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REVIEW

Intervening Early in the Cardiovascular-Kidney-Metabolic Syndrome: Expert Recommendations from the United Arab Emirates on the Management of Prediabetes

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Abstract: The emerging concept of the cardiovascular-kidney-metabolic (CKM) syndrome encapsulates the interrelated nature of metabolic processes and metabolic dysfunction. Prediabetes, which describes the presence of elevations of blood glucose measurements insufficient to provoke a diagnosis of type 2 diabetes (T2D), is an important, – and crucially, reversible – early manifestation of the CKM syndrome. Numerous clinical studies and meta-analyses have shown that a substantial minority of people with prediabetes have microvascular and/or macrovascular complications reminiscent of those seen in clinical T2D. Prediabetes therefore represents an early stage of a continuum of increased insulin resistance, hyperglycaemia and associated vascular risk that begins at blood glucose concentrations that are well below those required for a diagnosis of diabetes. This condition also provides an opportunity for early intervention. All people with prediabetes should receive a multifactorial lifestyle intervention that focuses of weight management, nutrition, physical activity and smoking cessation. Where this is insufficient, ineffective or not followed, metformin remains the best studied pharmacotherapy for the management of prediabetes, with formal therapeutic indications for this purpose in many countries and support within international guidelines. Weight management is crucial for diabetes prevention, and weight loss during receipt of incretin agonist drugs is effective in diabetes prevention in populations with prediabetes, although consideration should be given to how long the treatment should be maintained and how the patient should be managed when it is ultimately withdrawn.

Keywords: diabetes, prediabetes, diabetes complications, cardiovascular disease, CKM syndrome

Introduction

Metabolic dysregulation does not arise in a single physiological system and the concept of the cardiovascular-kidney-metabolic (CKM) syndrome (Figure 1) has emerged in recent years to emphasise the closely interrelated pathophysiology of dysglycemia, diabetes, chronic kidney disease (CKD) and cardiovascular disease (CVD).[1,2] The CKM concept is especially valuable as it recognises the progressive nature of metabolic dysfunction and associated CVD, and emphasises the potential for intervention in its early stages to support improved long-term clinical cardiovascular outcomes. The strong associations between type 2 diabetes (T2D, = stage 2 CKM) and adverse cardiovascular outcomes have been

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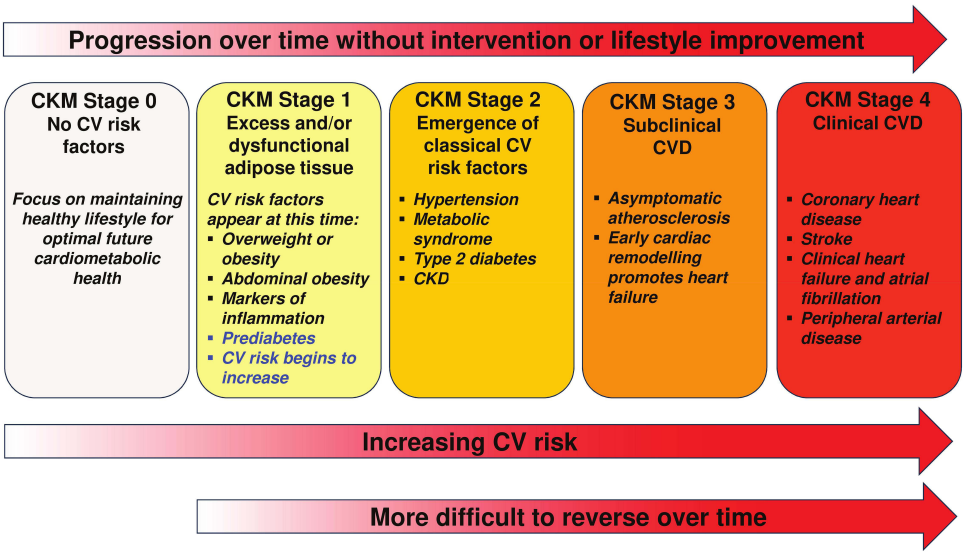

Figure 1 Stages of the cardiovascular-kidney-metabolic (CKM) syndrome. Drawn from information presented in refs[1–3].
Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease.

understood for decades. Stage 1 CKM syndrome describes an earlier situation where excess adiposity (with ectopic fat deposition in the liver and other key organs involved in metabolism) drives an inflammatory phenotype that promotes the abnormal glucose regulation characteristic of prediabetes (impaired glucose tolerance [IGT] and/or impaired fasting glucose [IFG]).[1–3] The importance of prevention of progression of CKM syndrome cannot be overstated: for example, data for 2011–2020 have showed that 89% of the US population had CKM syndrome of at least class 1, and 15% were already at stages 3–4, where atherosclerosis becomes established and the risk of mortality increases sharply.[4,5]

A huge number of individuals worldwide have prediabetes, with elevation of measures of blood glucose that are insufficient to provoke a diagnosis of T2D, but which signal a markedly increased risk of progression to clinical diabetes in the shorter term, and a longer-term risk of macrovascular and microvascular complications reminiscent of those seen in people with T2D.[6–8] In the United Arab Emirates, where the authors practice medicine, the prevalence of diabetes is high, at 12.3%, but the prevalence of prediabetes is half as high again at 18.3%.[9]

The large population of people with prediabetes will continue to drive a high incidence and prevalence of T2D for decades to come. There is no doubt that prediabetes appears as an early manifestation of the CKM syndrome, as described above. However, how (and indeed, whether) to intervene at the stage of prediabetes in order to preserve long-term clinical outcomes remains a matter for debate. We have not seen the advances in therapy for prediabetes that we have seen for T2D, which would be needed for to support a truly evidence-based approach to its management for optimization of long-term outcomes in this population. The purpose of this review is to consider the evidence base for early intervention in people with prediabetes as a strategy for addressing the early stages of the CKM syndrome, and to provide our own expert recommendations in this area.

