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The prevention of type 2 diabetes

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SUMMARY

Type 2 diabetes mellitus (T2DM) affects more than 7% of adults in the US and leads to substantial personal and economic burden. In prediabetic states insulin secretion and action—potential targets of preventive interventions—are impaired. In trials lifestyle modification (i.e. weight loss and exercise) has proven effective in preventing incident T2DM in high-risk groups, although weight

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REVIEW CRITERIA

We searched MEDLINE and PubMed for original articles published between 1960 and 2007 that focused on type 2 diabetes prevention trials. The search terms used were “type 2 diabetes”, “prevention”, “impaired glucose tolerance” and “prediabetes”. We included English-language, full-text articles that reported trials in which diagnosis of diabetes was a predefined study outcome. We also searched the reference lists of identified articles for additional papers and we sought expert opinion on relevant trials.

Competing interests

SE Kahn and SM Haffner have declared associations with the following companies: Astra Zeneca, GlaxoSmithKline, Merck, Novartis and Pfizer. See the article online for full details of the relationships. The other authors declared no competing interests.

loss has the greatest effect. Various medications (e.g. metformin, thiazolidinediones and acarbose) can also prevent or delay T2DM. Whether diabetes-prevention strategies also ultimately prevent the development of diabetic vascular complications is unknown, but cardiovascular risk factors are favorably affected. Preventive strategies that can be implemented in routine clinical settings have been developed and evaluated. Widespread application has, however, been limited by local financial considerations, even though cost-effectiveness might be achieved at the population level.

Keywords

impaired glucose tolerance; prediabetes; prevention; type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is rapidly becoming the most common chronic disease in the US, with more than 7% of the adult population affected and 1,500,000 new cases diagnosed per year.¹ T2DM is most prevalent among the elderly and in specific ethnic groups, including African Americans, Hispanic Americans, Asian and Pacific Island Americans and American Indians. Diabetes is accompanied by a multitude of severe, long-term complications that ultimately cause more adult cases of blindness, renal failure and amputations in the US than any other disease. In addition, people with T2DM have a twofold to fourfold increase in their risk of developing cardiovascular and peripheral vascular disease and stroke. The enormous human and financial costs that accompany T2DM, and the challenge of treating it effectively once it has developed, make it an appropriate target for prevention. As reviewed here, substantial progress has been made in the past decade in developing and evaluating effective preventive strategies.

PREVENTIVE STRATEGIES BASED ON PATHOPHYSIOLOGY

T2DM is characterized by insulin resistance and β-cell dysfunction (impaired insulin secretion), the balance between which varies widely between individuals.^{2,3} Insulin resistance is frequently well established in individuals with impaired glucose tolerance, and it is the presence of β-cell dysfunction that distinguishes those in whom glucose intolerance worsens from those in whom it remains stable.⁴ Interventions that decrease insulin resistance and preserve or improve β-cell function are likely to be effective in slowing progression from impaired glucose tolerance to diabetes, or even allowing reversion to normal glucose tolerance. Many interventions, such as drugs, weight loss and physical activity, are thought to improve insulin resistance and might also affect insulin secretion.

EARLY PREVENTION STUDIES

Randomized clinical trials of preventive strategies for T2DM began in the 1960s, notably before the current definitions were established for impaired fasting glucose and impaired glucose tolerance—both of which indicate a high risk of T2DM. Three early trials examined drugs then in common use to treat T2DM. In the Whitehall study, 204 men with impaired glucose tolerance were randomly assigned either phenformin or placebo.⁵ In the 181 patients who completed 5 years of follow-up, the cumulative incidence of diabetes was 14% in the phenformin-treated patients and 16% in placebo-treated patients, with a cumulative incidence rate ratio (drug versus placebo) of 0.9 (95% CI 0.4–1.8).⁶ In the Bedford study, 241 men and women with impaired glucose tolerance were randomly assigned either the sulfonylurea, tolbutamide, or placebo. The 8.5-year cumulative incidence of diabetes was 9% in the tolbutamide group and 8% in the placebo group (incidence rate ratio 1.1, 95% CI 0.5–2.5) and a subsequent report of 10 years' follow-up of these patients also showed no significant effect of tolbutamide on the incidence of diabetes.⁷ The third major study of this era was conducted

in 147 men in Malmöhus, Sweden.⁸ Men with impaired glucose tolerance (defined according to local criteria) received dietary advice to limit their carbohydrate and lipid intake and, if overweight, their total energy intake. They were also randomly assigned tolbutamide, placebo or no drug treatment. The 10-year cumulative incidence of diabetes was 10% in men assigned tolbutamide treatment and 13% in the two groups assigned placebo or no drug (incidence rate ratio 0.8, 95% CI 0.3–2.0).⁶

