Benefit of lifestyle-based T2DM prevention is influenced by prediabetes phenotype

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Abstract | The prevention of type 2 diabetes mellitus (T2DM) is a target priority for the WHO and the United Nations and is a key priority in the 2018 Berlin Declaration, which is a global call for early actions related to T2DM. Health-care policies advocate that individuals at high risk of developing T2DM undertake lifestyle modification, irrespective of whether the prediabetes phenotype is defined by hyperglycaemia in the postprandial state (impaired glucose tolerance) and/or fasting state (impaired fasting glucose) or by intermediate HbA_{1c} levels. However, current evidence indicates that diabetes prevention programmes based on lifestyle change have not been successful in preventing T2DM in individuals with isolated impaired fasting glucose. We propose that further research is needed to identify effective lifestyle interventions for individuals with isolated impaired fasting glucose. Furthermore, we call for the identification of innovative approaches that better identify people with impaired glucose tolerance, who benefit from the currently available lifestyle-based diabetes prevention programmes.

Type 2 diabetes mellitus (T2DM) is a persistent and prevalent threat to global health. The number of people with T2DM is projected to reach 700 million by 2045 (REF.[1]), with the greatest increases expected in low-income and middle-income countries. In these settings, the burden of T2DM is substantial and access to highly trained health-care professionals is the most limited. In addition, the number of adults at high risk of developing T2DM because of impaired glucose tolerance (IGT) (TABLE 1) is projected to rise from 373.9 million in 2019 to 548.4 million by 2045 (REF.[1]). Therefore, interventions that prove to be cost-effective and effective in preventing or delaying progression to T2DM among high-risk individuals are of the utmost importance to public health[2].

The prevention of T2DM has been declared a target priority by the WHO[3] and the United Nations[4] and forms a key priority in the 2018 Berlin Declaration, which is a global call for early actions related to T2DM[5]. In an attempt to curtail the progression of T2DM, health-care policies now advocate that individuals at high risk of developing T2DM undertake lifestyle modification[6–8]. These lifestyle modifications generally focus on weight reduction by modifying nutrition, increasing physical activity and other health-related behaviours[6–9] (TABLE 2). Strong evidence now exists from large randomized, controlled trials (RCTs) and meta-analyses demonstrating that for individuals with IGT, modification of lifestyle is effective in producing reductions in progression to T2DM of ~30–60% (REFS[10–18]). Reductions in T2DM progression could be sustained for up to 30 years after the active intervention phase, as shown by the Da Qing Diabetes Prevention Outcome Study; however, in that study more than 80% of participants eventually developed T2DM[19].

In this Perspectives, we review evidence on the effectiveness of lifestyle interventions in reducing T2DM incidence among different prediabetes phenotypes and discuss the implications for clinical and public health practice.

Prevalence of prediabetes

Prediabetes encapsulates a number of heterogeneous metabolic states; that is, impaired fasting glucose (IFG), IGT or intermediate HbA_{1c} level (TABLE 1). Although not a clinical entity in itself, prediabetes identifies individuals with hyperglycaemia who do not meet the criteria for T2DM but whose glucose levels are higher than those considered normal[20,21]. Individuals with prediabetes are at high risk of developing T2DM. Health-care policies recommend that these individuals undertake lifestyle modification, irrespective of whether the prediabetes phenotype is defined by hyperglycaemia in the postprandial state (IGT) or the fasting state (IFG), or is based only on intermediate HbA_{1c} level criteria[6–8].

The prevalence of isolated IFG, isolated IGT, a combination of IFG and IGT and intermediate HbA_{1c} levels is quite variable across studies[22] and is dependent on the diagnostic criteria used, population characteristics and ethnicity[20,21,23,24]. For example, a 2017 review of 24 studies conducted across European white and Chinese Asian populations showed that, among those with prediabetes, the average proportional prevalence of isolated IFG was higher in European white individuals than in Chinese Asian individuals, irrespective of the criteria used; however, despite these differences being large, they were not statistically significant (WHO criteria 43.9% versus 29.2%; American Diabetes Association criteria 58.0% versus 48.1%)[22]. In India, a large-scale nationwide study showed that isolated IFG is a far more common form of prediabetes than IGT[25], with the ratio of isolated IFG to IGT reaching as high as 5:1 when the American Diabetes Association criteria are used[25].