Definitions, Terminology and Review Methodology

Diagnosing Prediabetes

The most commonly used diagnostic criteria for prediabetes are those proposed by the American Diabetes Association (ADA)[10] and other societies. Briefly, these are fasting plasma glucose (FPG) of 5.7–6.9 mmol/L (100–125 mg/dL), elevated post-load glucose 2 h following administration of a 75 g oral glucose tolerance test (OGTT) of 7.8–11.0 mmol/L (140–199 mg/dL), or HbA1c 5.7–6.4% (39–47 mmol/mol). Within the prediabetes diagnosis, "impaired fasting glucose" (IFG) and impaired glucose tolerance (IGT) identify states of elevated FPG without elevated post-load glucose and vice-versa.

Terminology

A number of terms, including "prediabetes", "non-diabetic hyperglycemia", "impaired glucose regulation", or "abnormal glucose regulation", among others, have been used by clinical scientists and expert groups to describe the state of elevated, but non-diabetic measures of blood glucose that is the subject of our review. These terms will continue to be debated but "Prediabetes" is the most common terminology in current use, driven largely by its adoption by the ADA to encompass IFG, IGT or elevated HbA1c.[11,12] For simplicity, we have taken a similar approach and discuss different forms of prediabetes separately where necessary, while acknowledging "prediabetes" as an umbrella term that encompasses all of them.

Search Strategy

This is a narrative review based on a structured search approach. A search term to identify publications on prediabetes was as follows:

> *(Prediabetes [ti] OR* "impaired fasting glucose" *[ti] OR IFG [ti] OR* "impaired glucose tolerance" *[ti] OR IGT [ti] OR* "non-diabetic hyperglycemia" *[ti] OR* "impaired glucose regulation" *[ti] OR* "abnormal glucose regulation" *[ti]) AND (macrovascular [ti] OR microvascular [ti] OR coronary [ti] OR cardiac [ti] OR cardiovascular [ti] OR ischemic [ti] OR neuropathy [ti] OR nephropathy [ti] OR retinopathy [ti])*

The second part of the search string was modified as necessary to explore different aspects of the pathophysiology of prediabetes, eg classes or names of individual pharmacotherapies. The order of preference for consideration was randomized, controlled trials (RCTs), meta-analyses/systematic reviews, and larger observational studies. Reference lists of identified publications and authors' reference collections provided further source material.

Prediabetes and Clinical Cardiometabolic Outcomes

Risk Factors for Prediabetes

Risk factors for prediabetes are generally the same as for T2D. Accordingly, a higher risk of prediabetes has been observed in subpopulations with older age and/or modifiable risk factors suggestive of insulin resistance, including obesity (especially abdominal obesity), atherogenic dyslipidemia (low HDL-C and high triglycerides), hypertension, smoking, or sedentariness.[13–15] Recent research has implicated deposition of ectopic fat deposits in key metabolic organs such as the liver, heart, pancreas and muscle as a key driver of insulin resistance and increased risk of diabetes and cardiovascular disease in the setting of obesity.[16]

Outcomes

Type 2 Diabetes

Overall, about 5–10% or people with prediabetes progress to clinical type 2 diabetes each year, with higher risk in those with higher blood glucose or combined IGT and IFG.[17,18] The lifetime risk developing diabetes varies between populations but has been estimated to be at least 75% for an overweight 45 year-old with IFG.[18] Prediabetes can also regress spontaneously to normoglycemia. For example, one study followed 23,293 adults with prediabetes for 5 years and found that 36% regressed to normoglycemia and 23% progressed to T2D, with the remainder remaining in the prediabetes category.[17]

Vascular Complications

A series of meta-analyses or systematic reviews published during the last 15 years have confirmed a higher prevalence of premature mortality and/or diabetes-like complications in populations with various definitions of prediabetes, compared with normoglycemic control groups (Table 1). [19–32] These complications affected both the microvasculature (eg neuropathy or retinopathy) and the macrovasculature (eg cardiovascular death, coronary heart disease (CHD), or stroke). One of these analyses[27] suggested a significant association between prediabetes and coronary artery disease (CAD) or stroke; the same publication also presented a causal interference analysis that demonstrated a causal relationship between prediabetes and CAD. Prediabetes also increased the risk of major adverse CV events (MACE) in people with an acute

Table 1 Principal Results of Meta-Analyses (MA) or Systematic Reviews (SR) That Described the Impact of Prediabetes on Clinical outcomes

