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REVIEW ARTICLE

Prevention of type 2 diabetes mellitus: is it feasible?

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Abstract

The increasing global prevalence of type 2 diabetes mellitus (T2DM) requires the implementation of preventive strategies to halt this trend, tailored to the specific needs of individual regions. Risk factors for T2DM are among the main targets for improving health outcomes and curbing the development of diabetes; excessive weight and obesity are two of the most important risk factors that need to be addressed. A growing body of evidence suggests that subjects with pre-diabetes who lose body weight and increase physical activity can delay or prevent the onset of T2DM, and in some cases, blood glucose levels may return to normal. Several studies have shown that moderate to intensive levels of exercise are effective in reducing both intra-abdominal and total adiposity among obese subjects, both improving cardiovascular risk profile and reducing the risk of T2DM development. These consistent observations have given rise to large-scale randomized controlled trials that use lifestyle intervention (including behavioural strategies for the reinforcement of prescribed changes in nutritional intake, physical activity or both), with or without pharmacological treatment, in populations at high risk of developing T2DM. In this review, large-scale national trials that have focused on the prevention of T2DM are critically evaluated. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords type 2 diabetes; prevention; lifestyle intervention; delay; diet; exercise

Introduction

What is the global extent of type 2 diabetes and obesity?

Type 2 diabetes mellitus (T2DM) is the one of the most prevalent chronic diseases worldwide and one of the major public health challenges of the 21st century. The diabetes epidemic results from economic improvements and associated lifestyle changes, with the progressive reduction of physical activity and the consequent increase in the number of people classed as overweight and obese. A systematic analysis of reports on global diabetes prevalence by Danaei *et al*. showed that the number of adults with diabetes has more than doubled over the last three decades, rising from 153 million in 1980 to 347 million in 2008 [1]. Similarly, the World Health Organization estimated an increase of diabetes prevalence from 2.8% in 2000 to 4.4% in 2030 [2]. Although there are increases in incidence in Europe and North America, it is clear that the bulk of the epidemic is associated with increases in non-European populations, mainly in regions undergoing rapid Westernization, with a major rise in the Middle Eastern Crescent, Sub-Saharan Africa and India. Moreover, prevalence

appears to be slightly higher in men aged <60 years and in women >60 years, probably because of a greater number of elderly women than men, and the increasing prevalence of diabetes with age [2]. In addition, the majority of people from developed countries with diabetes are >64 years of age, whereas in developing countries, the highest percentage is found in subjects aged between 45–64 years [3].

One of the greatest contributors to the increasing prevalence of diabetes is weight gain, illustrated by a parallel rise in the number of people who are overweight with the rise in incidence of T2DM, and evidence from several studies. The precise prevalence of obesity-related diabetes varies with age, race and gender, and the degree of diabetes is proportional to the rate of increasing obesity. Currently, more than one billion adults are overweight, and at least 300 million of them are clinically obese [4,5]. The prevalence of obesity in the US has increased dramatically since 1980, in both adults and children. In fact, the most recent data on obesity prevalence among US adults show that more than one-third of adults were classed as obese in 2009–2010 [4]. However, the obesity epidemic is not limited to the US and has been documented in several regions worldwide. Indeed, the only region in which obesity is not common is Sub-Saharan Africa [5] probably because of the lack of epidemiological studies.

What are the main risk factors for type 2 diabetes mellitus?

The etiology of T2DM is multifactorial and involves a complex interaction between genetic, epigenetic and environmental factors. It is well-established that the increasing prevalence of T2DM cannot be explained by genetics alone, and that lifestyle also plays a crucial role [6]. The influence of environmental factors is well known, both *in utero* and after birth [7]. Several studies have highlighted that a low birth weight or small fetus size may be a predisposition for the development of diabetes in adulthood and may be caused by maternal obesity or maternal diabetes [8,9].