None of these pioneering studies established whether diabetes could be prevented or delayed, and their findings were inconclusive owing to the small sample sizes used. Whether pharmacologic prevention of T2DM was possible remained unknown into the 1990s. The Malmöhus study, however, provided two additional provocative findings. The results of the study were originally reported according to patients' estimated adherence to drug treatment, rather than according to their original treatment assignment (i.e. by intention to treat).⁸ Of the few tolbutamide-treated participants who were estimated to have taken the drug throughout the study, however, none developed diabetes. This outcome has been widely cited as evidence that tolbutamide has the potential to prevent diabetes. This conclusion of the article was, however, inappropriately based on the analysis of adherence. Analysis by intention to treat, generally considered the proper way to assess treatment effects in a clinical trial, did not support a preventive effect of tolbutamide. In addition, although treatment and formal follow-up of the study participants ended in 1975, the investigators continued to follow up participants until 1987 for mortality and cause of death. The all-cause mortality rate ratio (drug compared with placebo or no drug) was 0.66 (95% CI 0.39–1.10) and the ischemic heart disease mortality rate ratio was 0.42 (95% CI 0.16–1.12).⁹

While the conclusions of this study were limited by its small size and wide CIs, the Malmöhus study provided early support for the hypothesis that the benefits of treatments for hyperglycemia might persist long after active intervention ends. This hypothesis has been supported by later, much larger clinical trials.^{10,11}

STUDIES OF LIFESTYLE MODIFICATION

Diet and exercise

Over the past 10 years several randomized clinical trials have formally tested the hypothesis that lifestyle modification, namely weight loss and/or increased activity or exercise, can prevent T2DM.¹² Their findings indicate that such changes can prevent the onset of diabetes in people at risk (Table 1).

The first of these studies was conducted in Chinese community health clinics and included 577 individuals with impaired glucose tolerance.¹³ Individuals were assigned, according to which clinic they attended, to a program of dietary modification, exercise, or both, and were followed up for 6 years. The dietary intervention focused on increased consumption of vegetables and reduced consumption of alcohol and simple carbohydrates; overweight individuals ($BMI \geq 25 \text{ kg/m}^2$) were also advised to limit their energy intake. Participants in the exercise-only group were instructed to increase their daily activity by the equivalent of at least 20 min of brisk walking. The diet plus exercise group received both interventions, and patients who attended usual-care clinics served as a control group. The 6-year cumulative incidence of diabetes was high in all groups (48%, 41%, 46% and 68% in the diet-only, exercise-only, diet plus exercise and control groups, respectively). The relationship between the amount of weight lost and diabetes incidence was inconsistent and all three interventions were similarly effective in preventing diabetes.

The Finnish Diabetes Prevention Study (DPS)¹⁴ was a randomized study of 522 over-weight, middle-aged adults with impaired glucose tolerance. The lifestyle intervention included dietary

and exercise components. The weight-loss goal was 5% or more of baseline weight, and to achieve this target participants were instructed to reduce fat intake and increase consumption of fiber, whole grains, vegetables and low-fat dairy products. The exercise component required participants to do moderate-intensity exercise for at least 30 min per day. The intervention group lost an average of 4.2 kg in the first year of the study and, compared with the control group, had a 58% reduction in diabetes incidence during the whole study (~4 years). Although this study was not designed to assess the individual contributions of the diet and exercise components, participants who undertook particularly vigorous leisure-time physical activities had a markedly reduced risk of diabetes.¹⁵ After cessation of the intervention, the reduction in diabetes risk persisted—over 7 years of follow-up, the intervention group had an overall reduction in their risk of diabetes of 43% compared with the control group; during the post intervention period, the risk reduction was 36% in the subset of participants who were free from diabetes at the end of the intervention period despite modest weight regain (1.3 kg regained of the original 3.1 kg lost by this subgroup) in the intervention group.¹⁶ As might be expected, individuals who maintained the changes to their lifestyle during the extended follow-up period had the greatest reduction in their risk of diabetes (a 46% risk reduction compared with those who did not achieve their goals). In a multivariate analysis that considered the success of achieving all five lifestyle goals, only weight reduction remained a significant determinant of diabetes risk.