Ref, Year, No. Studies	Overview of Key Findings
[19](SR), 2024, 7	Most studies (5/7) showed that regression from prediabetes to normoglycemia reduced the risk of cardiovascular or all-cause mortality (RRs 0.50–0.78)
[20](MA), 2023, 17	Normoglycemia was associated with lower risk ratios vs prediabetes for all-cause mortality, (0.66 [0.52 to 0.84]), MI (0.76 [0.61 to 0.95]) and cardiac death (0.58 [0.39 to 0.87]) in patients undergoing PCI
[21](MA), 2021, 24	Lower average prevalence of retinopathy in populations with NGT (3.2%) vs prediabetes (6.6%), based on studies that provided comparisons between these populations
[22](MA), 2021, 9	Higher prevalence of retinopathy for prediabetes vs NGT in cross-sectional studies: OR 1.55 (1.10 to 2.20), p=0.01
[23](MA), 2021, 29	Higher than expected prevalence of peripheral neuropathy in prediabetes vs NGT, mostly affecting small nerve fibres
[24](MA), 2021, 11	Higher prevalence of cardiac autonomic neuropathy in prediabetes (9%) vs NGT (4.5%)
[25](MA), 2020, 35	Prediabetes vs NGT was associated with increased RR of all cause mortality (1.13 [1.10 to 1.17]), cardiovascular disease (1.15 [1.11 to 1.18]), CHD (1.16 [1.11 to 1.21]), and stroke (1.14 [1.08 to 1.20])
[26](MA), 2020, 12	Prediabetes vs NGT was independently associated with MACE in patients undergoing PCI (risk ratio 1.53 [1.25 to 1.87])
[27](SR), 2020, 35	Prediabetes was associated with increased risk of CAD (RR 1.16 [1.09 to 1.23]) and stroke (RR 1.11 [1.03 to 1.18]), but not CKD (RR 1.05 [0.98 to 1.12])
[28](MA) 2019, 8	Increased risk of stroke with prediabetes vs NGT: HR 1.42 (1.13 to 1.80); outcomes tended to be more adverse in the prediabetes group
[29](MA), 2016, 35	Meta-analysis of prospective studies associated prediabetes (IFG or IGT) vs NGT with increased risk of CVD, CHD, stroke or death (RRs 1.13–1.32)
[30](MA), 2015, 17	Prediabetes increased the risk of CHD vs NGT: RR 1.11 (1.02 to 1.21) in prospective cohort studies
[31](MA), 2015, 26	IGT vs NGT increased risks of CV mortality (RR 1.33 [1.24 to 1.42]) and overall mortality (RR 1.23 [1.11 to 1.36]); IFG only increased mortality risk if WHO criteria[a] were used (RRs 1.12 [1.05 to 1.20] and 1.19 [1.05 to 1.35], respectively), and the effect of ADA IFG[b] was not significant (RR 1.07 [0.92 to 1.26] and 1.16 [0.94 to 1.42], respectively)
[32](MA), 2010, 5–18	Risks of CVD vs NGT were 1.18 (1.09 to 1.28) for IFG. 1.20 (1.07 to 1.34) for IGT and 1.10 (0.99 to 1.23) for combined IFG + IGT.

Notes: [a]FPG 6.1–6,9 mmol/L (110–125 mg/dL). [b]See text. Figures in parentheses accompanying risk or hazard estimates are 95% confidence intervals.
Abbreviations: ADA, American Diabetes Association; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; MACE, major adverse cardiovascular event(s); MI, myocardial infarction; NGT, normal glucose tolerance (no prediabetes); PCI, percutaneous coronary intervention; RR, relative risk; WHO, World Health Organization.

myocardial infarction.[33] Impaired endothelial function, an early precursor of vascular dysfunction, has also been observed in people with prediabetes.[34] In general, the prevalence of diabetes-like complications in populations with prediabetes appears to lie between that observed in populations with normoglycemia and clinical type 2 diabetes, as would be expected.[7]

Improving the Diagnosis of Prediabetes

For diagnosing prediabetes, HbA1c measurement using the ADA criteria (5.7–6.4% [39–47 mmol/mol]) provides the most convenient and widely available test for diagnosing prediabetes. Measurement of FPG (again, ADA criteria of 5.7–6.9 mmol/L 9100–125 mg/dL]) provides an alternative. Evidence of insulin resistance (eg in HOMA-IR is calculated) may provide useful supportive information.

Case finding is the major barrier to diagnosing prediabetes. We recommend earlier age (40 years or less) and more intensive screening for elevated HbA1c of at-risk individuals such as those with a family history of diabetes, overweight or obesity, cardiometabolic risk factors (especially atherogenic dyslipidemia or hypertension), CVD, higher risk ethnicity (eg Asian heritage), prior gestational diabetes, polycystic ovary syndrome, or signs of severe insulin resistance such as acanthosis nigricans.[35] This approach provides an opportunity to identify people with prediabetes in time to intervene to prevent progression of the CKM syndrome to a more dangerous and less reversible stage.

Place of Lifestyle Intervention in the Management of Prediabetes

Evidence Base

Landmark randomized trials such as the Diabetes Prevention Program (DPP, USA),[36] the Diabetes Prevention Study (DPS, Finland)[37] and the Da Qing study (China, a cluster randomized trial)[38] proved that intensive lifestyle interventions, based on improved diet and more physical activity, delivered substantial reductions (–58%, –58%, and –42%, respectively) in the risk of conversion of IGT to T2D. Numerous other studies have confirmed the efficacy of intensive lifestyle interventions for preventing diabetes.[39]

The DPS showed that the risk of developing diabetes fell as the number of lifestyle goals achieved increased: no one who achieved all five lifestyle goals developed diabetes during the randomized phase of the trial. Observational data have confirmed that the presence of cardiometabolic risk factors decreases the odds of regression to normoglycemia and increases to risk of incident T2D.[40]

