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Modern-Day Management of the Dysglycemic Continuum: An Expert Viewpoint from the Arabian Gulf

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Abstract: Prediabetes is the first stage of a continuum that extends through the diagnosis of clinical type 2 diabetes towards long-standing diabetes with multiple comorbidities. The diagnosis of prediabetes provides an opportunity to interrupt the diabetes continuum at an early stage to ensure long-term optimization of clinical outcomes. All people with prediabetes should receive intervention to improve their lifestyles (quality of diet and level of physical activity), as this has been proven beyond doubt to reduce substantially the risk of conversion to diabetes. Additionally, a large base of clinical evidence supports the use of metformin in preventing or delaying the transition from prediabetes to clinical type 2 diabetes, for some people with prediabetes. For many years, guidelines for the management of type 2 diabetes focused on lowering blood glucose, with metformin prescribed first for those without contraindications. More recently, guidelines have shifted towards prevention of diabetes complications as the primary goal, with increased use of GLP-1 receptor agonists (or multi-agonist incretin peptides) or SGLT-2 inhibitors for patients with existing atherosclerotic cardiovascular disease, heart failure or chronic kidney disease. Access to these medications often remains challenging. Metformin remains a suitable option for initial pharmacologic intervention to manage glycemia for many people with prediabetes or type 2 diabetes along with other therapy to maintain control of blood glucose or to address specific comorbidities as the patient progresses along the diabetes continuum.

Keywords: type 2 diabetes, prediabetes, diabetes continuum, metformin, antidiabetic therapy, diabetes complications

Introduction

The landscape of diabetes has changed dramatically in recent times, with a substantial proportion of the population with, or at short-term risk of developing type 2 diabetes: a recent survey covering 204 countries estimated that 529 million people were living with diabetes in 2021 (96% of these people have type 2 diabetes), a number projected to increase to 1.3 billion by the year 2050.[1] Complications of diabetes relate to the microvascular system (eg nephropathy, neuropathy, diabetic foot) and the macrovascular system (atherosclerosis, increased risk of major adverse cardiovascular outcomes such as myocardial infarction, heart failure, stroke).[2] Moreover, the pathogenesis of diabetes complications begins for many people long before a clinical diagnosis of diabetes.[3–6] Indeed, prediabetes and diabetes exist within a continuum,

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from the earliest adverse metabolic changes associated with insulin resistance and subsequent β-cell dysfunction, through the initial diagnosis of type 2 diabetes, to the familiar complications of long-standing type 2 diabetes.[7]

The increasing challenge of addressing the adverse consequences of the diabetes continuum has been accompanied by a large increase in the choice of antihyperglycaemic treatments in recent years. While the options for personalized medicine for people with type 2 diabetes are greater than ever, designing an optimum treatment regimen has become more challenging. In this review, we, a group of physicians caring for people with dysglycemia in countries in the Arabian Gulf, consider pragmatic treatment options for managing people with any severity of dysglycemia.

Prediabetes, Diabetes and Outcomes

Clinical Relevance of the Dysglycemic Continuum

The association between unaddressed hyperglycemia and an increased risk of diabetes complications in people with type 2 diabetes has been understood for decades. For example, an epidemiological analysis of the UK Prospective Diabetes Study (which reported in 1998) showed that a reduction in HbA1c of 1% was associated with clinically and statistically significant reductions in the risk of a range of adverse outcomes, including all-cause mortality (–14%), diabetes-related death (–21%), any diabetes-related endpoint (–21%), myocardial infarction (–14%) and heart failure (–16%), among others.[8] Many other studies have confirmed these landmark findings (reviewed elsewhere[9]). One recent study used casual glucose measurements in a prospective cohort of 159,731 subjects to explore the relationships between prevailing glycemia and cardiovascular risk during an average of 13 years of follow-up.[10] Borderline hyperglycemia (defined as 7.8–11.0 mmol/L) and more severe elevations of blood glucose (>11 mmol/L) were associated with an increased risk (HR [95% CI]) of stroke (1.29 [1.12 to 2.49] and 1.79 [1.31 to 2.43], respectively), cardiovascular death (1.29 [1.12 to 2.48] and 1.90 [1.42 to 2.55], respectively), and all-cause death (1.27 [1.16 to 1.38] and 1.69 [1.38 to 2.05], respectively), each compared with a "normal" level, defined as <7.8 mmol/L.