Most evidence of benefit from lifestyle programmes for prediabetes has been based on interventions in individuals with IGT[10–13,26]; to date, few studies have assessed isolated IFG[27–30] and none has examined isolated intermediate HbA_{1c} levels. Of note, IGT can be diagnosed only by the oral glucose tolerance test (OGTT). This 2-hour test is time consuming, is costly, shows large intraindividual variability and is difficult to accommodate within the primary care setting, where most of the diagnoses occur. As such, the use of the OGTT has

thus far been considered less feasible to detect high-risk individuals for many T2DM prevention programmes[7,31]. Therefore, in clinical practice, lifestyle programmes commonly use the levels of fasting plasma glucose (FPG), HbA_{1c} level or a non-invasive risk score to identify high-risk individuals as alternatives to an OGTT[8,32]. However, studies from different populations have shown that the agreement of such tests with the OGTT in identifying those with IGT is low[18,29,33,34].

Diabetes risk scores commonly include risk factors such as age, family history of T2DM, waist circumference, BMI, high blood pressure, smoking history and physical activity[35]. Although the use of such a risk score reduces the number of people who undergo further blood testing, a large proportion of those identified as high risk tend to have either normal plasma glucose levels or isolated IFG[29,36]. In a T2DM prevention study in a Spanish primary health-care setting, among those with a high Finnish Diabetes Risk Score (greater than 4), nearly 60% had normal plasma glucose levels[36]. A 2018 T2DM prevention study in India showed that, among those identified as high risk using a non-invasive risk score, five times as many people had isolated IFG than IGT[29]. Although individuals with isolated IFG have a slower rate of progression to T2DM than those with isolated IGT or a combination of IFG and IGT[37–39], as mentioned earlier, isolated IFG is a more common form of prediabetes in certain populations[22,25]. From a public health point of view, this observation is highly important, as the absolute number of persons with incident T2DM from the isolated IFG subgroup might equal the number from the other prediabetes categories that have higher risk of T2DM.

Prediabetes phenotype

The use of the term prediabetes as a 'cover-all' term for prediabetes phenotypes has led to the appearance that lifestyle interventions have been effective across the board at reducing progression to T2DM; however, most studies assessing lifestyle interventions were undertaken only among individuals with IGT[13–18,40,41].

Clinical trials in individuals with IGT. Most of the influential clinical trials of lifestyle-related diabetes prevention programmes (DPPs) recruited participants on the basis of their having IGT, and these studies showed a clear benefit of the interventions[10–12,14–18]. For example, after 6 years of follow-up of 577 individuals with IGT in the Da Qing IGT and Diabetes Study[13], the incidence of T2DM was 43.8% in the diet-only group, 41.1% in the exercise-only group and 46.0% in the diet plus exercise group, all of which were statistically significantly lower than the incidence in the control group (67.7%). Furthermore, in the Finnish Diabetes Prevention Study[12], a physical activity and dietary intervention among 522 participants with IGT and overweight resulted in T2DM incidence being reduced by 58% in the intervention group compared with the control group after 4 years of follow-up (HR 0.4, 95% CI 0.3–0.7). In the US Diabetes Prevention Program[11], among participants with IGT and overweight, participants in the lifestyle intervention group showed a 58% (95% CI 48–66%) reduction in T2DM incidence compared with the control group participants after a mean follow-up of 2.8 years. In addition, in the Indian Diabetes Prevention Programme[10], 531 individuals with IGT showed a 28.5% reduction in T2DM incidence in the lifestyle intervention group compared with the control group after a median follow-up of 30 months.