The largest and most comprehensive lifestyle modification study was the US Diabetes Prevention Program (DPP; for a list of members of the DPP Research Group see Supplementary information online).^{17,18} The DPP randomly allocated 3,234 overweight, mostly middle-aged adults with impaired glucose tolerance and fasting plasma glucose values of 5.3 mmol/l or higher to intensive lifestyle intervention, metformin or placebo. An additional 585 participants were randomly assigned troglitazone therapy, but recruitment to this group and participants' ongoing treatment were terminated prematurely owing to concern over possible hepatotoxic effects.¹⁷ Troglitazone was not approved as a study drug in some locations that had enrolled American Indian participants. The DPP preferentially enrolled individuals at high risk of developing T2DM: overall, 45% of participants were from high-risk ethnic groups, and 20% were aged 60–85 years at baseline.

The DPP intensive lifestyle intervention was intended to achieve a 7% loss in body weight over 24 weeks. Participants were instructed to perform 150 min moderate-intensity physical activity (such as brisk walking) per week and to eat a low-fat, reduced-calorie diet. They also received one-to-one counseling to aid these changes in behavior that was continued (generally monthly) after the initial 24-week period to help maintain weight loss and activity levels. The lifestyle-intervention group achieved a mean weight loss of 7% (an average of 7.0 kg) within the first year, and had an overall mean weight loss of 5.6% (an average of 5.6 kg) during follow-up (mean duration 2.8 years); the physical activity goals were met by 74% of participants in the first 24 weeks of the study.

The DPP lifestyle intervention was associated with a 58% reduction in the incidence of diabetes, compared with placebo plus standard lifestyle recommendations.¹⁹ Weight loss was the predominant predictor of reduced diabetes incidence, with a 16% reduction in risk per kilogram of weight lost.²⁰ However, participants who achieved their exercise goals but not their weight loss goals also experienced some reduction in diabetes risk (44%, compared with placebo-treated individuals). The effectiveness of the DPP lifestyle intervention was similar in all ethnic groups and both sexes, and was greatest in older participants (age 60–85 years).²¹ Changes in physical activity and diet (primarily, a reduced calorie intake from fat) predicted weight loss, and weight loss, in turn, was associated with a reduced risk of developing T2DM. Interventions to reduce diabetes risk in overweight or obese individuals should, therefore, primarily aim to induce weight loss.

Studies of diabetes prevention in Japan²² and India²³ also confirmed the benefit of lifestyle-modification programs. Even with quite modest weight losses (0–2 kg), risk reductions of 67% and 28% were achieved in the Japanese and Indian studies, respectively. The differences in study design and participant characteristics make direct comparisons difficult, but these findings do seem to support the effectiveness of lifestyle modification across a broad range of ethnic groups and cultures.

Bariatric surgery

Bariatric surgery can effectively reverse or prevent T2DM. Pories *et al.*^{24–26} noted the marked effect of weight-reduction surgery on diabetes. Although their data were retrospectively reviewed, they reported an annual diabetes incidence of 4.5% in the control group, compared with only 1.0% in the surgically treated group. In a prospective study of individuals with impaired glucose tolerance and severe obesity, diabetes incidence rates were 4.7 cases per 100 person-years of follow-up in the untreated (control) group, compared with 0.15 cases per 100 person-years in patients who underwent bariatric surgery.²⁷

The Swedish Obese Subjects (SOS) Study was a prospective trial of more than 2,000 individuals who underwent a variety of surgical procedures (most commonly, vertical banded gastroplasty) and matched controls who received standard care.²⁸ The odds ratio for diabetes in the surgically treated group was 0.14 (95% CI 0.08–0.24) at 2 years and 0.25 (95% CI 0.17–0.38) at 10 years of follow-up. As expected, the incidence of diabetes was related to the amount of weight lost. Of participants who lost more than 12% of their initial body weight none developed diabetes, in contrast to a 2-year diabetes incidence of 7% in those with a 2% weight loss, and 9% in those who gained weight.²⁹ Other studies showed that laparoscopic adjustable gastric banding in patients with established diabetes resulted in remission of diabetes in 64% and major improvements in glycemic control in another 26%,³⁰ which suggests that this surgery could also successfully prevent diabetes.