Focusing on key risk factors is crucial for the improvement of health outcomes and preventing the risk of diabetes occurrence. These risk factors are the following:

Excessive weight gain and obesity

Being overweight is the most important modifiable risk factor for T2DM, especially in youth. It is estimated that 10% of children worldwide are currently either overweight or obese [10]. The relationship between obesity and the risk of developing diabetes remains unclear; however, it is known that adipose tissue is a source of circulating free fatty acids and inflammatory proteins, including cytokines that are mechanistically related to insulin resistance [11]. An exception to this is adiponectin, a cytokine produced by adipocytes, the serum levels of which are paradoxically lower in adults with obesity, T2DM and cardiovascular disease compared with healthy individuals. Furthermore, adiponectin exhibits beneficial effects on energy homeostasis and cardiovascular functions that are attributed to its direct modulation of a pro-inflammatory factor, interleukin 6. Accordingly, obese children show low serum concentrations of adiponectin and high levels of tumour necrosis factor α and interleukin 6 [12,13]. Given the chronic comorbidity associated with obesity and the fact that obesity is difficult to treat, prevention is extremely important for improving global health.

Pre-diabetes

Type 2 diabetes mellitus evolves through pre-diabetes, defined as impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Individuals with pre-diabetes have an increased risk of developing T2DM and a higher prevalence of cardiovascular diseases than normoglycaemic subjects [14].

A growing body of evidence suggests that people with IFG or IGT who lose weight and increase physical activity can prevent or delay T2DM and, in some cases, return their blood glucose levels to normal [15].

Unhealthy lifestyle

Approximately half the risk of developing diabetes can be attributed to certain lifestyle habits, among them physical inactivity and overeating. Several studies have shown that an intensive exercise intervention strategy was effective in reducing both intra-abdominal and total adiposity among obese subjects, improving the cardiovascular risk profile and reducing the overall risk of T2DM, independent of changes in body mass index (BMI). In fact, regular physical activity induces an increase of glucose uptake by skeletal muscle, adipose tissue and the liver; the glucose is stored as glycogen, independent of effects on weight and body composition. Moreover, moderate-intensity and vigorous-intensity exercise training reduces the risk of evolution from IFG or IGT to T2DM, improving β-cell function and increasing insulin peripheral sensitivity [16]. This also induces a significant reduction in inflammatory biomarkers and consequently improves the cardiovascular risk profile [17]. Similarly, overeating and an unhealthy diet are regarded as risk factors for the development of diabetes [18]; however, the relationship between the amount and type of dietary fat and carbohydrate intake, and the risk of diabetes is still under debate. Traditionally, dietary recommendations promoted low-fat diets with relatively high doses of carbohydrates, with the aim of reducing insulin resistance. Specifically, a high intake of saturated fat can have a negative effect on glucose

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metabolism, whereas a diet rich in unsaturated fats has a beneficial effect on plasma levels of triglycerides and, consequently, glycaemic control. [19] Moreover, an adequate intake of dietary fibre and minimally processed wholegrain products seems to improve glucose metabolism. In addition, several micronutrients such as minerals could increase insulin peripheral sensitivity [20,21]. Finally, dietary recommendations to prevent obesity should be focused more on the quality of fat and carbohydrates than on the amounts, and also on balancing total energy intake with energy expenditure [22].

Can type 2 diabetes mellitus be prevented or its development delayed?

Epidemiological studies have repeatedly demonstrated that low levels of physical activity and obesity are prominent, independent and modifiable risk factors for the development of insulin resistance, metabolic syndrome and T2DM, in addition to genetic predisposition and other environmental or acquired risk factors [12,17]. These consistent observational results have given rise to large-scale randomized controlled trials that have used lifestyle interventions (including behavioural strategies for the reinforcement of prescribed changes in nutritional intake, physical activity or both), with or without pharmacological treatment, in individuals at high risk of developing T2DM (Table 1). The aim of these trials was to reduce the incidence rate and to ameliorate risk factor profiles associated with both T2DM and cardiovascular morbidity and mortality.