The 7 mmol/L/126 mg/dL cut-off value for plasma glucose used in the diagnosis of diabetes was originally adopted following observations that the risk of diabetes complications (especially retinopathy) appeared to increase sharply at higher severities of hyperglycemia.[11] Currently diabetes is diagnosed according to a categorical cut-off value of the level of blood glucose (fasting glucose >7 mmol/L [126 mg/dL], 2-hour glucose during a 75 g oral glucose tolerance test [OGTT] >11.1 mmol/L [200 mg/dL]), random blood glucose >11.1 mmol/L [200 mg/dL], or HbA1c ≥6.5% [≥47 mmol/mol]),[12] showing that this glycemic cut-off for plasma glucose has persisted over time.

The UKPDS and the other studies in this area did not find any lower threshold level of blood glucose that denoted an absence of risk of diabetes complications.[8,9] Moreover, a recent systematic review has shown that an increased risk of mortality or other adverse outcomes is present at levels of blood glucose that are below the diagnostic cut-off for clinical type 2 diabetes.[13] The concept of "prediabetes" has arisen to address this issue, by identifying a population who are at enhanced risk of early development of type 2 diabetes and, more recently, of diabetes-like complications.[14–16] Three separate diagnoses of prediabetes can be made. According to the most commonly used criteria proposed by the American Diabetes Association (ADA), impaired fasting glucose (IFG) is present when fasting blood glucose is 5.7–6.9 mmol/L and impaired glucose tolerance (IGT) is diagnosed when 2-hour post-OGTT glucose is 7.8–11.0 mmol/L; HbA1c 5.7–6.4% (39–47 mmol/mol) can also be used to diagnose prediabetes.[12]

All forms of prediabetes are associated strongly with increased risk of conversion to type 2 diabetes and about 5–15% of people with prediabetes convert to clinical type 2 diabetes each year (although some also regress spontaneously to normoglycemia, at least temporarily).[17] In addition, it has been know for more than three decades that people with prediabetes tend to display a pattern of atherogenic cardiovascular risk factors (eg obesity and hypertension) that likely contribute to both the excess prevalence of cardiovascular disease in this population and also to cardiovascular disease that develops after a subsequent conversion to clinical type 2 diabetes.[18]

Systematic reviews have demonstrated an increased risk of diabetes-like long-term cardiovascular complications, or premature cardiovascular or all-cause mortality, in populations with any form of prediabetes.[3–6,19,20] There is limited evidence that different forms of prediabetes predispose to different outcomes to some extent. For example, a meta-analysis associated IGT more strongly with all-cause mortality than prediabetes diagnosed using high-normal HbA1c,[19] although other studies linked prediabetes in general to macrovascular complications,[14] or reported similar strengths of

association between prediabetes and microvascular vs macrovascular outcomes.[4] For example, Figure 1 summarizes key results from a systematic review from 2021 that demonstrated an increased risk of premature cardiovascular or all-cause mortality and of a range of adverse clinical cardiovascular outcomes in subjects with prediabetes, irrespective of the diagnostic criteria used.[3,21] A lack of standardization of definitions of prediabetes over the years has probably hampered a precise evaluation of the impact of different manifestations of this condition on different forms of adverse cardiovascular outcomes, and attempting to unravel this issue is beyond the scope of our review.[20] Endothelial dysfunction, a precursor of established cardiovascular disease, has also been observed in people with prediabetes.[22]

An excess prevalence of microvascular complications, especially relating to retinopathy and neuropathy, has also been demonstrated in populations with prediabetes, usually with a prevalence value intermediate between those seen in true normoglycemia and clinical type 2 diabetes.[7,14,15,23] Overall, therefore, the association of prediabetes with an increased risk of diabetes-like vascular complications is no longer controversial.