In a randomized, controlled trial of gastric banding, diabetes remission was reported in 73% of the surgically treated patients, compared with 13% of recipients of conventional therapy.³¹ Biliopancreatic diversion, the bariatric procedure that results in the most dramatic and sustained weight loss, has also been reported to normalize glucose tolerance in obese patients with either impaired glucose tolerance or established diabetes.³² Glucose tolerance has been reported to improve rapidly after bariatric surgery, even before much weight has been lost; neurohormonal mechanisms are reported to be involved.³³

STUDIES OF PHARMACOLOGIC INTERVENTIONS

Various pharmacologic agents have been studied (Table 2), including drugs commonly used to treat established diabetes (metformin, acarbose, thiazolidinediones) and a weight-loss drug (orlistat).³⁴

Metformin

The biguanide, metformin, is the most thoroughly studied drug used for diabetes prevention. By far the largest group of metformin-treated patients studied was included in the DPP, in which high-risk individuals with impaired glucose tolerance were randomly allocated 850 mg metformin twice daily ($n = 1,073$) or placebo ($n = 1,082$). Mean follow-up was 2.8 years. Adherence to metformin was excellent³⁵ and, despite the anticipated gastrointestinal side effects and twice-daily dosing regimen, metformin reduced the risk of developing diabetes by 31% compared with placebo. Metformin was most effective in individuals whose baseline BMI was higher than 35 kg/m^2 , in whom it reduced the incidence of diabetes by approximately 50%. Metformin had little beneficial effect in older participants (those aged 60–85 years). An average

1.7 kg weight loss was reported in the metformin group, compared with a 0.3 kg weight gain in the placebo group; weight loss explained 64% of the beneficial effect of metformin on diabetes risk. Favorable changes in insulin sensitivity and in secretion of pro insulin also contributed to the decreased diabetes risk seen in metformin-treated patients.³⁶

Two smaller studies in India²³ and in China³⁷ also reported similar reductions in diabetes risk with 250 mg of metformin administered two or three times daily. The excellent safety record, long experience with this drug in the treatment of diabetes and low cost of metformin make it an attractive option for diabetes prevention.

Thiazolidinediones

The insulin-sensitizing properties of the thiazolidinediones have generated enthusiasm for their role in diabetes prevention. Troglitazone reduced the development of diabetes by around 50% over 2.5 years in a group of women with prior gestational diabetes (~60% also had impaired glucose tolerance at baseline).³⁸ Troglitazone administration in the DPP was discontinued prematurely owing to its hepatotoxic effects, but during the average 0.9 years of exposure, diabetes incidence was reduced by 75%.³⁹ Administration of rosiglitazone over 3 years has since been studied in 5,269 patients with impaired fasting glucose, impaired glucose tolerance, or both.⁴⁰ The incidence of diabetes was reduced by 62%, and 50% of rosiglitazone-treated patients reverted to normoglycemia (compared with 30% of placebo-treated patients).

Like metformin, rosiglitazone seems to be most effective in individuals with a high BMI (rosiglitazone confers risk reductions of 40% for BMI <28 kg/m² and 68% for BMI >33 kg/m²). Notable side effects, including weight gain (rosiglitazone-treated patients gained 2.2 kg more than placebo-treated patients) and edema were observed, as they are when rosiglitazone is used to treat established diabetes. The frequency of congestive heart failure was also increased in the rosiglitazone group (hazard ratio 7.03, 95% CI 1.60–30.9), but there were few cases in this generally healthy population. Questions have been raised about potential cardiovascular toxic effects of rosiglitazone and this issue remains to be resolved.⁴¹ Additional concerns about rosiglitazone include one report of an increased rate of osteoporotic fracture among diabetic women treated with this drug.⁴² These concerns might indicate an unacceptable risk-to-benefit ratio for thiazolidinediones, particularly rosiglitazone, in diabetes prevention.^{43,44}

Acarbose

The α-glucosidase inhibitor, acarbose, has been studied in a number of clinical trials.^{37,45,46} Most notably, the STOP-NIDDM (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) trial⁴⁷ reported that acarbose treatment was associated with a 25% reduction in the incidence of diabetes in a large ($n = 1,429$), cohort of high-risk individuals with impaired glucose tolerance. Approximately one-quarter of the cohort (including 31% of the acarbose group) did not complete the study, however, with the consequence that this estimate of the magnitude of acarbose's effect on diabetes incidence might be unreliable. The particularly high drop-out rate in acarbose-treated patients was attributed to its well-known gastrointestinal side effects. Acarbose might, therefore, have limited value for diabetes prevention in general practice.