The Da Qing impaired glucose tolerance and diabetes study [23]. The aim of this study was to investigate whether improving diet and exercise in subjects with IGT could delay and reduce the incidence of conversion to T2DM. Five hundred and seventy seven individuals attending clinics in China were identified as having IGT. Subjects were randomized to one of the following four groups: control, dietary-based intervention, exercise-based intervention or an intervention of diet with exercise. Follow-up was undertaken every 2 years, up to a maximum of 6 years, to identify those subjects who had developed T2DM. At 6 years, cumulative T2DM incidence was 68% in the control group, *versus* 44% in the diet group, 41% in the exercise group and 46% in the diet with exercise group ($p < 0.05$, for each intervention group *versus* the control group). A proportional hazards analysis was performed with adjustment for baseline differences in fasting glucose and BMI; diet, exercise and diet with exercise interventions were associated with 31% ($p < 0.03$), 46% ($p < 0.0005$) and 42% ($p < 0.005$) reductions in the risk of T2DM development, respectively. The authors demonstrated that diet intervention, either alone or combined with exercise, could significantly decrease the incidence of T2DM in individuals with IGT over a 6-year period.

The Finnish diabetes prevention study [24]. In this large prospective, randomized control trial, the authors evaluated whether T2DM could be prevented by lifestyle interventions in subjects at high risk of developing the disease. Over 500 middle-aged, overweight/obese people with IGT (mean age, 55 years) were randomized to either a lifestyle intervention group or a control group. Lifestyle intervention involved personalized counselling which

Table 1. Prevention trials in type 2 diabetes (diet and exercise intervention, including metformin)

Trial	Participants (*n*)	Population	Follow-up (years)	Interventions	Relative Risk (95% CI)
Da Qing IGT and diabetes [23]	577	IGT (China)	6.0	i. Diet, ii. exercise, iii. diet and exercise	0.66 (0.53–0.81) 0.56 (0.44–0.70) 0.49 (0.33–0.73)
Finnish Diabetes prevention study [24]	522	IGT and overweight (Finland)	3.2	Diet and exercise	0.42 (0.3–0.7)
US Diabetes Prevention Program [25]	3,234	IGT (USA)	2.0	i. Diet and Exercise ii. Metformin	0.42 (0.34–0.52) 0.69 (0.57–0.83)
Indian Diabetes Prevention Program [26]	531	IGT (India)	2.5	i. Diet and exercise ii. Metformin iii Metformin + Diet and exercise	0.72 (0.62–0.80) 0.74 (0.65–0.81) 0.72 (0.62–0.80)
Västerbotten Intervention Programme [27]	168	IGT (Sweden)	1.0–5.0	Diet and exercise	Not significantly different to control
Asti Diabetes Prevention Program [28]	335	Metabolic syndrome (Italy)	1.0	Diet and exercise	0.23 (0.06–0.85)
Study on Lifestyle Intervention and IGT Maastrict [29]	147	IGT (Dutch)	6	Diet and exercise	0.53 (0.29–0.97)

IGT, impaired glucose tolerance.

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aimed to help achieve weight reduction, reduction of total and saturated fat intake, as well as increasing consumption of dietary fibre and the amount of physical activity. The follow-up period was approximately 3 years. Subjects in the intervention group lost significantly more body weight than those in the control group, both by the end of year one and end of year two ($p < 0.001$ at both time points). After 4 years, the cumulative incidence of diabetes was 11% in the intervention group *versus* 23% in the control group. By the end of the trial, the risk of developing T2DM was reduced by 58% ($p < 0.001$) in the intervention group. The reduction in the incidence of diabetes was directly associated with changes in lifestyle.

The US Diabetes Prevention Program (DPP) [25]. Knowler *et al*. hypothesized that modifying T2DM risk factors with either a lifestyle-intervention program or the administration of metformin would prevent or delay diabetes development. A total of 3234 individuals with IFG and IGT, who had not yet progressed to T2DM, were randomized to placebo, metformin or a lifestyle modification program that aimed to achieve a minimum 7% reduction in body weight overall and a minimum of 150 min of physical activity per week. Participants had a mean age of 51 years, with a mean BMI of 34.0 kg/m^2. Follow-up duration was almost 3 years. Results suggested that those who were assigned to the lifestyle intervention experienced much greater weight loss and a higher increase in physical activity than participants receiving metformin or placebo. Diabetes incidence was 11.0, 7.8 and 4.8 cases per 100 person-years in the placebo, metformin and lifestyle groups, respectively. Incidence was reduced by 58% by lifestyle intervention treatment and by 31% with metformin compared with placebo; lifestyle intervention was significantly more effective than metformin. Extrapolation of these results suggested that over 3 years, the prevention of one case of diabetes requires 6.9 people to participate in the lifestyle-intervention program compared with 13.9 people having to receive metformin.