Diabetes and hyperglycemia have also been linked to an increased risk of developing malignant disease,[24] the development of a more aggressive cancer phenotype,[24,25] and reduced effectiveness of anticancer treatments.[24,26] These associations are incompletely understood, and we lack evidence that interventions to prevent or delay conversion of prediabetes to type 2 diabetes (see below) will reduce the incidence of specific cancers or improve outcomes of patients with them. More real world evidence, in particular, will be needed to answer this question in the future.

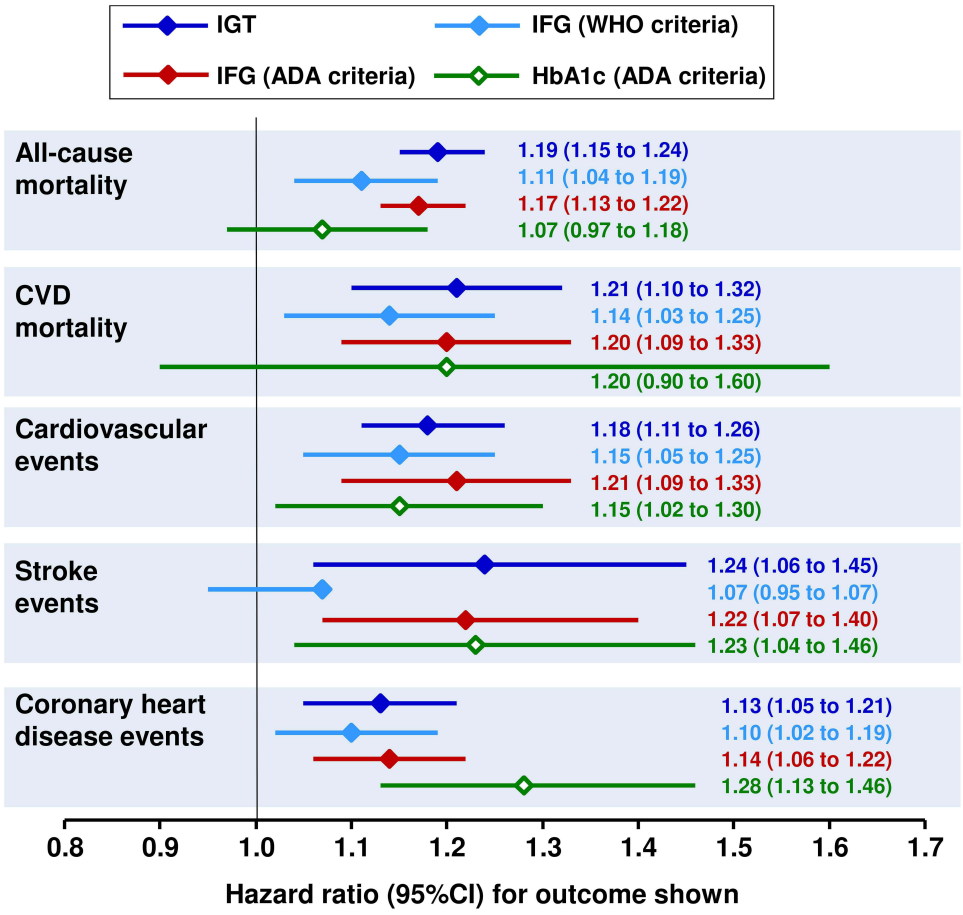

Figure 1 Associations between different definitions of prediabetes states and adverse clinical cardiovascular outcomes.
Notes: Definitions of prediabetic states shown here were according to American Diabetes Association criteria. Data from Farmaki et al[2] and Palladino et al.[14]
Abbreviations: CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