Thirty years of post-trial follow up of the Da Qing cohort showed that initial randomization to the lifestyle group was associated with an average 3.4-year delay in the onset of diabetes and a reduced long-term risk of cardiovascular disease events (HR 0·74 [95% CI 0.59 to 0.92]), cardiovascular deaths (HR 0.67 [95% CI 0.48 to 0.94]), microvascular complications (HR 0.65 [95% CI 0.45 to 0.95]), and all-cause death (HR 0.74 [95%CI 0.61 to 0.89]).[41] The LOOK-AHEAD Study found that randomization of overweight or obese people with T2D to an intensive weight loss programme did not reduce the incidence of the primary composite CV outcome (3-point MACE) or secondary MACE outcomes, despite significant weight loss (–2.5% vs placebo at study end) and improved CV risk factors in the intervention group.[42] However, a post hoc analysis of the trial suggested that those who lost at least 10% of initial weight benefitted from a significant 21% reduction in the primary outcome, compared with those who did not lose weight or regained weight.[43]

A meta-analysis of prospective cohort studies (2020, 142 studies) reported that subjects with the healthiest lifestyles overall had lower risk of cardiovascular or overall mortality, or incident cardiovascular disease, compared with those with the least healthy lifestyles.[44] Lifestyle interventions therefore have the potential to improve outcomes. However, a recent meta-analysis of RCTs has suggested that intensive lifestyle interventions did not reduce rates of cardiovascular mortality (RR 0.99 [95% CI 0.79 to 1.23]) or all-cause mortality (RR 0.93 [95% CI 0.85 to 1.03]), compared with usual care.[45] The authors speculated that the provision of at least some lifestyle advice in the control groups of the studies they analysed may have attenuated the differences in outcomes between groups. Further studies are required to resolve this apparent paradox.

Therapeutic Application

Consensus guidelines from the Emirates Diabetes Society, which apply where the authors practice medicine, recommend that all with prediabetes should be encouraged to undertake an initial 6 months of lifestyle intervention that encompasses weight management, medical nutrition therapy, exercise and smoking cessation (Figure 2).[35] These recommendations are broadly similar to those proposed by the ADA.[46] Follow-up at 3 months may be useful to check progress and adherence. Few people adhere well to long-term lifestyle interventions and lack of acceptance of this approach by patients is common, however.[47] Importantly, patients are usually more prepared to engage with treatment for prediabetes if given concise, meaningful information.[48]

Overall, the benefits of lifestyle intervention in prediabetes are proven beyond doubt, although the apparently substantial weight loss needed to improve CV outcomes in LOOK-AHEAD (described above) will be challenging to achieve for many via lifestyle intervention. Nevertheless, all people with – or at risk of – prediabetes should be encouraged to improve their diet and increase their level of physical activity.

Place of Pharmacotherapy for People with Prediabetes

Pharmacotherapy is an option where patients cannot, or will not, adhere sufficiently to a lifestyle intervention to control their weight and glycemia sufficiently.[46] Numerous treatments have been evaluated in subjects with prediabetes, and a brief overview of the effects and place in therapy of the main drug classes is given below.