The Indian Diabetes Prevention Program (IDPP) [26]. The authors of this study tested whether interventions in native Asian Indian people with IGT could influence progression to diabetes. Five hundred thirty one subjects with IGT (421 men and 110 women; mean age, 45.9 ± 5.7 years) were randomized into the following four groups: group one was the control group, group two underwent lifestyle modification, group three received metformin and group four underwent lifestyle modification plus metformin. The primary outcome measure was the rate of onset of T2DM. The median follow-up period was 30 months, and the 3-year cumulative incidences of T2DM were 55.0%, 39.3%, 40.5% and 39.5% in groups one to four, respectively. The relative risk reduction was 28.5% with lifestyle modification, 26.4% with metformin and 28.2% with lifestyle modification plus metformin, compared with the control group. The number needed to treat and prevent one incidence of diabetes was 6.4 for lifestyle modification, 6.9 for metformin and 6.5 for lifestyle modification plus metformin. This trial showed that both lifestyle modification and metformin administration independently reduced the incidence of T2DM in Asian Indian people with IGT and that there was no additional benefit from combining them.

Västerbotten intervention programme [27]. This is a randomized lifestyle intervention trial conducted in Sweden in 168 subjects overweight with IGT. At 1-year follow-up, an extensive cardio-metabolic risk factor reduction was demonstrated in the intensive intervention group, along with a 70% decrease of progress to type 2 diabetes. At 5-year follow-up, most of these beneficial effects had disappeared.

The Asti Diabetes Prevention Program (ADDP) [28]. Bo *et al*. hypothesized that a program of moderate lifestyle intervention could reduce metabolic abnormalities in the general population. They devised a two-arm randomized controlled 1-year trial, which enrolled 335 patients (intervention group, 169; control group, 166). Patients were identified from a dysmetabolic population-based cohort of 375 individuals aged between 45 and 64 years in northwestern Italy. Both control and intervention groups received standard verbal advice on living a healthy lifestyle from a general practitioner. Additionally, the intervention group received personalized recommendations from trained professionals, both verbally and in writing. Results showed total and saturated fat intakes were significantly reduced ($p < 0.001$ for both), while polyunsaturated fat and fibre intakes ($p < 0.001$ for both), and exercise levels ($p < 0.001$), were significantly increased in the intervention group compared with the control group. This resulted in a decrease in the components of metabolic syndrome after 1 year. The incidence of metabolic syndrome was significantly reduced in the lifestyle intervention group ($p < 0.001$), with an absolute risk reduction of 31%, which corresponded to a requirement for a mean of 3.2 patients to receive the intervention to prevent one case of metabolic syndrome after 1 year. There was a significant reduction in central obesity, hypertriglyceridemia and diabetes incidence in the intervention group compared with the control group ($p < 0.001$, $p < 0.001$ and $p = 0.03$, respectively).

The Study on Lifestyle intervention and IGT Maastricht (SLIM) [29]. This study evaluated the efficacy of lifestyle intervention for reducing the incidence of T2DM in a Dutch population with IGT. A total of 147 Caucasian subjects with IGT were randomized to an intervention group (individual advice regarding a healthy diet and physical

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activity) and a control group. The lifestyle group decreased their saturated fat intake, and significantly increased their carbohydrate intake ($p < 0.05$) and maximal aerobic capacity ($p = 0.04$), compared with the control group. There was no significant difference in body weight between the groups after 4.1 years, and 2-hour glucose levels increased overall in the lifestyle group but resulted in significantly lower values than the control group ($p = 0.04$). In general, T2DM incidence was lower in the lifestyle group than the control group. Patients who dropped out had lower aerobic fitness and socio-economic status, and a higher BMI and 2-hour glucose level compared with patients that completed the trial. The authors concluded that prolonged feasible changes in diet and physical activity prevented the deterioration of glucose tolerance and reduced the risk of the development of T2DM.