Weight-loss agents

Weight-loss agents have been studied in small numbers of individuals with impaired fasting glucose, impaired glucose tolerance, or both. Orlistat, an intestinal lipase inhibitor, reduced the development of diabetes by 40–52% in obese people with impaired glucose tolerance.^{48,49} The effect of this drug on diabetes might be attributable to weight loss, which was greater than that achieved with lifestyle change alone. The drop-out rate approached 50%, which

suggests that this therapy has limited acceptability, and potentially makes the estimates of the size of treatment effects unreliable.

Other drugs

Following post hoc analyses that suggested angiotensin-converting-enzyme inhibitors might reduce diabetes risk,⁵⁰ ramipril was studied for diabetes prevention in the DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial.⁵¹ The hazard ratio for developing diabetes was 0.91 (95% CI 0.80–1.03). There was no additive effect of therapy in participants who were randomly allocated both ramipril and rosiglitazone.

A post hoc analysis of data from a study of coronary artery disease prevention suggested that statins might have diabetes-prevention benefits,⁵² but this finding has not been replicated^{53–55} and the hypothesis has not been tested in a randomized clinical trial.

Preliminary investigation of incretin-based therapies (e.g. exenatide and dipeptidyl peptidase IV inhibitors) suggests these agents not only enhance insulin secretion, but also promote β-cell proliferation.⁵⁶ These agents might, therefore, be suitable for diabetes prevention, but clinical trials will be needed to address this hypothesis.

MECHANISMS OF DIABETES PREVENTION

In the DPP, both the intensive lifestyle intervention and metformin increased insulin sensitivity.⁵⁷ Intensive lifestyle intervention was more effective than metformin in slowing progression to diabetes, partly because lifestyle modification gave greater improvements in insulin sensitivity and β-cell function.⁵⁷ Similarly, in the DPP³⁹ and TRIPOD (Troglitazone in Prevention of Diabetes)³⁸ studies, improvements in both insulin sensitivity and β-cell function explained the observed reduction in progression to diabetes seen with troglitazone. Data on the mechanistic effects of rosiglitazone in the DREAM study are not yet available.⁴⁰

Prevention versus masking of incident diabetes

Whether the antidiabetic medications used for prevention truly prevent disease development or merely mask its presence is unclear. This issue has been addressed most directly in the DPP, in which a formal 1–2-week washout period was employed following completion of the initial randomized, double-blind trial.⁵⁸ When an oral glucose-tolerance test (OGTT) was performed after washout, diabetes was more frequently diagnosed in metformin recipients than in placebo recipients (hazard ratio 1.49, 95% CI 0.93–2.38, $P = 0.098$). Even when these new cases of diabetes were included, however, the overall incidence of diabetes was still reduced by 25% in metformin-treated patients, which suggests that the benefit of metformin was not limited to its acute pharmacologic effects. Similar results were noted with acarbose in the STOP-NIDDM trial.⁴⁷

In the TRIPOD study of women with a history of gestational diabetes, 84 women were followed up for less than 1 year after drug discontinuation, during which time seven new cases of diabetes developed. Six of these cases occurred in the former placebo group and one in the former troglitazone group. These findings were interpreted as evidence for a persistent drug effect.³⁸ By contrast, in the DPP, the diabetes incidence in the former troglitazone group was almost identical to that in the former placebo group after drug withdrawal,³⁹ and remained so during 3 years of follow-up. Results of long-term follow-up of individuals treated with rosiglitazone in the DREAM trial have not yet been published.

Vascular outcomes

Despite substantial evidence for the effectiveness of both lifestyle change and medications in the prevention of diabetes, few data are available on the delay or prevention of vascular outcomes of diabetes. Acarbose treatment in the STOP-NIDDM trial was associated with a 49% reduction in patients' relative risk of cardiovascular events (hazard ratio 0.51, 95% CI 0.28–0.95, $P = 0.03$), although the number of events was small.⁵⁹ A reduction was also seen in the risk of hypertension (hazard ratio 0.66, 95% CI 0.49–0.89, $P = 0.006$). The other diabetes-prevention trials that are large enough to detect differences in low-frequency events have not yet reported vascular outcomes. However, in the DPP, improvements in various risk factors for cardiovascular disease, including serum lipids, C-reactive protein and fibrinogen, were seen with intensive lifestyle intervention and, to a lesser extent, with metformin.^{60,61} The incidence of metabolic syndrome was reduced by 41% ($P < 0.001$) in the lifestyle-modification group and by 17% ($P = 0.03$) in the metformin group, compared with its incidence in the placebo group.⁶² Likewise, indices that reflect cardiac autonomic function (heart rate variability) and physical fitness (resting heart rate) were also improved in the intensive lifestyle intervention group.⁶³ Extended follow-up of this cohort is underway, which will include assessments of measures of subclinical atherosclerosis and cardiovascular disease events. Fibrinolysis (i.e. levels of plasminogen activator inhibitor 1) was improved by lifestyle intervention in the Finnish DPS.⁶⁴