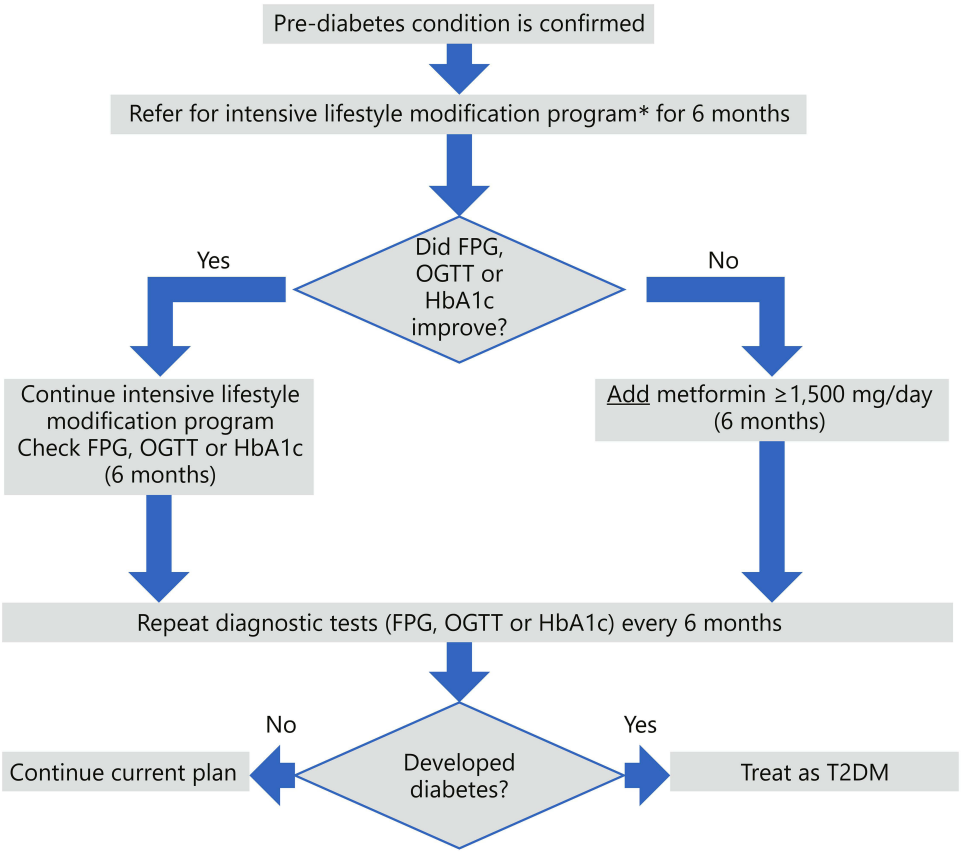

Figure 2 Overview of recommendations for the initial management of prediabetes from the 2020 Emirates Diabetes Society Consensus Guidelines for the Management of Type 2 Diabetes Mellitus. *The target is to achieve and maintain 5–10% weight loss and increase moderate-intensity physical activity (such as brisk walking) to at least 150 min/week. Reproduced unaltered from ref[35] under the Creative CC BY-NC-ND license (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Metformin

Evidence Base

Metformin is currently the most widely studied pharmacotherapy for diabetes prevention and now has a therapeutic indication for this purpose in numerous countries. Many studies have described a reduction in the risk of diabetes following administration of metformin to populations with prediabetes, especially those with IGT.[49–51] In the DPP, randomization to metformin was associated with a –31% reduction on the risk of conversion of IGT to T2D, compared with a –58% reduction for the intensive lifestyle intervention, both compared with standard lifestyle advice.[36] Average weight loss of –2.06 kg in the metformin vs the control group was observed in the randomized phase of the DPP, and weight remained lower in patients formerly randomized to metformin vs placebo throughout the DPP Outcomes Study, the observational follow-up to the trial.[36,52] A meta-analysis has confirmed that metformin treatment is associated with modest long-term weight loss[53] (the potential for use of metformin as an adjunctive weight loss therapy in combination with a GLP-1 receptor agonist [GLP-1RA] is discussed later in this review).

Subgroup analyses showed that the efficacy of metformin and the lifestyle intervention for prevention of diabetes vs the control group was more similar for younger subjects (25–44 years, –44% and –48% risk reductions), heavier subjects (BMI ≥35 kg/m^2, –53% and –51% risk reductions) and those with higher fasting plasma glucose (FPG) at baseline (6.1–6.9 mmol/L [110–125 mg/dL], –48% and –63% risk reductions). For this reason, guideline recommendations supporting consideration of metformin for diabetes prevention focus on this subgroup: the ADA, for example, currently recommends use of metformin for individuals with prediabetes who are aged 25–59 years, with higher blood glucose (FPG ≥6.1 mmol/L [110 mg/dL] or HbA1c ≥6.0% [≥42 mmol/mol]) and BMI ≥35 kg/m^2.[46] The DPP also showed that metformin reduced the risk of T2D by –40% in women at elevated diabetes risk due to a prior history of gestational

diabetes (GDM; the risk reduction with the intensive lifestyle intervention was –35%).[54] The ADA Standards of Care guideline also supports consideration of metformin for diabetes prevention for women with a prior history of GDM.[46]

The large (N=1,678), randomized Chinese Diabetes Prevention Program (CDPP) recruited a population with IGT, IFG or both.[55] Unlike the DPP, the CDPP evaluated the effects of a lifestyle intervention (30 minutes of exercise each day, plus beneficial dietary and lifestyle changes) with or without additional metformin 1,700 mg/day. The risk of conversion to diabetes was significantly lower in the metformin + lifestyle group vs lifestyle alone over a follow-up period of 2 years (HR 0.83 [95% CI 0.70 to 0.99], p=0·043), accompanied by an additional weight reduction of 2.1 kg in the metformin-containing group. As in the DPP, metformin was more effective for diabetes prevention in younger or heavier subjects, as well as in males. Subjects with hypertension also benefitted more from metformin + lifestyle vs lifestyle alone, suggesting efficacy on diabetes prevention in subjects with CKM comorbidities.

Metformin was well tolerated in the DPP and in the CDPP with no serious safety concerns.[52,55] The familiar gastrointestinal side-effects of metformin were more common on metformin (28% vs 16% for placebo during the first 4 years of the DPP, with no difference between groups for 6 years of treatment onwards,[52] and 15.2% for metformin + lifestyle vs 0.9% for lifestyle alone in the CDPP[55]). Reduced levels of vitamin B_{12}, a well-known side-effect of long-term metformin treatment in people with T2D, also occurs in people with prediabetes during long-term treatment with metformin and this should be checked periodically and corrected as necessary, particularly where neuropathy or anemia are present.[46,56]

Therapeutic Application

Metformin is the most studied option for use in prediabetes, as described above, and has a therapeutic indication for diabetes prevention in more than 60 countries.[50] Glycemic status should be retested every 6 months while receiving metformin (Figure 2).[35] In our experience, metformin is often under-dosed, especially in the setting of prediabetes. Treatment with metformin should be titrated cautiously from a low dose (eg 500 mg/day) towards a maintenance dose of at least 1,500 mg/day, as used in major RCTs such as the DPP and CDPP, as described above.[35] The prolonged-release formulation (XR or SR) has a superior side-effect profile to the immediate-release version.[57,58] Starting at a high dose or titrating too quickly is likely to provoke severe gastrointestinal side-effects that will lead to poor adherence to treatment.[58] This is an important issue, as the magnitude of weight loss with metformin during the DPP was greater in subjects who adhered better to the metformin regimen.[52]