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) [30]. This trial assessed the efficacy of acarbose in preventing or delaying conversion of IGT to T2DM. In this multicenter, placebo-controlled randomized trial, patients with IGT were randomly allocated to treatment with 100-mg acarbose, or a placebo, three times per day for 3 months. Fewer patients developed T2DM in the acarbose group (32%) compared with the placebo group (42%). In addition, acarbose recipients had significant increase in the reversion of impaired to normal glucose tolerance ($p < 0 \cdot 0001$), whereas placebo recipients experienced an increase in the conversion of IGT to T2DM. This study demonstrated that acarbose, either with or without accompanying changes in lifestyle, can delay the onset of T2DM in patients with IGT. However, 31% of patients in the acarbose group and 19% of patients in the placebo group discontinued treatment early because of flatulence and diarrhoea, which are among the most frequent side effects of acarbose treatment.

The Actos Now for the prevention of diabetes (ACT-NOW) trial [31]. This randomized controlled study investigated the effects of treatment with pioglitazone on the onset of T2DM in subjects with IGT. A total of 602 patients were assigned to receive pioglitazone or a placebo, with a median follow-up of just under 2.5 years. T2DM incidence rates were reported as 2.1% with pioglitazone, and 7.6% with the placebo, annually. Conversion to T2DM in the pioglitazone group was associated with a hazard ratio of 0.28 ($p < 0.001$), and conversion to normal glucose tolerance was observed in 48% of the patients taking pioglitazone, and in 28% of patients taking the placebo. Pioglitazone treatment was associated with significantly reduced levels of fasting and 2-hour glucose ($p < 0.001$ at both time points) and HbA_{1C} ($p < 0.001$) compared with placebo. Pioglitazone recipients also had a reduction in blood pressure ($p = 0.03$), reduction in carotid intima–media thickening rate ($p = 0.047$) and a larger increase in high-density lipoprotein cholesterol ($p = 0.008$). The study showed that pioglitazone was able to reduce the risk of conversion from IGT to T2DM by 72%, but weight gain and edema were significant with pioglitazone compared with placebo ($p < 0.001$ and $p = 0.007$, respectively). For this reason, loss to follow-up was relatively high (30%) in the pioglitazone treatment group.

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study [32]. This double-blind, placebo-controlled randomized trial, assessed the effect of nateglinide in reducing the risk of diabetes or cardiovascular events in people with IGT and cardiovascular disease/cardiovascular risk factors. Both treatment groups took part in a lifestyle modification program. The cumulative incidence of diabetes was not significantly reduced by nateglinide compared with the placebo within a median of 5 years [36% and 34% incidence, respectively; hazard ratio (95% CI), 1.07 (1.00–1.15); $p = 0.05$]. Patients in the nateglinide group had improved glycaemic control, but at the same time, the risk of hypoglycaemia was increased in this group.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study [33]. This trial aimed to establish whether treatment with insulin glargine could delay the onset of cardiovascular disease and T2DM. In fact, evidence that exogenous insulin may slow the decline in pancreatic function with time [34] suggests that it can also reduce the incidence of diabetes in people at risk for the disease. At the end of the follow-up (6.2 years), rates of incidence in cardiovascular outcomes were similar in the insulin glargine and standard-care groups. Of 1456 patients that did not have T2DM at baseline, those randomized to the insulin glargine group were 28% less likely to develop T2DM during the trial period than patients receiving standard treatment (odds ratio, 0.72; $p = 0.006$). The authors concluded that insulin glargine did not affect cardiovascular outcomes and cancers, and reduced new-onset diabetes, but increased hypoglycaemia and modestly elevated body weight.

Do prevention interventions have sustained effects?

Many studies indicate that lifestyle interventions can reduce the progression to development of T2DM in people with IGT, but it remains unclear how long these benefits extend beyond the period of active intervention and whether such interventions reduce the risk of cardiovascular disease and mortality. In order to answer this

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question, we refer to the follow-up of the major intervention studies mentioned previously.

