Prediabetes: lifestyle, pharmacotherapy or regulation?

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Abstract: The rapidly rising number of people with diabetes worldwide has led to multiple attempts to identify effective means of preventing type 2 diabetes. Lifestyle interventions have shown impressive efficacy in multiple clinical trials of people with impaired glucose tolerance, but, as currently formulated, appear to have very little impact on impaired fasting glucose. Attempts to roll out lifestyle interventions beyond clinical trials have generally recruited too few people to have a chance of influencing the population prevalence of diabetes. Several drugs have also been shown to reduce the incidence of diabetes, but until such drugs can be shown to prevent the clinical consequences of diabetes, it is unlikely that guidelines will recommend their widespread use for diabetes prevention. Population-level interventions, including education and regulation, are attractive, as they have the potential to influence a high proportion of the population. Favourable effects of a sugar sweetened beverage tax on consumption are encouraging, but data on its influence on diabetes are not yet available.

Keywords: diabetes, impaired fasting glucose, impaired glucose tolerance, lifestyle intervention, prevention, prediabetes

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Introduction

Diabetes affects over 400 million adults worldwide and is projected to surpass 600 million in just over 20 years.[1] Its prevalence has risen rapidly over the last 50 years, and no part of the world is left unaffected. In most parts of the world, it is the leading cause of kidney failure, of visual loss in people of working age, and of nontraumatic lower limb amputation, as well as being a major contributor to cardiovascular disease,[2–5] and a myriad of other complications and comorbidities.

Approximately 90% of all cases of diabetes are type 2 diabetes, and lifestyle change is at the heart of the rise in the prevalence of type 2 diabetes. In an attempt to turn around this global epidemic, the last 20 years has seen a multiplicity of studies and programmes aimed at identifying interventions that prevent, or at least delay the onset of, type 2 diabetes. Many of these studies have reported significant success in well-designed clinical trials. In the setting of an ongoing rise in the number of people with diabetes, it is appropriate to reflect on how these interventions should be mobilized to deliver benefits at the population level. This requires careful review of their strengths and weaknesses, and of their capacity to be delivered and to be effective at the population level.

Broadly, the interventions that have been tested can be divided into lifestyle interventions and drug therapy. Both of these approaches have focused on the so-called high-risk approach, in which people identified as being at high risk of developing type 2 diabetes are offered the intervention. To have any impact on the population risk of diabetes, it is clear that such interventions need to have both efficacy and reach. In other words, individuals undertaking the intervention must achieve adequate benefit, and the number of individuals engaged in the intervention must be high enough to meaningfully influence the number of people in the whole population who develop diabetes. An alternative approach is to target the whole population, without attempting to enrol specific individuals in a specific programme. This can be achieved in a variety of ways, including health promotion, education campaigns, infrastructure changes (e.g. town planning and public

transport) to influence lifestyle choices, and regulatory changes aimed at restricting access to or increasing the cost of unhealthy foods. Small changes across the whole population may lead to meaningful changes in the incidence of type 2 diabetes. The capacity of the high-risk and population approaches to deliver population change are considered in the following.

Intensive lifestyle change

Following on from the landmark studies in China, Finland and the United States,[6–8] there is abundant evidence of the efficacy of intensive lifestyle programmes in reducing the risk of developing type 2 diabetes among those with prediabetes. In a recent meta-analysis, the risk reduction was estimated to be 36% for interventions running for between 6 months and 6 years.[9] Approaches to lifestyle change have varied somewhat among the studies, but all involve achieving both caloric restriction and increased physical activity. Delivery mechanisms have also varied, with one successful trial relying predominantly on text messaging to deliver lifestyle advice.[10] Several studies have reported the long-term effects of lifestyle change, extending many years beyond the end of the trial intervention period. In the Diabetes Prevention Program (DPP), by 15 years, most people in all three study arms (lifestyle, metformin and placebo) had developed diabetes, but the risk of diabetes in the lifestyle group was, nevertheless, 27% lower than in the placebo group.[11] In the 23-year follow up of the Chinese Da Qing study, once again, the large majority of all study participants had developed diabetes, but the risk remained 45% lower in those originally assigned to the 6-year lifestyle interventions than in the control group.[12] This same analysis also reported a 41% reduction in cardiovascular mortality and a 29% reduction in total mortality for the lifestyle groups. However, at this stage, this is the only diabetes prevention trial to report benefit for long-term 'hard' outcomes. The DPP has not reported cardiovascular outcomes, but has reported the effects on microvascular outcomes, but no convincing effect of either lifestyle intervention or metformin therapy on such outcomes was apparent.[11]