The Diabetes Continuum in the Arabian Gulf

The Arabian Gulf countries have not been spared the increasing burden of prediabetes and diabetes in recent decades.[1,27,28] Figure 2 shows the age-adjusted prevalence of diabetes, IGT, IFG and obesity in the countries of the Gulf Cooperation Council (GCC; the authors' region), alongside corresponding data from selected countries in other continents (Germany, USA and China), for comparison.[29–32] The age-adjusted adult prevalence of obesity in most GCC countries is comparable to that in the USA. Age-adjusted adult prevalence rates of diabetes, IGT and IFG are higher in all six GCC countries, compared with the USA, Germany or China, with a substantial burden of prediabetes (IGT and IFG) guaranteeing that the high rates of diabetes are likely to persist for some time in these countries.

Implications for Intervention

Prediabetes

Treatments

Prediabetes is an asymptomatic condition and diagnosed opportunistically during routine healthcare visits, or dedicated screening programs. The majority remains undetected, 80% of individuals with prediabetes in the USA are unaware of having the condition.[33] The ADA has provided criteria for identifying individuals who should be considered for screening for prediabetes or diabetes, based on the presence of overweight or obesity (BMI ≥25 kg/m^2, or ≥23 kg/m^2 in people of Asian heritage) together with at least one risk factor for developing diabetes (such as dyslipidemia, hypertension, family diabetes history, high-risk ethnicity, existing cardiovascular disease, or sedentariness).[12]

Weight loss through lifestyle modification is often difficult to maintain over the long term[34] and pharmacologic treatment may be required for the management of prediabetes where lifestyle intervention is insufficient.[35] The majority of data on pharmacologic diabetes prevention in people with prediabetes are from clinical studies with metformin, including the randomised DPP (reviewed elsewhere[34,36,37]). Metformin was most effective in subjects who were younger (25–44 years), with more severe hyperglycemia (fasting glucose ≥6.1 mmol/L [110 mg/dL]) and with more severe obesity (BMI ≥35 kg/m^2). The DPP also showed that randomization to metformin reduced the risk of conversion to diabetes significantly in women with prior gestational diabetes. The randomized phase of the DPP was relatively short (3 years), raising the question of whether this was prevention or simply delay of diabetes. However, long-term follow-up has demonstrated continued benefit in terms of a lower incidence of diabetes in those originally randomized to the initial intensive lifestyle intervention or metformin arms of the study.[38] Also, microvascular events,[39] cardiovascular events[39] and adverse kidney outcomes[40] were more prevalent in those who developed diabetes, compared with those who did not,

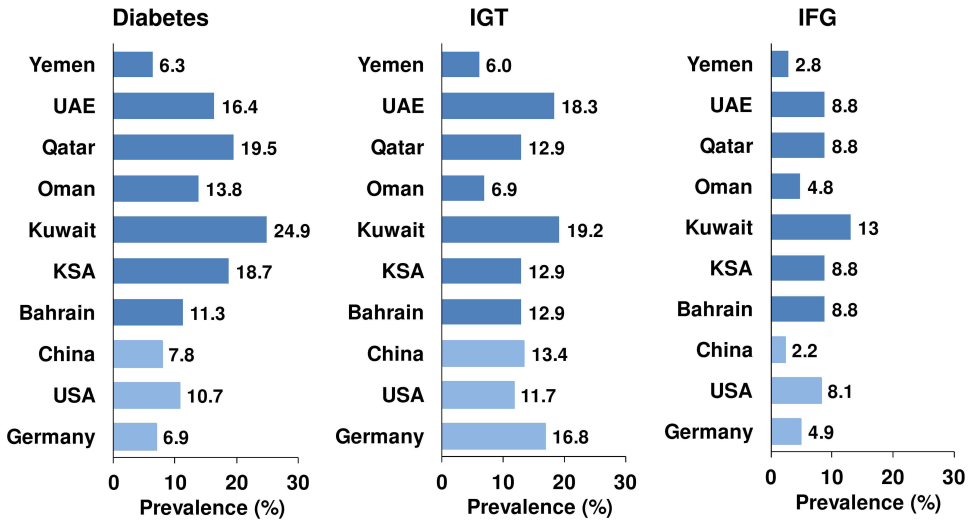

Figure 2 Incidence of diabetes and prediabetes in countries in the Arabian Gulf, compared with Germany, USA and China. Data are adjusted for age. Data from these studies[29–32].