The Da Qing diabetes prevention study [35]. Results showed a 51% lower incidence of T2DM in the group receiving the combined lifestyle and diet intervention compared with the control group during the intervention period (6 years), and a 43% lower incidence over a total of 20 years. Annual T2DM incidence was an average of 7% in the intervention group compared with 11% in the control group, whereas the cumulative incidence over 20 years was 80% in the intervention group *versus* 93% in the control group. T2DM was present for 3.6 fewer years on average in participants from the intervention group than those in the control group. The authors concluded that 6 years of lifestyle intervention could delay or prevent T2DM for up to 14 years after the intervention was stopped.

The Finnish diabetes prevention study [36]. In the extended follow-up of the Finnish Diabetes Prevention Study, those patients free of diabetes by the end of the original trial (median of 4 years) were followed for a further 3 years, making a total follow-up period of median 7 years. The incidence of T2DM over this period was 4.3 and 7.4 per 100 person-years in the intervention and control group, respectively, which indicated a relative risk reduction of 43%. This reduction in risk was attributed to attainment of the dietary and physical activity goals of the intervention. Beneficial lifestyle changes achieved by the participants in the intervention group were maintained after the discontinuation of the intervention, and the corresponding incidence rates during the post-intervention follow-up were 4.6 and 7.2, indicating the relative risk of developing T2DM after stopping the intervention continued to be reduced (by 36%) as a result of sustained lifestyle changes post-intervention.

Ten-year follow-up of the diabetes prevention program outcomes study [37]. Those patients in the non-intervention treatment groups were offered the intervention, with the group previously assigned to metformin treatment continuing this treatment in addition to the intervention. During the 10-year follow-up, there was partial regaining of weight by the original lifestyle group. The weight loss achieved with metformin during the original trial was maintained during this subsequent investigation. Although incidence of T2DM differed between groups at the end of the original trial, incidence was similar at the completion of this follow-on trial; 5.9 cases per 100 person-years in the lifestyle group; 4.9 in the metformin group; and 5.6 in the placebo group. 10 years after the start of the original trial, diabetes incidence had been reduced by 34% in the lifestyle group and 18% in the metformin group, *versus* the placebo. However, cumulative incidence of diabetes incidence was lowest in the lifestyle group, suggesting maintenance of the intervention over 10 years.

In conclusion, these trials show that lifestyle intervention in people at high risk for the development of T2DM resulted in sustained lifestyle changes and a reduction in the development of T2DM. This reduced risk was maintained even after individual lifestyle counselling was discontinued. Compared with lifestyle intervention, pharmacological intervention (Table 2) appears to be less effective and in some cases, associated with side effects that may limit compliance.

What have we learned from intervention studies?

At present, the one strategy that stands out as effective in the prevention of T2DM is the implementation of a healthy lifestyle through the promotion of regular physical activity and consumption of a healthy diet tailored to the calorific needs of the individual (i.e. to decrease body weight). As far as pharmacological intervention for T2DM prevention is concerned, it is important to distinguish between treatment and real prevention. The STOP-NDDIM and DPP studies demonstrated that, after drug discontinuation, diabetes incidence in the pharmacological treatment groups is more than doubled compared with the control groups, indicating that the major beneficial effect of the drug was lost upon discontinuation. In both trials, the two drugs acted by 'pre-treating' the IFG and IGT subjects but not by changing the natural history of the disease. This concept is demonstrated more clearly in the NAVIGATOR study, where nateglinide, although able to reduce the HbA_{1c} and plasma glucose levels in the treatment group, did not reduce the incidence of the disease. In contrast, the DREAM [38] and the ACT-NOW studies that assessed rosiglitazone and pioglitazone, respectively, appeared to genuinely prevent T2DM development. This prevention may have resulted from reducing insulin resistance and protecting the beta cells. In the DREAM study, the relative risk reduction for T2DM in the treatment group was 62%, significantly higher than the control group. After drug discontinuation, although the incidence of T2DM increased in the previously treated group, it was similar to the control group. This indicates that thiazolidinediones have a significant effect on the natural history of T2DM development, even after discontinuation.

What are we doing now? Which models should we choose?