The findings from these four landmark efficacy trials are supported by several other RCTs conducted with individuals with IGT[42]. Of note, most successful lifestyle intervention RCTs, particularly those conducted predominantly in white populations, have included people with overweight or obesity with IGT. However, trials from Asian populations with IGT, who are relatively leaner, have also shown a significant reduction in the proportion of individuals progressing to T2DM after lifestyle intervention[10,13,29]. More importantly, this reduction was seen without significant weight loss.

Lifestyle interventions in isolated IFG. Existing data suggest that lifestyle intervention programmes in their current form (TABLE 2) might not prevent progression to T2DM in individuals with isolated IFG[27–30]. In a well-controlled RCT conducted in Japan, a subgroup analysis by glucose metabolism phenotype was applied to 641 Japanese individuals with overweight (aged 30–60 years) who had participated in a 36-month trial of lifestyle modification[28]. Compared with the control arm, the intervention was remarkably effective in preventing progression to T2DM in individuals presenting with combined IGT and IFG (HR 0.41, 95% CI 0.24–0.69), but not for those with isolated IFG (HR 1.17, 95% CI 0.50–2.74). Similarly, the Diabetes Community Lifestyle Improvement Program (D-CLIP)[27] trial from India failed to demonstrate a significant reduction in the risk of T2DM among those with isolated IFG (relative risk (RR) reduction 12%, 95% CI −80% to 57%) at 36 months of follow-up, whereas a strong benefit was observed for the IGT plus IFG group (RR reduction 36%, 95% CI 3–57%)[27]. Furthermore, most (76.5%) of those with isolated IFG in the D-CLIP trial required metformin at 4 months, indicating the lifestyle intervention failed to curtail disease progression.

The results from these two studies are further supported by the Kerala Diabetes Prevention Program (K-DPP)[29], a cluster randomized trial in India in which most of the study participants had isolated IFG (57.5%). After 12 months of the lifestyle intervention (both diet focused and

Table 1 | **Diagnostic criteria for prediabetes**

Parameter	Test used	Prediabetes range	
		mg/dl or % (HbA_{1c})	mmol/l or mmol/mol (HbA_{1c})
American Diabetes Association criteria[20]			
IFG	FPG test	100–125	5.6–6.9
IGT	OGTT	140–199	7.8–11.0
HbA_{1c}	HbA_{1c} test	5.7–6.4	39–46
IEC criteria[a67]			
HbA_{1c}	HbA_{1c} test	6.0–6.4	42–46
WHO criteria[b21]			
IFG	FPG test	110–125	6.1–6.9
IGT	OGTT	140–199	7.8–11.0

FPG, fasting plasma glucose; HbA_{1c}, haemoglobin A_{1c}; IEC, International Expert Committee; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test. [a]Prediabetes defined by HbA_{1c} level is referred to as 'high risk' by the IEC. Whereas the IEC suggests this definition, it noted that there was a lack of evidence for any specific lower threshold. [b]The WHO currently does not have HbA_{1c} criteria for defining prediabetes. Prediabetes is referred to as 'intermediate hyperglycaemia' by the WHO.

