes and obesity should be supported through preferential use of glucose lowering drugs that are associated with weight loss, avoiding glucose lowering and non-diabetes drugs associated with weight gain, and aiming for weight loss of 12-15% as appropriate, to achieve maximum benefits.^{7 140}

Equity and affordability of diabetes care

Affordability, accessibility, and feasibility of implementing the diabetes care plan are major considerations in shared decision making. In the US, the high and rising costs of insulin and non-insulin drugs¹⁴⁵ have contributed to diabetes distress,¹⁴⁶ cost related non-adherence^{147 148} with a detrimental effect on diabetes health outcomes¹⁴⁹ and rationing of other vital expenses.¹⁵⁰ Therefore, healthcare providers must discuss concerns about affordability with all people with diabetes, ensure that prescribed drugs are available and accessible, and leverage care team and community support systems to reduce the financial burden of the management of diabetes.^{151 152}

To deal with the growing concerns about affordability of insulin in the US, out-of-pocket costs have been capped in 2023 by the Centers for Medicare and Medicaid Services (which oversee publicly funded insurance for seniors, low income individuals, and people with disabilities or end-stage kidney disease), several private insurance plans, and insulin manufacturers, and the effect of these changes on cost related non-adherence and rationing will need to be assessed. The cost of drugs is generally much lower outside of the US because of highly regulated policies on drug pricing and cost effectiveness in other high income countries,^{153 154} but 80% of people with diabetes live in low and middle income countries¹⁵⁵ and half do not have access to recommended diabetes treatments.¹⁵⁶ These findings call for multifaceted policy solutions to lower costs, increase supply, and improve accessibility of evidence based diabetes treatments and technologies in all settings and populations.¹⁵⁷

Socioeconomic barriers to optimal management of diabetes are multifaceted and include not only the high costs of diabetes drugs, technology, and

equipment, but also foundational social determinants of health, such as the home environment with access to healthy food choices and space for physical activity, environmental pollution and endocrine disrupting chemicals, stable housing with access to electricity and refrigeration, employment type and stability, and educational attainment.¹⁵² Geographical differences in the quality of care and prevalence of type 2 diabetes and its complications exist across levels of rurality,^{158 159} neighbourhood disadvantage,^{158 160} and geopolitical environment.¹⁶¹⁻¹⁶³ Several interventions have been shown to be successful in improving the management of diabetes, including community health worker programmes, diabetes prevention and self-management programmes adapted specifically to the needs of underserved and disadvantaged populations, expansion of health insurance as part of the Affordable Care Act, food and housing support programmes, and others.¹⁵²

We must also be cognisant of pervasive racial and ethnic inequalities in the quality of diabetes care and health outcomes. In the US, racial and ethnic minority populations are disproportionately affected by diabetes¹⁶⁴ and its complications.^{152 165 166} Multiple studies have shown worse glycaemic control^{165 167 168} and higher rates of acute complications (hypoglycaemia,^{160 165 169-172} diabetic ketoacidosis, and hyperglycaemic hyperosmolar state),^{160 165 170 173} chronic complications (kidney disease,^{165 174-178} amputation,^{165 175} cardiovascular disease,^{165 175} and retinopathy),^{176 179} and mortality^{180 181} among black people with type 2 diabetes relative to other racial and ethnic groups. People with type 2 diabetes from racial and ethnic minority groups are also substantially less likely to be treated with GLP1RAs and SGLT2is than non-Hispanic white people.^{182 183} Similar inequalities in the prevalence, management, and health outcomes of diabetes have been described in Europe^{184 185} and around the world.^{186 187} These inequalities highlight the need for structural solutions and multisector collaborations that deal with the barriers to optimal diabetes management and health at all levels to ensure that all people, regardless of race, ethnic group, socioeconomic status, or place of residence, receive high quality care.

Conclusions

The paradigm of diabetes management has shifted over the past decade from a predominantly glucose-centric approach to approaches that prioritise prevention of diabetes complications and addressing the underlying causes of diabetes and metabolic dysfunction, such as obesity (figure 2). High quality, evidence based management of diabetes therefore requires reducing glucose levels to a safe, patient centred range; using glucose lowering drugs with a strong evidence base for reduction of diabetes

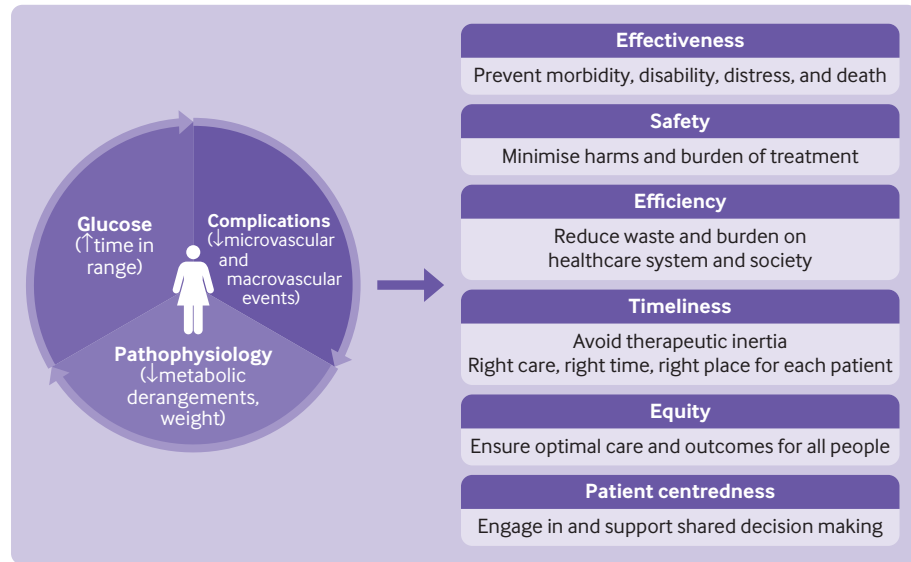


Figure 2 | Person centred goals of treatment of type 2 diabetes

complications and excess adiposity, not just lowering levels of HbA_{1c}; minimising burden of treatment and improving quality of life; and implementing care delivery models that support high quality (effective, efficient, safe, equitable, timely, and person centred) care.¹⁸⁸ Access and affordability remain major barriers, as is the sustainable implementation of effective lifestyle interventions.

QUESTIONS FOR FURTHER RESEARCH

- ⇒ What are the short term and long term health outcomes associated with combined GLP1RA and SGLT2i treatment?
- ⇒ What is the optimal weight loss target (>10% or 15%) in the management of type 2 diabetes?
- ⇒ What is the comparative effectiveness and safety of drug treatments for obesity compared with metabolic surgery for long term metabolic, microvascular, and macrovascular complications?
- ⇒ How can effective lifestyle treatments for long term weight loss be implemented effectively, sustainably, and equitably?
- ⇒ What are effective and sustainable ways to engage people with diabetes, care partners, and communities in the prevention and management of diabetes to ensure equitable access to care?
- ⇒ How can structural barriers to optimal metabolic health be removed?

PATIENT INVOLVEMENT

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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