Insights from genetic studies

Genetic analyses have provided insights into the determinants of diabetes risk and the interaction of genes with responses to specific preventive interventions. The role of *TCF7L2* polymorphisms in the development of diabetes has been confirmed. Furthermore, the association between the TT allele of the single-nucleotide polymorphism rs7903146 and decreased β -cell function was established in the DPP cohort.⁶⁵ Metformin and the DPP intensive lifestyle intervention both had protective effects against the development of diabetes in those with high-risk alleles (American Indian participants were not well represented, since some centers did not approve the genetics studies). Similar results with respect to diabetes risk, insulin secretion and the effects of lifestyle modification were also obtained in the Finnish DPS.⁶⁶

Several genes are associated with the risk of developing T2DM, including *KCNJ11* (which encodes islet ATP-sensitive inward rectifier potassium channel 11, also known as Kir6.2) and the adjacent gene *ABCC8* (which encodes sulfonylurea receptor 1). Polymorphisms in *KCNJ11* and *ABCC8*, as well as the common Pro12Ala polymorphism of *PPARG* were shown to influence the risk of developing diabetes in the prospective Botnia study,⁶⁷ the Finnish DPS,⁶⁸ and the DPP^{69,70} populations. The roles of these genetic polymorphisms need to be confirmed in prospective studies. In the DPP, *PPARG* polymorphisms seemed not to influence the effectiveness of troglitazone in improving insulin sensitivity.⁶⁹

Translational studies

Clinical trials that proved the effectiveness of lifestyle interventions in reducing diabetes risk were designed from the outset as efficacy trials. As such, they were conducted in resource-intensive settings with limited consideration as to how the intervention strategies might be adapted for population-wide use. Studies to investigate strategies for translating the findings of these efficacy trials into the public-health arena are in their infancy. Published studies of diabetes-prevention strategies have targeted populations known to be at high risk of developing T2DM,⁷¹ including selected ethnic groups^{72–79} and individuals with prediabetes,^{80–83} although many of these studies preceded publication of the DPP and, therefore, were not based on DPP evidence. Most of the studies combine dietary and exercise strategies as the basis of their interventions and use quasiexperimental designs for evaluation.⁷¹

Some community-based studies that preceded randomized clinical trials such as the DPP and DPS focused on implementation of school-based programs designed to increase physical activity and improve health awareness in young people.^{74,75,78,79} Results of these studies were varied, but suggested that these interventions improved participants' knowledge about healthy lifestyle choices and increased their adoption of risk-reducing behaviors, although effects on diabetes development have not been reported.

Studies in adults have focused primarily on interventions that increase levels of physical activity and promote consumption of a healthy or a weight-loss diet.^{76,77,84–88} In general, improvements were seen in rates of physical activity and some groups experienced weight loss, but these changes generally did not reach significance because of the study designs used, including the lack of control groups.

The most dramatic evidence that the DPP lifestyle intervention can be translated into community settings is offered by the work of Ackermann *et al.*⁸⁰ and Ackermann and Marrero,⁸¹ who used the Young Men's Christian Association as a delivery site for strategies that implemented the DPP intensive lifestyle intervention. These same researchers studied a group-based version of the DPP curriculum in a randomized clinical trial; they reported significant weight loss in the intervention group that was sustained at 12 months after the curriculum ended. In addition, Finland has implemented a national program to prevent T2DM.⁸⁹ The FIN-D2D (Finnish Type 2 Diabetes Prevention Plan 2003–2007) is being conducted in five hospital districts and covers a population of 1.5 million people. Primary and occupational health-care providers are the agents of intervention. The effectiveness, feasibility, and costs of the program are being evaluated.

COST-EFFECTIVENESS OF DIABETES PREVENTION

Although intervention can clearly reduce the incidence of T2DM in well-funded research settings, can those who fund health-care services afford such programs in practical settings? The economic evaluation performed by the DPP Research Group concluded that the DPP interventions would be cost-effective from societal and health-system perspectives, with costs per case of T2DM prevented or per quality-adjusted life-year gained similar to or lower than those of many other well-accepted interventions.⁹⁰ Another analysis, however, suggested that such programs are too expensive for widespread implementation.⁹¹ Much of the uncertainty and disagreement between these analyses derive from their different assumptions about rates of progression to diabetes and its complications, as well as their different analytic approaches.⁹² This question is, therefore, difficult to resolve with currently available data.