Table 2 | **Characteristics of lifestyle interventions used in DPPs**

Study	Lifestyle intervention type	Intervention goals and/or content	Intervention delivery structure
US Diabetes Prevention Program[11]	Physical activity and dietary intervention	7% weight loss through a healthy low-calorie, low-fat diet and by engaging in moderate physical activities for at least 150 min per week	Case managers taught a 16-lesson curriculum on an individual basis during the first 6 months after enrolment; individual and group sessions were organized at monthly intervals (usually) thereafter; the intervention lasted for a mean of 2.8 years
Chinese Da Qing study[13]	Diet only, physical activity only and both diet and physical activity intervention groups	Increase vegetable intake, reduce intake of simple sugars and control alcohol intake; increase leisure time exercise; participants with elevated BMI were encouraged to reduce total calorie intake for weight loss	Participants received individual counselling sessions by physicians; group counselling sessions were conducted weekly in the first month, at a monthly interval for the following 3 months and then every 3 months for up to 6 years
Finnish Diabetes Prevention Study[12]	Physical activity and dietary intervention	Weight loss of ≥5%; <30% of daily energy intake from fat; <10% of daily energy intake from saturated fat; fibre intake of 15 g per 1,000 kcal or more; moderate physical activities for at least 30 min a day	Participants received one-to-one counselling sessions from nutritionists; 7 sessions were delivered in the first year and 1 session was delivered every 3 months thereafter. The intervention lasted for a median of 4 years
Indian Diabetes Prevention Programme[10]	Physical activity and dietary intervention	Avoid sugars and refined carbohydrates, reduce intake of total fat and saturated fats and increase fibre intake; moderate-intensity activities for at least 30 min a day for those who were sedentary or physically less active	Intervention was delivered on a one-to-one basis at 6-monthly intervals for 3 years; monthly phone calls to maintain the behavioural change

physical activity focused) and 24 months of follow-up, the RR in those with IGT was 0.66 (95% CI 0.45–0.98, $P = 0.038$), but no impact of the intervention was seen in those with isolated IFG (RR 0.95, 95% CI 0.68–1.33, $P = 0.77$)[29]. Although the Japanese study showed that those with a combination of IFG and HbA_{1c} level of 6.0% or greater had a 76% RR reduction (HR 0.24, 95% CI 0.12–0.48), such an effect was not observed in the K-DPP trial (RR 0.91, 95% CI 0.58–1.42) (T.S., B.O., R.J.T, J.E.S., P.Z.Z. and K.R.T., unpublished data).

Heterogeneous metabolic states in prediabetes. IFG and IGT differ substantially in their underlying pathophysiology. Although people with IFG or IGT manifest both insulin resistance and β-cell dysfunction, the metabolic abnormalities are very distinct between the two conditions. For example, in the Inter99 study[43], it was found that isolated IFG was characterized by dysfunction in insulin secretion followed by reduced hepatic insulin sensitivity, whereas isolated IGT was associated with reduced whole-body insulin sensitivity followed by a decline in β-cell function.

IGT is characterized by marked peripheral (skeletal muscle) insulin resistance, with only a moderate degree of hepatic insulin resistance, whereas individuals with IFG have severe hepatic insulin resistance with near normal peripheral insulin sensitivity[40,41]. With regard to β-cell function, in people with IFG, the first-phase insulin secretion in response to intravenous glucose is severely impaired. By contrast, individuals with IGT have a marked decrease in both first-phase and second-phase insulin secretion[40,44]. Furthermore, some ethnic groups, such as Asian Indians, have an innate susceptibility for early decline in β-cell function[45].

The clinical importance of the distinct prediabetes phenotypes is that individuals with isolated IFG, in contrast to IGT and IGT plus IFG, might not necessarily benefit from lifestyle modifications in terms of T2DM prevention in their current form (TABLE 2). We propose that this difference occurs because DPP-style lifestyle modifications target pathophysiological mechanisms that are not prominent in isolated IFG[27]. However, a 2019 study reported similar clinical and metabolic responses to a lifestyle intervention in different glycaemic status groups[46]. Nevertheless, this study supports our conclusion that lifestyle interventions might not successfully prevent T2DM in individuals with IFG in their current form (TABLE 2). In the aforementioned article, it was reported that lifestyle intervention had no effect on FPG levels and 2-hour postload glucose levels in individuals with IFG, whereas both measures decreased in individuals with IGT[46]. However, after adjustment for baseline FPG levels and 2-hour postload glucose levels, the difference in effect between IFG and IGT disappeared. We do not see the benefit of comparing IGT and IFG after adjustment for differences in glucose levels, and we propose that the most relevant findings from this study are the unadjusted ones.