Metformin can be prescribed for people with CKD as long as the eGFR is >30 mL/min/1.73 m^2. However, it is important to monitor people with CKD who receive metformin to ensure that the eGFR remains above this level. Also, discontinue metformin temporarily during situations that may acutely decrease renal function such as administration of iodinated contrast media. Mitochondrial disease has emerged as a recent contraindication to metformin. Individuals with conditions typically related to the m.3243A>G mutation in mitochondrial DNA (such as the syndromes of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [MELAS] and maternally inherited diabetes and deafness [MIDD]) often develop diabetes[59] and, if undiagnosed, may receive metformin. Treatment of these individuals with metformin has been associated with an increased risk of severe adverse outcomes, especially lactic acidosis or stroke-like episodes[60–64] and metformin should be avoided. A combination of young age at diabetes onset, short stature, low body weight, and deafness can be suggestive of MIDD or MELAS,[61,62] and may prompt genotyping for a definitive diagnosis. Genotyping is not available everywhere, unfortunately, and remedying this situation would be an important facilitator of achieving precision medicine within the prescription of metformin. Other contraindications and precautions for the use of metformin are summarized in the product labelling.

Incretin Receptor Agonists and SGLT2 Inhibitors

Evidence Base

GLP-1RA and agents that activate additional metabolic hormone receptors such as GIP and/or glucagon have also been studied in trials that included substantial populations of people with prediabetes. These drugs have the potential to prevent diabetes in at-risk subjects due to the substantial weight loss, with consequent amelioration of insulin resistance, that is seen in most recipients of these drugs.[65] Reductions in the rate of conversion of prediabetes to diabetes (or

increases in the proportion regressing to normoglycemia) have been observed within randomized trials in overweight or obese populations that involved treatment with incretin agonists, including semaglutide (GLP-1RA),[66–69] liraglutide (GLP-1RA),[70–73] tirzepatide (dual GLP-1/GIPRA),[74] and retatrutide (triple GLP-1/GIP/glucagon RA).[75] Reduction of visceral ectopic fat appears to be a key mechanism underlying these effects.[76]

It is well known that GLP-1RA improve CV risk factors (especially weight and blood pressure),[77] as well as clinical CV and renal outcomes and mortality,[78–80] in populations with T2D, via mechanisms believed to act via reduced progression of atherosclerosis.[81] Two-thirds (66%) of the population of the SELECT study, the first randomized trial to demonstrate reduced mortality with a pharmacologic weight loss intervention (semaglutide) in a population with CVD but no T2D, had prediabetes (HbA1c >5.7%).[82] There was no heterogeneity in this outcome according to prediabetes status, suggesting that improved clinical outcomes may be feasible via weight loss in this population. The 2025 ADA Standards of Care notes these studies, but does not currently provide a recommendation on their use to manage prediabetes; its recommendation to achieve weight reduction of at least 7% of initial body weight in this population is based on the results from the lifestyle intervention arm of the DPP.[46]

SGLT2I are not currently approved for the management of prediabetes, although a substantial number of patients enrolled in SGLT2I trials in populations with HF or CKD did have HbA1c 5.7–6.4, which is consistent with having prediabetes.[83] These agents reduced the incidence of T2D in subjects with prediabetes and comorbid heart failure (HF) or chronic kidney disease (CKD).[83–85] Moreover, SGLT2i have demonstrated potentially antiatherosclerotic effects in addition to their well-described effects on weight, glycaemia, and blood pressure, including modulation of inflammation and oxidative stress, antifibrotic effects, and improved vascular function in experimental studies.[86] Consistent with these observations, SGLT2i have reduced the incidence of adverse CV outcomes in patients with T2D or established atherosclerosis,[87,88] although they did not appear to reduce the risk of stroke.[89] Although prospective outcomes trials with SGLT2i conducted exclusively in populations with prediabetes are lacking at present, systematic reviews show that there was no heterogeneity in the effects of these agents between subpopulations with prediabetes or T2D in CV outcomes trials with these agents,[90] and that SGLT2i were associated with significant improvements in CV and/or renal outcomes in populations without T2D.[91,92]

HF and CKD may themselves justify intervention with a SGLT2i and more data in populations without these additional complications will be needed before a more general recommendation for their therapeutic use in prediabetes can be justified, especially as the outcomes benefits observed with SGLT2i have been observed in patients with or without T2D.[93] Weight loss is generally more modest with SGLT2i than with incretin agonists.[94]

Therapeutic Application

Current guidelines for the management of type 2 diabetes support selection of initial pharmacotherapy based on stratification for cardiovascular risk at presentation, with support for initial use of a GLP-1RA or SGLT2i (see below) especially for patients with atherosclerotic cardiovascular disease, or HF or CKD, respectively.[35,95] These conditions are not uncommon in people with prediabetes, as summarized above. The reductions in glycemia and weight associated with the newer classes of agents may also lead to reduced risk of diabetes, as well as reducing the risk of MACE or the onset or worsening of CKD or HF in people with prediabetes and very high cardiovascular risk.[96]