In India, preventive lifestyle or metformin interventions were deemed cost-effective,⁹³ and might similarly be cost-effective in other developing countries. A systematic review of T2DM prevention strategies published in 2006 concluded that the interventions were highly cost-effective, but noted that this interpretation was based on very few studies.⁹⁴ The cost-effectiveness of genotyping for gene variants with emerging evidence of an increased risk of T2DM remains to be assessed.

PREVENTION VERSUS EARLY DETECTION AND TREATMENT

Debate prevails about whether resources (human and financial) would be better spent on T2DM prevention or on its early detection and treatment. Early detection is feasible through use of the same simple tests used in prevention programs, and could be done much more economically than attempting to prevent diabetes at the population level. Allocation of resources to intensive management of patients with newly diagnosed diabetes could be preferable to prevention. A major drawback of this approach, however, is that many people will have already developed macrovascular disease (and, rarely, microvascular disease) before diagnosis. Nonetheless, no

data from clinical trials that have specifically compared prevention with early detection and intensive treatment have yet been reported.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Application of the research findings requires identification of individuals who are at risk of developing diabetes. Screening for prediabetes should be considered in people aged 45 years and older, and for adults younger than 45 years who are overweight or obese and have additional risk factors, such as a family history of diabetes, prior gestational diabetes or belonging to a high-risk ethnic group.⁹⁵ Measurement of fasting plasma glucose levels will identify individuals with impaired fasting glucose, but an OGTT is necessary to identify impaired glucose tolerance. Impaired fasting glucose and impaired glucose tolerance are considered to confer equivalent increases in risk for the development of diabetes; the combination of impaired fasting glucose and impaired glucose tolerance confers a greater increase in risk than either variable alone.^{96,97} Strategies that employ measurements of fasting glucose and routine clinical variables to identify high-risk individuals have been proposed and have the advantage of not requiring administration of an OGTT.^{98,99} Such management algorithms seem to be capable of discriminating between individuals with varying levels of diabetes risk in clinical practice.

Lifestyle modification, including a weight-loss goal of 5–10% of initial weight and moderate-intensity physical activity for 30 min per day, can provide the greatest reduction in diabetes risk and should be implemented for all individuals at risk for diabetes. This approach has an excellent safety profile and might also be the most cost-effective intervention. The role of pharmacologic agents is somewhat less clear. However, substantial evidence supports the use of metformin in patients who either fail to achieve these lifestyle goals or who have additional risk factors at baseline (such as both impaired fasting glucose and impaired glucose tolerance, a strong family history of diabetes, dyslipidemia, or hypertension), especially if they are younger than 60 years and have a BMI of 35 kg/m² or greater.^{2,96} Acarbose might be considered for these patients, but it is less well tolerated and more expensive than metformin, and requires three doses daily. Although effective, routine use of thiazolidinediones cannot currently be recommended because of their high cost and emerging evidence of adverse effects.

CONCLUSIONS

Tremendous progress has been made over the past decade in the identification of effective strategies to prevent or delay onset of T2DM. Important limitations in our current knowledge, however, include the lack of adequate data to determine whether these preventive approaches can slow the development of serious vascular complications of diabetes and ultimately reduce diabetes-related mortality. In addition, although important efforts in this regard are underway, the public-health messages implicit in diabetes risk and diabetes prevention remain underappreciated. Probably the greatest challenge continues to be in translating scientific discoveries into programs that are adequately funded and broadly available to individuals at high risk of developing diabetes.

KEY POINTS

- Type 2 diabetes mellitus is a common chronic disease that is responsible for enormous human and financial costs
- Lifestyle modification (i.e. modest weight loss and increased physical activity) is the most consistently effective approach to diabetes prevention
- Medications, including metformin, acarbose and thiazolidinediones, are effective therapies for preventing or delaying diabetes

- Interventions are effective across different ages and ethnic groups
- Application of these findings to public-health initiatives has been slow, at least partly because of their financial implications

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Randomized, clinical trials that aimed to prevent diabetes by lifestyle modification.