Abbreviations: KSA, Kingdom of Saudi Arabia; UAE, United Arab Emirates; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

during long-term post-trial follow-up. A recent (2023) study from China also demonstrated significant diabetes prevention with metformin in people with IGT.[41] Guidelines on the use of metformin for the prevention or delay of type 2 diabetes from the ADA[35] and the UK National Institute for Health and Care Excellence[42] generally follow the results of the DPP, in that its use is recommended for younger, heavier and more severely hyperglycemic individuals (Table 1).[35,43]

Prediabetes is managed largely in primary care. As physicians managing patients with diabetes, referrals in our experience are typically of patients with long-standing diabetes, usually with significant diabetes complications. Senior physicians have an important role in providing guidance and training for their colleagues in primary care to facilitate early intervention.[44–47] Metformin is also often under dosed in people with prediabetes, in the experience of the authors: it should be noted that the evidence-based use of metformin is based on administration of a dose of 1,700 mg/day in the DPP, which was tolerated by 84% of the study population.[34]

Other pharmacologic agents developed for the management of prediabetes have been shown to reduce the risk of type 2 diabetes in at-risk populations in randomized studies, post hoc analyses or meta-analyses, including thiazolidinediones),[47–50] acarbose[51,52] basal insulin glargine,[53] SGLT-2 inhibitors,[54,55] and incretin agonists (GLP-1 agonists or multi-agonist incretin peptides).[56–60] Concerns over safety and/or tolerability have prevented widespread use of thiazolidinediones, acarbose or insulin for diabetes prevention.

Weight loss with the new incretin agonist drugs is potentially of benefit in the setting of prediabetes, but this is variable between patients.[61–63] The US Centers for Disease Control and Prevention advises the public that loss of 5–7% of initial body weight (along with increased physical activity) is effective in preventing diabetes, based on findings from the lifestyle arm of the DPP.[64] This is certainly feasible with an incretin agonist; a meta-analysis of studies with GLP-1 agonists found that half of subjects lost at least 5% of their initial body weight.[65] However, half did not, and people with prediabetes taking incretin agonists for weight loss need follow-up to ensure that they respond adequately to treatment. Newer multi-agonist peptides are more effective for weight loss than agents that stimulate only GLP-1 receptors.[66] Finally, weight loss usually reverses after withdrawal of an incretin agonist,[67] and future guidelines need to address how to manage a patient with prediabetes and overweight or obesity who discontinues one of these drugs.

Table 1 Summary of Guidance on the Use of Pharmacologic Therapy for Diabetes Prevention

Guideline	Key recommendations
American Diabetes Association (2024)[35]	No drug has a specific indication for diabetes prevention in the USA Consider metformin[a] especially for subjects with: • BMI ≥35 kg/m^2, • Age 25–59 years • Fasting glucose >6.1 mmol/L or HbA1c >6.0% • Prior history of gestational diabetes • Measure vitamin B12 periodically during administration of metformin Medications should not impede weight management goals (consider use of pharmacologic interventions to promote and maintain weight loss in overweight or obese people with prediabetes) Consider additional pharmacologic therapy if needed for individuals at high risk of diabetes (α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, thiazolidinediones, and insulin have been shown to lower the incidence of diabetes in specific populations)
National Institute for Health and Care Excellence (2020)[42]	Consider a trial[b] of metformin[a] for people: • With insufficient response to lifestyle intervention (based on routine HbA1c measurements) • Who are unable to undertake a lifestyle intervention Consider metformin especially for people with BMI ≥35 kg/m^2 Consider orlistat for weight loss if BMI ≥28 kg/m^2
International Diabetes Federation (2016)[43]	Metformin can be considered as an effective and cost-effective option for the prevention of delay of type 2 diabetes that can provide considerable health gains.