Clinical experience with newer classes of pharmacotherapy, including the incretin agonists, is not yet sufficient to support formal indications and guideline recommendations. Some patients will be taking these drugs for principal reasons other than managing prediabetes, eg incretin agonists for weight management. Weight loss is key to the management of both prediabetes and established T2D.[46,97] For an individual with dysglycemia and obesity, loss of 3–7% of initial weight is likely to improve a range of cardiometabolic risk factors, while loss of at least 10% of initial weight may improve long-term clinical outcomes.[97] Thus, it is not surprising that individuals with prediabetes who lose substantial body weight during treatment with an incretin agonist will have a reduced risk of progression to T2D and an increased chance of regression to normoglycemia (see above for citations of the relevant RCTs). Drawbacks to the clinical use of these agents include a high rate of treatment withdrawals, including for side-effects, and issues relating to cost and limitations on patients' access to this treatment.[98–101] One large cohort study showed that 65% of people without T2D who initiated

a GLP-1RA withdrew within one year of treatment.[98] Discontinuation of these drugs appears to be more common in people receiving them for obesity compared with T2D.[99]

There remains no consensus on the optimal duration of therapy with a GLP-1RA, and also on how to manage patients after withdrawal of an incretin agonist, as the weight loss largely reverses after treatment discontinuation.[102] Metformin increases secretion of GLP-1,[103] suggesting a complementary action between metformin and GLP-1RA, and multiple other mechanisms contribute to modest long-term weight loss on metformin.[104] Although metformin does not appear to modulate the CV effects of a GLP-1RA (or an SGLT2 inhibitor),[105] it may be a rational choice for inclusion in a regimen after withdrawal of a GLP-1RA. A study in women with polycystic ovary syndrome, a prediabetic state characterized by overweight/obesity and insulin resistance, who received co-administered semaglutide and metformin followed the weight trajectory after withdrawal of semaglutide.[106] The metformin-treated women regained only one-third of the prior semaglutide-induced weight loss. Additional evidence supports a role for older classes of pharmacologic agents, including metformin, as adjunctive therapy to GLP-1RA to help maintain weight loss.[107] Recent (2023) expert opinion has recommended metformin as an adjunct to weight-loss therapies in the absence of contraindications for some people with prediabetes.[108] Further clinical experience with GLP-1RA will clarify their optimal role in the guideline-driven management of prediabetes in the future.

Other Treatments

Pioglitazone has been shown to reduce conversion of prediabetes to T2D.[109,110] This treatment was associated with reduced risk of MACE in people with prediabetes or insulin resistance (RR 0.77 [95% CI 0.64 to 0.93]) in a 2017 meta-analysis of nine trials with >1 year of follow-up, but at a cost of an increased incidence of heart failure, fractures, oedema and weight gain.[111] Pioglitazone also appears to reduce the risk of recurrent stroke in prediabetes.[112] Safety and tolerability issues have prevented the widespread use of pioglitazone (or other thiazolidinedione drugs) for diabetes prevention. The possibility of improved liver histology with pioglitazone in the setting of prediabetes and comorbid metabolic dysfunction-associated fatty liver disease is a current focus of research.[113]

Acarbose (α-glucosidase inhibitor) has been shown to reduce the rate of conversion to T2D in populations with IGT and a meta-analysis reported reduced weight and improved glycemia and lipids with acarbose vs placebo in subjects with IGT.[114] A report from one evaluation of acarbose in subjects with IGT suggested a reduction in the risk of cardiovascular events vs placebo, though there were very few events.[115] Acarbose increased costs without increasing the number of quality-adjusted life-years vs placebo in a more recent RCT in 6,522 patients with CAD and IGT.[116] Troublesome gastrointestinal side-effects have limited the clinical use of acarbose in most countries,[117] although this drug is widely prescribed for people with diabetes in the far East, where carbohydrate from rice makes up a greater proportion of the daily diet.[118]

Basal insulin (glargine) was evaluated in comparison with usual care in the randomized ORIGIN trial, which included 1,456 people with prediabetes, treated for a median period of 6.2 years.[119] Glargine treatment was associated with a 28% reduction in new diabetes incidence in these subjects, despite an increase in weight in glargine-treated patients (about +2 kg vs usual care in the overall population). There was an approximately three-fold increase in the incidence of severe hypoglycemia in the glargine vs usual care groups (1.0 vs 0.3/100 patient-years).

These pharmacologic agents are not widely prescribed for the prevention of T2D due to tolerability and safety issues and their properties have been described above for completeness. Bariatric (weight loss) surgery also has the potential to induce substantial weight loss and has been associated with diabetes prevention and/or remission of prediabetes.[120–123] This approach is too costly, invasive and risky for wide use in prediabetes management per se.

Summary of Recommendations – What More Do We Need to Do to Manage Prediabetes Effectively?

Applying Evidence-Based Approaches to T2D Prevention

Authors' recommendations on the optimal management of prediabetes are summarized in Box 1 and Figure 2. All should be considered to be strong recommendations, designed to challenge and address therapeutic inertia, encompassing the actions needed to improve the detection and diagnosis of prediabetes, and to promote earlier intervention with evidence-