Evidence to date shows that lifestyle interventions have heterogeneity in their effects, resulting in discordant T2DM risk reduction across the spectrum of prediabetes phenotypes (as defined by glucose levels). These differences are most likely explained by the heterogeneous metabolic states occurring in the pathophysiology of IFG and IGT[40,41,43,44,47–50] (FIG. 1).

Potential modifications to DPPs

Data captured from healthy individuals indicate that physical activity levels are associated with postprandial plasma glucose levels but not FPG levels[51]. The Mediterranean diet (a diet high in vegetables, fruits, beans, whole grains, olive oil, nuts and seeds) has been shown to be inversely associated with IFG, which might make it a better diet than those currently used in DPPs (TABLE 2) for this high-risk group[52]. Furthermore, high-intensity interval training in isolation[53] or in combination with the Mediterranean diet[54] has been shown to reduce FPG levels and insulin resistance in people with obesity. Research in patients with established T2DM demonstrates that a much more demanding dietary intervention with greater caloric restriction than that used in DPPs[55] results in considerable reductions in hepatic adiposity, with a consequent normalization of hepatic glucose production and thus decreased FPG levels[56].

Findings from the cluster-randomized DiRECT trial have shown that individuals with T2DM who achieve significant weight loss through a substantial reduction in calories (~800 kcal per day for 3–5 months)

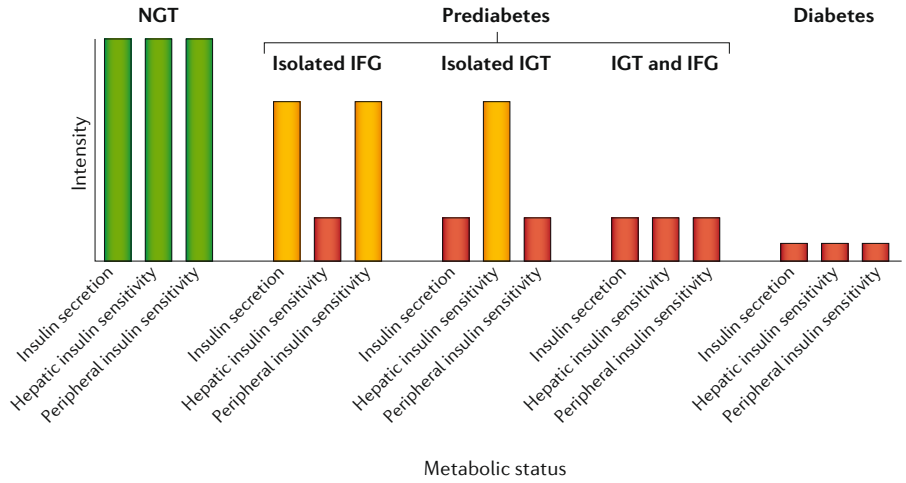

Fig. 1 | **Distinct pathophysiological profiles of prediabetes phenotypes.** Peripheral insulin sensitivity is decreased in individuals with isolated impaired glucose tolerance (IGT) and those with IGT combined with impaired fasting glucose (IFG), whereas individuals with isolated IFG typically have lesser reductions in peripheral insulin sensitivity but greater reductions in hepatic insulin sensitivity. Individuals with IFG are able to partially combat hepatic insulin resistance with increased insulin secretion, whereas individuals with IGT and individuals with IGT combined with IFG are not. Green (unimpaired), amber and red (most impaired) colours relate to the degree of metabolic impairment in each phenotype. NGT, normal glucose tolerance.

followed by progressive food reintroduction can and are more likely to achieve remission to a non-diabetic state. Moreover, this trial concluded that such an intervention is feasible for implementation in primary care[57]. Therefore, from our current understanding of the pathophysiology of T2DM[58], it might be necessary for DPPs to adopt a more intensive caloric restriction to achieve improvements in individuals with isolated IFG, possibly with complementary pharmacological therapy[59].