Note: All should also receive a lifestyle intervention. [a]In the absence of contraindications to metformin. [b]Discontinue metformin after 6–12 months if there is no improvement in glycaemia.

Average weight loss with SGLT-2 inhibitors has been about 2–4% of initial weight in clinical trials.[68] This would be useful in the setting of prediabetes, though many subjects are likely to need an additional intervention to meet weight loss targets. Further evidence is required on the safety and efficacy of the newer classes of SGLT-2 inhibitors and incretin agonist peptides, to define their therapeutic roles and to support future therapeutic indications for the management of prediabetes in the routine care setting.

Why and When to Intervene?

Addressing the early (prediabetes) stage of the diabetes continuum provides an opportunity to intervene before the development of life-limiting complications. While the sections above discuss options for pharmacologic management of the diabetes continuum, it is important to note that overweight and obesity are recognized increasingly as key drivers of the progression and adverse clinical consequences of dysglycemia, independently of other cardiovascular risk factors.[33] Obesity has been shown to increase the risk of developing diabetes by 10-fold, compared with normal weight, in one study, which was similar to the 11-fold increase in risk observed in people with IFG.[69] Moreover, the problem of increasing rates of obesity is no longer limited to high-income countries: the "vast majority" of obese children live in developing countries, according to the World Health organization.[70] For this reason, lifestyle interventions aimed at addressing overweight or obesity are an indispensable component of management strategies for people at all stages of the diabetes continuum, and all with or at risk of diabetes and/or cardiovascular disease should be encouraged to improve their diet and engage in more physical activity in parallel with any pharmacologic intervention to address prediabetes or type 2 diabetes.[71–75]

Both intensive lifestyle intervention (vs no intervention or metformin) and metformin (vs no intervention) have been found to be cost-effective, especially in the high-risk individuals that guidelines identify as most suitable to receive metformin.[12,33,37,76,77] It should be noted, however, that the prevalence of prediabetes is high: a recent estimate found that 298 million worldwide had IFG and 464 million had IGT, and these figures were projected to increase to 414 million and 638 million, respectively, by 2045.[20] Accordingly, treating all people with prediabetes would be challenging for healthcare systems.[78] However, prediabetes itself places heavy burdens on healthcare systems: for example, prediabetes was estimated to cost the US healthcare system USD 43 billion in 2017,[79] despite <10% of people with prediabetes in the USA receiving treatment with metformin around this time.[80,81] The use of metformin for prediabetes was similarly uncommon (7.2%) in the Arabian Gulf.[82]

How, and whether, to address the challenge of prediabetes is a matter for each individual country/health system, according to its prevailing health and other priorities.[78] While all with prediabetes should be encouraged to improve their lifestyle, guidelines state already that pharmacologic intervention is not for everyone. Metformin, for example, is recommended for younger subjects with more severe obesity and hyperglycaemia,[35] as described above, which provides a framework for identifying those individuals likely to benefit most from this treatment.

Established Diabetes

For many years, guidelines for the management of diabetes recommended metformin as the initial pharmacologic intervention for all newly diagnosed type 2 diabetes patients without contraindications to its use. More recently, the completion of a series of cardiovascular and renal outcomes trials with newer classes of GLP-1RA and SGLT-2 inhibitors has led to support for their use as an option for first-line pharmacologic therapy (alongside lifestyle intervention) for people with type 2 diabetes who have established atherosclerotic cardiovascular disease (principally GLP-1RA), or heart failure or CKD (principally SGLT-2 inhibitors).[71–73] In addition, management of body weight is emphasized in the most recent ADA guidance.[72,74] Better support from healthcare systems and insurers has offset the relatively high cost of SGLT-2 inhibitors and (especially) GLP-1 receptor agonists in some areas.[83] However, surveys of real-world practice have shown consistently that the therapeutic use of these agents has remained relatively limited, even among patients with a clear therapeutic indication for their use, and barriers to the therapeutic use of these evidence-based agents need to be identified and removed.[84–86]