Study ^a	Number of patients by treatment group	BMI of participants (kg/m^2)	Duration of intervention (years)	Lifestyle goals	Weight loss achieved at 1 year (kg)	Cumulative incidence of T2DM in controls	Risk reduction (95% CI)
Pan <i>et al.</i> (1997) ¹³	130 diet 141 exercise 126 diet and exercise 133 control	26	6	Weight loss + maintenance of a healthy diet ± exercise	NR	68% (15.7% per year)	Diet 31% (NR) Exercise 46% (NR) Both 42% (NR)
Tuomilehto <i>et al.</i> (2001) ¹⁴	265 active 257 control	31	4	5% weight loss on low-fat, high-fiber diet + 30 min exercise per day	4.2	23% (6% per year)	58% (30–70%)
DPP Research Group (2002) ¹⁹	1,079 active 1,082 control	34	2.8	7% weight loss + 150 min exercise per week	7	28.9% at 3 years	58% (48–66%)
Kosaka <i>et al.</i> (2005) ^{22b}	356 active 102 control	24	4	Reduction in BMI to $\leq 22 \text{ kg}/\text{m}^2$ by 30–40 min exercise per day	2.5	9.3% (assessed by FPG $> 7.8 \text{ mmol/l}$)	67.4% (NR)
Ramachandran <i>et al.</i> (2006) ²³	133 active 136 control	26	3	Weight maintenance by diet low in refined carbohydrates and fat + 30 min exercise per day	0	55%	28.5% (20–37%)

^a All study populations had impaired glucose tolerance.

^b In this study, the oral glucose tolerance test used 100 g glucose and modified criteria for impaired glucose tolerance.

Abbreviations: DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; NR, not reported; T2DM, type 2 diabetes mellitus.

Table 2
Randomized clinical trials of medications used in diabetes prevention.

Study	Number of patients by study group	Study population	Duration of intervention (years)	Medication	Cumulative incidence of T2DM in controls	Risk reduction (95% CI)
DPP Research Group (2002) ¹⁹	1,073 active 1,082 placebo	IGT BMI 34 kg/m ²	2.8	Metformin 850 mg twice daily	28.9%	31% (17–43%)
Ramachandran <i>et al.</i> (2006) ²³	133 active 136 control	IGT BMI 26 kg/m ²	2.5	Metformin 250 mg twice daily	55%	26% (19–35%)
Wenying <i>et al.</i> (2001) ³⁷	88 active 85 control	IGT BMI 25 kg/m ²	3.0	Metformin 250 mg three times daily	11.6% per year	77% (NR)
DPP Research Group (2005) ³⁹	585 active 582 placebo	IGT BMI 34 kg/m ²	0.9	Troglitazone 400 mg once daily	12% per year	75% (NR)
Buchanan <i>et al.</i> (2002) ³⁸	133 active 133 placebo	Former GDM IGT (<i>n</i> = 167) BMI 30 kg/m ²	2.5	Troglitazone 400 mg once daily	30% (12% per year)	50% (28–89%)
Gerssein <i>et al.</i> (2006) ⁴⁰	2,365 active 2,634 placebo	IGT, IFG or both BMI 31 kg/m ²	3.0	Rosiglitazone 8 mg once daily	25%	62% (35–46%)
Chiasson <i>et al.</i> (2002) ⁴⁷	714 active 715 placebo ^a	IGT BMI 31 kg/m ²	3.2	Acarbose 100 mg three times daily	42.0% (12.4% per year)	25% (10–37%)
Wenying <i>et al.</i> (2001) ³⁷	88 active 85 control	IGT BMI 25 kg/m ²	3.0	Acarbose 50 mg three times daily	11.6% per year	88% (NR)
Torgerson <i>et al.</i> (2004) ⁴⁸	1,640 active 1,637 placebo ^b	IGT (<i>n</i> = 694) BMI 37 kg/m ²	4.0	Orlistat 120 mg three times daily	14.2%	IGT 52% All 41% (NR)
Heymsfield <i>et al.</i> (2000) ⁴⁹	359 active 316 placebo	IGT (<i>n</i> = 120) BMI 36 kg/m ²	2.0	Orlistat 120 mg three times daily	7.6%	40% (NR)
Bosch <i>et al.</i> (2006) ⁵¹	2,623 active 2,646 placebo	IGT, IFG or both BMI 31 kg/m ²	3.0	Ramipril 10 mg once daily	18%	9% (0–20%)

^aThis study had a 25% drop-out rate.

^bThis study had a 50% drop-out rate.

Abbreviations: DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NR, not reported; T2DM, type 2 diabetes mellitus.