Findings from the ongoing PREVIEW trial might provide further insight. The PREVIEW trial enrolled people with prediabetes (including 64% with isolated IFG)[60], who underwent an 8-week intensive weight-loss phase, using a formula low-calorie diet (~800 kcal per day), followed by a 148-week maintenance phase[60]. After the 8-week intervention, significant weight loss was achieved (~10% body weight, which is ~10 kg), along with improvements in metabolic parameters, including decreases in FPG level, fasting insulin level and insulin resistance as defined by homeostatic model assessment[60]. Furthermore, ~35% of the individuals with IFG determined by screening at the baseline reverted to normal glucose tolerance, with this proportion increasing to ~40% among those who met a predefined weight-loss target of a reduction of 8% or more of initial body weight[60]. A 2019 study showed that the anticipated cardiovascular risk reduction that should accompany the reversion to normoglycaemia extends only to individuals with IGT, and not to individuals with IFG[61]. Nevertheless, the wider-reaching benefits of general lifestyle improvement should not be underestimated.

Diagnostic tests

Given the logistical challenges of large-scale use of the 2-hour OGTT, the inability of HbA_{1c} and FPG levels to identify people with IGT[18] and the limitations of currently available risk scores, other diagnostic means should be sought to detect high-risk individuals who could benefit from lifestyle-based DPPs. Although extensive literature exists on the association of several biomarkers with the risk of developing T2DM, the utility of these biomarkers in clinical prediction and DPPs remains largely unknown[62]. However, evidence is emerging for the utility of some novel biomarkers such as betaine (a plasma metabolite), the levels of which increased on lifestyle intervention, and this improvement was associated with lower T2DM incidence[63]. Such biomarkers could complement the standard clinical and biochemical measures that help predict blood glucose responses to a lifestyle intervention.

Precision medicine in T2DM could be greatly enhanced by knowing the prediabetes phenotype, thereby allowing improved individualized treatment recommendations in the future. The accurate identification of high-risk individuals by phenotype could accelerate the development of new treatments and provide novel care pathways, particularly in resource-poor settings. Technologies are currently being developed to allow an OGTT to be performed at home, which could assist in overcoming the logistical challenges of the current 2-hour OGTT[64]. In 2018, however, researchers petitioned to scrap the 2-hour OGTT and use a 1-hour OGTT instead[65]. Notwithstanding this, maybe it is time to move away from traditional assessments to identify risk and include methods to predict DPP responsiveness on the basis of underlying pathophysiology. Artificial intelligence approaches using non-invasive imaging techniques might provide a scalable and inexpensive test to distinguish prediabetes phenotypes from a retinal image[66]. Through the use of new, innovative technology, research has provided strong evidence regarding the potential value of deep learning artificial intelligence to predict HbA_{1c} level, age, sex and blood pressure from a retinal image alone[66].

Conclusions

Despite some advances in our understanding of the pathogenesis of T2DM, effective means of reducing the incidence of this disease have been elusive. Moreover, a translational gap between trial evidence and implementation into routine care is apparent. The evidence to date indicates that lifestyle interventions in their current format have not succeeded in preventing the relentless progression to T2DM in individuals with isolated IFG. We propose that further research is needed to identify effective lifestyle interventions for individuals with isolated IFG. While efforts to expand the evidence for effective lifestyle interventions in people with isolated IFG occur, those individuals should receive general lifestyle advice rather than be enrolled onto specific DPPs. A need also exists for research to identify people with IGT other than by using the currently available 2-hour OGTT. As the prevalence of T2DM increases, it is clear that if we are to transform DPPs, a new, innovative and aggressive approach to better identifying and providing targeted lifestyle interventions is needed. New approaches should attempt to counter the distinct pathophysiological and clinical course of progression to T2DM, with an emphasis on isolated IFG.

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R.J.T., M.D.C. and T.S. researched data for the article and wrote the article. R.J.T., M.D.C., T.S., K.R.T., P.Z.Z., B.O., D.R.O. and J.E.S. contributed substantially to discussion of the content. All authors reviewed and edited the manuscript before submission.

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