Box 1 Summary of Authors' Recommendations for the Management of Prediabetes

Diagnosis
HbA1c 5.7–6.4% (39–47 mmol/mol) is the most convenient and widely available test for diagnosing prediabetes
Cardiometabolic risk factors associated with the CKM syndrome, including overweight/obesity, components of the metabolic syndrome, prior GDM, sedentary lifestyle or other conditions characterized by insulin resistance (eg PCOS) indicate an elevated risk of prediabetes and may identify subjects suitable for testing for the condition
Lack of opportunities for screening for prediabetes remains a major unmet need
Education of primary care physicians on prediabetes is an urgent priority, to overcome treatment inertia and other barriers to effective treatments and to support them in motivating patients to engage with their prediabetes and its management
Management – lifestyle interventions
Weight management is key to the management of prediabetes
All with prediabetes should be encouraged to undertake lifestyle intervention that encompasses weight management, medical nutrition therapy, exercise and smoking cessation
Lifestyle intervention should be tried for 6 months initially, with intermediate follow-up at 3 months
Management – pharmacotherapy
Metformin is the most studied pharmacologic option for prediabetes management and can be titrated to a dose of at least 1500 mg/day (check glycemic status every 6 months and check vitamin B_{12} periodically)
Overweight or obese people with prediabetes who lose substantial weight while receiving an incretin agonist may improve their glycemic status
Withdrawals due to side-effects, and issues relating to cost/access to incretin agonists limits the overall utility of this therapy

Abbreviations: CKM, cardiovascular-kidney-metabolic; GDM, gestational diabetes mellitus; PCOS, polycystic ovary syndrome.

based approaches. We recommend an initial trial of lifestyle intervention aimed at improving health behaviors, particularly increased physical activity and improved diet to promote weight loss, together with smoking cessation.

Where pharmacotherapy is necessary, metformin is the most studied therapeutic option for a patient free of contra-indications and the management algorithm from the 2020 Emirates Diabetes Society Consensus Guideline (Figure 2) reflects this. It is important to ensure an adequate dosage of metformin is given, using careful dose titration to optimize tolerability. While formal recommendations for the use of incretin drugs are yet to appear in guidelines, we note that people with prediabetes who manage substantial weight loss on one of these agents may improve their glycemic status.

Future Directions and Unmet Needs

Improving the Evidence Base for Prediabetes Management

Prediabetes has not received the same intensity of research attention as established T2D, as discussed above. More studies are needed to quantify the impact of different interventions on long-term outcomes in populations with prediabetes, including when used in combination. Better information is also needed on how to apply interventions, and how to ensure that a regimen is adhered to. Patients are often unwilling to start medication for a condition that does not (yet) make them feel unwell. These observations are from our own clinical experience, but published evidence from around the world suggests that these are widespread issues in managing prediabetes.[124–127] In addition, given that GLP-1RA are usually taken for a relatively limited time only (as described above), we need evidence-based guidance on when, and how, to withdraw these agents without reversal of weight loss.

Improving Awareness and Understanding of Prediabetes and Its Management

Factors relating to the healthcare system and to patients themselves hinder the optimal management of prediabetes. Primary care physicians, in particular, often need education on prediabetes and its management. Therapeutic inertia and a lack of follow-up are compounded by a lack of referrals and unclear goals for lifestyle intervention.

Overcoming Barriers to Improved Lifestyles

A hot climate, as in the UAE and elsewhere, can represent a significant barrier to taking exercise outdoors.[128] A recent (published in 2024) qualitative study in Arabian Gulf countries, which included the UAE, reported multiple barriers to increased physical activity, including restrictions on exercising outdoors, limited amenities, a cultural bias towards less exercise for older and heavier individuals or women, a prevalent misconception that exercise is conducted only in a gym,

lack of understanding about how to increase activity, and concerns about injury.[129] An older (2010) survey of people with T2D in the UAE found that only one-quarter increased their physical activity after their T2D diagnosis, and less than one in thirty did so the extent recommended in guidelines, despite a high prevalence of cardiometabolic risk factors associated with the CKM syndrome, such as hypertension.[130] Other studies from the region reported comparable findings.[131–133]

Some recent data present cause for hope, such as a steady increase in the number of people increasing their physical activity in the region.[134] There remains much to do here, however. For example, a study from the UAE reported a tendency towards a healthier diet among people with vs without T2D in the UAE, implying a continued need for lifestyle education for the latter to help prevent T2D onset.[135] Also, increased physical activity in the T2D vs non-T2D group was seen only in males, with no difference for females, in this study.[135] Clearly, expert physicians have a key role in educating primary care physicians on the importance and delivery of improved lifestyles, as for the prescription of pharmacotherapy, as described above.

Conclusions

Thirty-five years ago, in 1990, Haffner et al observed an increased prevalence of cardiovascular risk factors in people with prediabetes and asked an important question: "Does the clock for CHD start ticking before the onset of clinical diabetes?".[15] The data summarized above show that many clinical studies since that time have answered this question in the affirmative, not only for CHD but for other diabetes-like complications. More recently, the concept of the CKM syndrome has highlighted the opportunities and potential benefits of intervening at the start of the CKM syndrome.[1,2] It is important to note that prediabetes represents an early, reversible stage of the CKM syndrome that provides an opportunity for intervention before intractable comorbidities become established.

We recommend that all people with prediabetes should receive a multifactorial lifestyle intervention that focuses of weight management, nutrition, physical activity and smoking cessation. Where this is insufficient, ineffective, or not followed, metformin should be considered: this is the best studied pharmacotherapy for the management of prediabetes, with formal therapeutic indications for this purpose in many countries and support for its use within international guidelines. It is important that overweight/obesity is addressed urgently: weight management is crucial for diabetes prevention, and weight loss during receipt of incretin agonist drugs is effective in diabetes prevention in populations with prediabetes. However, consideration should be given to how long the treatment should be maintained and how the patient should be managed when it is ultimately withdrawn.

Artificial Intelligence (AI)

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