The results of these studies raise questions about whether we have the appropriate tools to prevent T2DM and

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Table 2. Pharmacological preventive trials of type 2 diabetes

Trial	Participants (*n*)	Population	Pharmaceutical	Follow-up (years)	Relative risk (95% CI)	Change in body weight	Adverse event
DPP [25]	3234	IGT and overweight	Metformin (850 mg bid)	2.8	0.69 (0.57–0.83)	Decrease	Gastrointestinal symptoms
STOP-NIDDM [30]	1419	IGT	Acarbose (100 mg tid)	3.9	0.75 (0.63–0.90)	No change	Gastrointestinal symptoms
DREAM [38]	5269	Pre-diabetes	Rosiglitazone (8 mg/day)	3.0	0.40 (0.35–0.46)	Increase	Edema
ACT-NOW [31]	602	IGT	Pioglitazone(30–45 mg/day)	2.4	0.28 (0.16–0.49)	Increase	Edema, dyslipidemia
ORIGIN [33]	1456	Pre-diabetes	Glargine	6.0	0.80 (0.64–1.00)	Increase	Hypoglycaemia
NAVIGATOR [32]	9306	IGT	Netaglinide (up to 60 mg)	5.0	1.07 (1.00–1.15)	Increase	Hypoglycaemia

whether prevention is, in fact, feasible. Furthermore, there is an urgent need to address the socio-economic, behavioural, nutritional and public health issues that have led to the T2DM, obesity and cardiovascular disease epidemics. Therefore, it is necessary to focus on different strategies. More specifically, programs to promote lifestyle modifications, in addition to targeted treatment for groups of individuals at high risk of developing T2DM, to reduce its onset, using both behavioural and pharmacological interventions, should be developed and targeted at the general population. In this regard, several models have been proposed to evaluate the clinical and cost-effectiveness of T2DM prevention, together with strategies for screening and early diagnosis of diabetes. However, it has proved to be difficult to establish cost-effectiveness through long-term randomized clinical trials carried-out on the general population because cost-effectiveness is related to which population is screened (e.g. age specific).

To decrease the risk of development of T2DM on national scales, governments can either encourage healthy lifestyles by making more information and services available, or they can attempt to legislate, for example, against unhealthy foods. Some governments have focused their interest on initiatives aimed at school-age children, mostly promoting proper nutrition and increased physical activity. The real novelty in recent years, however, has been the introduction of taxes on unhealthy food and drinks to improve eating habits. Between 2011 and 2012, countries such as Denmark, Hungary and Finland have introduced a tax on foods high in fat content [39]]. The effect of these taxes will depend on the responsiveness of consumers, who in some cases may decrease the purchase of healthy products in favour of unhealthy ones with increased sugar content, therefore making any exercise counterproductive. In addition to that, foods high in fat content have greater palatability and are still cheaper to pay fat taxes than buying daily healthy food.

Several studies have used modelling to evaluate the effects of restriction on sugar-sweetened drinks, because of their association with obesity and diabetes. Specifically, one study has predicted that a 20% tax on sugar-sweetened drinks would reduce the prevalence of obesity by 3.5% in the United States [40]. Overall, these data support the potential health benefits of taxing selected food and beverages.

In other cases, financial incentive systems have been created specifically to promote weight loss. In this regard, Volpp *et al*. demonstrated that this approach resulted in a significant loss of weight during 16 weeks of financial incentives, but in the subsequent 3 months following termination of the incentives, the majority of the body weight lost was regained. To maintain weight loss for at least 12 months after the end of such a program, long-term studies that provide the effectiveness of economic

incentives are required [41]. Furthermore, it has been shown that a group-based financial incentive can be more effective than an individual incentive [42].

In summary, the prevention of obesity, diabetes and cardiovascular disease will require fundamental social and political changes. Public health programs will be required to make suitable, healthy foods available, and initiatives in education and community planning will be useful to encourage and facilitate physical activity. The food industry can play a crucial role in promoting healthy diets, reducing the fat, sugar and salt content of processed foods, ensuring that healthy foods are available to all consumers and promoting responsible marketing strategies.

The prevention of obesity and diabetes is a global issue and should be the focus of political strategies in both developed and undeveloped countries.

Conflicts of interest

The authors have no conflicts of interest to declare.

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