For all other patients, the ADA recommends the use of metformin or other agents with sufficient efficacy to achieve the patient's individualized glycaemic goal (including the use of antihyperglycemic combination therapy). Metformin is

included within these options on the basis of its proven efficacy and safety, with the potential to reduce the risk of cardiovascular events (based on the UKPDS[87]). Metformin can be combined with any other antidiabetic agent, as the severity of the underlying β-cell dysfunction in diabetes mandates the use of antidiabetic combination therapy. Metformin should be continued when starting insulin.

In our experience, metformin is often under-dosed, often as be a consequence of clinical inertia with failure to intensify treatment adequately, a common problem in diabetes management, as in other fields of medicine.[88,89] Alternatively, we have seen patients receive too high a dose of metformin initially, followed by discontinuation for the gastrointestinal side-effects. Starting with a low dose (500–1,000 mg) with cautious titration (eg addition of one tablet every week or every other week until reaching 2,000 mg) is vital for getting patients through the early and often troubling gastrointestinal side-effects of metformin, which may be a sign of the gut microbiota adjusting to the drug.[90] A temporary dose reduction can be helpful in restoring toleration if necessary. The use of the prolonged-release formulation of metformin also facilitates toleration of metformin for some people unable to tolerate the standard, immediate-release version.[91,92] However, we have encountered a fallacious belief among some primary care physicians that this formulation of metformin is less effective.

Remission of type 2 diabetes is possible for patients with relatively short diabetes duration (<10 years) who achieve substantial weight loss (at least 15% of initial body weight), whether this is achieved through pharmacologic therapy (to date, only incretin agonists have been shown to induce this magnitude of weight loss in an appreciable proportion of patients, see above), lifestyle intervention or bariatric surgery, and this area needs further study.[93,94]

Safety and Tolerability

All treatment classes bring their own set of adverse drug reactions. The gastrointestinal side-effects of metformin are well understood and easily managed, except when metformin is started at too high a dose, or intensified too quickly, as discussed above.[95] It is important that the contraindications to metformin are respected to minimize the risk of lactic acidosis, an extremely rare but serious adverse event described as occurring in <10/100,000 patient-years of treatment.[96] Older patients on metformin, especially, should be monitored to ensure that they do not develop renal contraindications to metformin during treatment. Patients on long-term metformin should be monitored appropriately for low vitamin B_{12}, a recognized side-effect.[97–99] GLP-1RA also cause gastrointestinal side-effects in a high proportion of patients: this usually resolves with continued use, but appears to be associated with treatment discontinuations.[100] Euglycemic diabetic ketoacidosis is a rare but serious complication of SGLT-2 inhibitor therapy.[101]

Conclusions

Prediabetes and diabetes are different stages of the same diabetes continuum and are associated with increased risk of adverse, long-term clinical outcomes. Prompt diagnosis of these conditions provides an opportunity to act early in the dysglycaemic continuum to promote improved long-term health outcomes. A large clinical evidence base supports roles for lifestyle intervention and metformin for the prevention type 2 diabetes, and evidence for newer agents (GLP-1 agonists and SGLT-2 inhibitors) is accumulating and may support indications for these agents for diabetes prevention in future. Early, intensive glycemic management in established type 2 diabetes provides clear, long-term clinical outcomes benefits.[102] The choice of initial pharmacologic therapy for newly-diagnosed type 2 diabetes (metformin or one of the newer agents) depends on the level of cardiovascular risk and its nature: atherosclerotic cardiovascular disease and heart failure or CKD may require intervention with a GLP-1 agonist or SGLT-2 inhibitor, respectively. Metformin remains a rational option for other patients, and can be continued throughout the diabetes continuum, up to and including when patients need insulin.

Artificial Intelligence (AI)

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Author Contributions

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