One important and inadequately recognized limitation of the lifestyle intervention studies is that the successful trials have all focused on people with impaired glucose tolerance (IGT). The small number of trials that have included adequate numbers of people with impaired fasting glucose (IFG) have shown no benefit for this subgroup unless they also have IGT.[13–15] There are no clear explanations for why this may be the case, but IGT and IFG represent different combinations of beta cell dysfunction, and muscle and liver insulin resistance, and therefore may respond differently to the 'standard' lifestyle programme. The important corollary of this observation is that since many of the large-scale rollouts of the diabetes prevention programmes predominantly recruit people with IFG or with elevated HbA1c (as the oral glucose tolerance test required to diagnose IGT is deemed to be too cumbersome), they may well be recruiting the wrong people. Unless they are able to recruit people with IGT, it seems unlikely that current lifestyle programmes will be effective.

Thus, the clinical trial evidence strongly supports the efficacy of lifestyle change, among people with IGT, in reducing the long-term risk of developing type 2 diabetes, though uncertainty remains over whether this will translate into benefit for hard outcomes such as kidney disease or symptomatic cardiovascular disease. However, this is only the first step in influencing population risk of diabetes. The next steps involve showing that these lifestyle change programmes can be successfully run in community rather than in trial settings, and can attract enough people to have a chance of changing the risk of diabetes at the population level. Given the costs of running such programmes both to healthcare systems and to individual participants, it is important to establish that there is, at the very least, a good chance of success.

Several studies have now shown that it is possible to deliver the lifestyle change programmes in settings that do not depend on resource-intensive research infrastructure, and although the results are typically less impressive than those seen in the intensive clinical trials, there is still evidence that they deliver behaviour change. The real challenge comes in considering the reach of the programmes. The difficulties here are illustrated by examining the reports of the Centers for Disease Control nationwide rollout of the DPP. Over a 4-year period, 12,775 individuals were enrolled across 220 sites.[16] Although this is an impressively large number, extrapolating this rate of recruitment, it would require 100,000 sites working for 10 years to recruit just 25% of the current estimate of 86 million people in the US with

prediabetes. There are some obvious challenges with this 'back of the envelope' calculation, but it gives a very clear indication that the magnitude of the problem is likely well beyond the capacity of this approach to deal with. Similar findings of limited reach have been reported elsewhere.[17] In reality, this should not come as a surprise. Most people at risk of diabetes do not want to or do not have the time or capacity to enrol in a lifestyle change programme. Whether this is because of previous failures with weight loss programmes, or socio-economic factors that make the programme unattractive, it is a common response to the invitation.

Pharmacotherapy

Several trials have demonstrated the efficacy of glucose-lowering and weight-loss drugs in reducing the incidence of diabetes in those at high risk. Drugs confirmed to have a benefit include metformin,[8] acarbose,[18] thiazolidinediones,[19,20] GLP1 agonists[21] and weight-loss drugs.[22,23] In regard to the glucose-lowering drugs, there has been debate about whether the reduced incidence of diabetes represents true prevention or is simply a masking of elevated glucose by a glucose-lowering agent. However, while this debate may be relevant for understanding the pathophysiological effects of the drugs on the natural history of glucose intolerance, it is of limited clinical relevance. It is unlikely that anyone would consider that having a 'course' of medication would lead to long-term diabetes prevention, so drugs used in preventing diabetes (just like those used for controlling lipids and blood pressure) will inevitably be thought of as ongoing and possibly lifelong. However, this raises the question of the impact of such drugs on hard outcomes. It is difficult to justify lifelong drug therapy without knowing that there is a high likelihood of benefit on hard clinical outcomes. The issue is particularly relevant since it has even been difficult to show that glucose lowering in people with established diabetes results in substantial cardiovascular risk reduction.[24] The DPP has shown no benefit of metformin for microvascular outcomes,[11] and has not reported on macrovascular disease. Early studies with acarbose suggested a cardiovascular benefit in small trials, but the ACE trial showed no cardiovascular benefit in over 6000 people with IGT, though progression to diabetes was reduced by 18%.[25] In the ORIGIN trial, glargine insulin reduced the risk of progression to diabetes in the subgroup with prediabetes, but there was no cardiovascular benefit.[26] The DREAM trial showed that rosiglitazone significantly reduced diabetes risk in IGT, but had no effect on CVD (apart from an increase in heart failure).[20] In contrast, a recent trial showed that among people with a prior stroke and insulin resistance, pioglitazone led to a 24% reduction in stroke recurrence.[27]

Thus, trials designed to test the effects of drugs on diabetes prevention have shown success in that narrow outcome, but have not shown the benefits on hard clinical outcomes needed to underpin their widespread and long-term use. However, an alternative approach among certain subgroups might emerge from a different set of trials. Trials of GLP1 agonists and SGLT2 inhibitors have shown major beneficial effects on both cardiovascular and renal outcomes in people with type 2 diabetes.[28,29] So impressive have been their results that there are now other trials looking at these drug classes in people without diabetes. These studies are primarily examining the effects on hard cardiovascular and renal outcomes, but since the drugs are glucose-lowering agents, and many trial participants will be at high risk of diabetes, they are also likely to show a reduced incidence of diabetes. It may therefore turn out that having failed to show cardiovascular benefit in trials aiming to prevent diabetes, we may yet achieve diabetes prevention in trials aimed at preventing cardiovascular outcomes.

Regulation

An alternative to targeting high-risk individuals is a whole-of-population approach that aims to achieve small–modest changes in metabolic parameters across the entire community. This can be achieved through a variety of measures, ranging from education and health promotion to regulation and taxation. This is an attractive approach, though as yet has little in the way of hard evidence for diabetes prevention. Among some of the most successful health and behaviour-change programmes in recent decades have been the antismoking and road safety campaigns. Both of these have, in many countries, yielded huge benefits in improvement of health outcomes through behaviour change. Their successes have been dependent on a multipronged approach including financial (taxation or fines), infrastructural (limiting access to cigarettes or unsafe vehicles), legal, and educational interventions. It is

hard to tease out the specific effects of any single measure, but it is notable that individually targeted interventions (e.g. smoking cessation clinics) were not a prominent component.

The regulatory intervention that has attracted the most interest is a tax on sugar sweetened beverages. Sugar sweetened beverages are an attractive target, because they are strongly linked to risk of both obesity and diabetes,[30,31] and are an entirely unnecessary part of a healthy diet. Thus, unlike sugar itself, there is no level of intake of sugar sweetened beverages that can be considered nutritious. Several countries have now introduced a tax on sugar sweetened beverages, using various different economic approaches. Most have added a tax onto the sales price of affected products, thereby discouraging people from purchasing sugar sweetened beverages. Others have taxed (or levied) manufacturers on the basis of the sugar concentration of drinks. Since manufacturers can choose to lower the sugar content in order to reduce the levy (and reduce the cost past onto the purchaser), it is argued that this approach benefits all consumers, even those whose purchasing behaviour is not affected by price increases. In both approaches, there is an option to use the money raised by the tax to fund health promotion activities, thus producing a double benefit from the tax.

In 2013, Mexico introduced a tax on sugar sweetened beverages. Mexico has a high prevalence of obesity and diabetes, and high intake of sugar sweetened beverages, making this a particularly important country in which to observe the effects of this intervention. Findings have now been reported on the effect of the tax. Based on household survey data, the consumption of taxed drinks fell by 12% by the end of December 2014, while purchases of nontaxed drinks (mainly water) increased by 4%.[32] A key finding of this analysis was that the effect was greatest in the lower socioeconomic groups: likely because their purchasing behaviour is the most price-sensitive. This is important, because diabetes and obesity, like many other chronic diseases, are more prevalent in lower socio-economic groups, and individuals in such groups are typically less likely to take up clinical interventions. The consumption data were subsequently used to model the impact these changes would have on obesity and diabetes.[33] Estimates suggest that 10 years after the introduction of the tax, the prevalence of obesity will fall from 33% to 32%, and over that time period, there will be 86,000–134,000 fewer cases of diagnosed diabetes.

Summary

Clinical trials show clear benefits of lifestyle interventions on the transition to diabetes for people with IGT. These benefits last for many years after the intensive intervention is completed, and incomplete evidence suggests a consequent reduction in cardiovascular disease and mortality. However, none of the major rollout programmes for diabetes prevention has succeeded in engaging anything more than a small minority of the at-risk population. Pharmacotherapy also reduces the risk of developing diabetes, but in the absence of trials showing benefit for hard clinical outcomes, widespread use of such drugs is not appropriate. A whole-of-population approach, including regulation and education, has so far shown promise, though still lacks definitive evidence.

At this stage, it would not be prudent to rely on the high-risk approach to reduce the population risk of developing type 2 diabetes, and whole-of-population approaches should be part of every country's strategy to curb the diabetes epidemic.

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