Prevention of Type 2 Diabetes

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Abstract

Diabetes is defined by elevated plasma glucose concentrations and characterized by metabolic disturbances and widespread tissue damage. Diagnostic criteria and classification of types of diabetes and the risk factors for T2DM are described in other chapters of this book. This chapter considers only T2DM. Diagnostic cut-points for diabetes have often been chosen to correspond to degrees of hyperglycemia associated with diabetes complications, usually retinopathy or nephropathy. Thus, it is widely believed that preventing increases in hyperglycemia to levels that are diagnostic of diabetes and associated with development of complications will also prevent development of the complications. It is also hypothesized that preventing diabetes complications is more feasible in this way than by postponing interventions until the disease is diagnosed, at which time some tissue damage may have already occurred and hyperglycemia may be more difficult to control. While

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these are very natural assumptions, evidence supporting them has been difficult to obtain. The assumption that preventing T2DM will also prevent its complications provides the main justification for the concept that it is better to prevent diabetes than to wait until it develops and then treat it.

Keywords
Type 2 diabetes · Prevention

Introduction

Randomized clinical trials in prevention of type 2 diabetes mellitus (T2DM) began as early as the 1960s. This chapter reviews randomized clinical trials in prevention of T2DM since that time. While not comprehensive, this review includes clinical trials with historical interest and a large impact on research in diabetes prevention. I also discuss treatment effects on long-term outcomes beyond diabetes itself. This chapter does not cover nonrandomized prevention activities, bariatric surgery, or randomized clinical trials that aim to prevent or delay type 1 diabetes. This chapter is based, on part, on previous commentaries and reviews I have co-authored with others (Knowler et al. 1995; Crandall et al. 2008; Knowler et al. in press) that include more details on some of the randomized clinical trials described in this chapter.

Why Is Preventing T2DM Important and Feasible?

Diabetes is defined by elevated plasma glucose concentrations and characterized by metabolic disturbances and widespread tissue damage. Diagnostic criteria and classification of types of diabetes and the risk factors for T2DM are described in other chapters of this book. This chapter considers only T2DM. Diagnostic cut-points for diabetes have often been chosen to correspond to degrees of hyperglycemia associated with diabetes complications, usually retinopathy or nephropathy. Thus, it is widely believed that preventing increases in hyperglycemia to levels that are diagnostic of diabetes and associated with development of complications will also prevent development of the complications. It is also hypothesized that preventing diabetes complications is more feasible in this way than by postponing interventions until the disease is diagnosed, at which time some tissue damage may have already occurred and hyperglycemia may be more difficult to control. While these are very natural assumptions, evidence supporting them has been difficult to obtain, as discussed later. The assumption that preventing T2DM will also prevent its complications provides the main justification for the concept that it is better to prevent diabetes than to wait until it develops and then treat it.

There has been disagreement over the years as to precise diagnostic criteria, but all widely accepted criteria have been based on some degree of hyperglycemia. The disagreements in diagnostic criteria derive from the continuity of glucose concentrations, both among people and within one person over time. T2DM has a long stage

of development that varies among people. The development of T2DM in an individual over time also appears to be a continuous process, although defining its nature precisely would require frequent (or continuous) measurement of glycemia over a lifetime in persons who develop T2DM. Most longitudinal studies of serial glucose measurements starting in normoglycemic persons measured glucose in intervals of 2 years or more (Mason et al. 2007; Tabak et al. 2009), thus being unable to define the precise trajectory of glucose concentrations prior to their increasing to diagnostic levels. These studies, however, suggest that glucose concentrations may be stable or gradually increasing for many years, with an increasing slope of glycemia over time in the few years prior to diagnosis. There is large variation among persons, however, in these patterns prior to onset of T2DM.

Such patterns of increasing glycemia are relevant for diabetes prevention, because they suggest the possibility of identifying persons on the way to developing T2DM before the disease is diagnosed. Such persons, whether identified by elevated glucose concentrations or other predictive factors, could be considered at high risk of T2DM, a concept allowing for the "high-risk" approach to T2DM prevention – identification and risk factor modification of persons at high risk. The vast majority of published T2DM prevention research, summarized below, has taken the "high-risk" approach. This approach assumes that the greatest benefit (i.e., most cases prevented) with the least cost and harm comes from treating persons at greatest risk where resources can be concentrated. This is likely true when preventive interventions are delivered to individuals, such as through counseling for lifestyle changes or giving medicines. Some argue, however, that the most benefit can come from "population" approaches in which interventions are designed to decrease risk factors in large numbers of the population without targeting individuals.

Population Approach to Prevention

Population interventions might, for example, aim to decrease body weight or increase physical activity in large numbers of people, thus decreasing their risk of developing T2DM. Examples of such interventions involve changes in the built environment that would encourage walking or cycling rather than vehicular transportation or food taxation and subsidization to encourage shifts in consumption from perceived unhealthy foods (such as high simple carbohydrate) to more healthy foods (such as high-fiber complex carbohydrates). Population approaches are described elsewhere (White 2016; Wareham and Herman 2016; Batis et al. 2016; Stevenson et al. 2016) but are not covered in this chapter.

As promising as these approaches are, research in this area has made limited progress because population interventions are difficult to implement and difficult to evaluate. Changes in the built environment generally require political action and may require large economic investment. They presumably fall outside the realm of medical expertise of most readers of this book. Population approaches are also difficult to evaluate (Ackermann et al. 2013, 2015; Knowler and Ackermann 2013).

Population approaches may have the greatest potential to prevent the largest numbers of cases of T2DM. For example, if obesity and sedentary behaviors could be eliminated through changes in food availability and the man-made environment (such as transportation systems and buildings), the incidence of T2DM should be decreased. It remains unknown, however, to what extent making and evaluating such changes is possible.

Individual Approaches to Prevention

Nearly all prevention trials conducted among individuals followed a "high risk" strategy rather than targeting members of the population at large. This has been necessary for practical reasons in that the power to detect treatment effects in a clinical trial depends in part on the number of events (incident diabetes cases) observed. Most trials identified high-risk persons who had impaired glucose tolerance (IGT) during an oral glucose tolerance test (OGTT), with or without requiring other high-risk characteristics such as obesity or elevated fasting plasma glucose (FPG). I am aware of only one major randomized clinical trial that used FPG as its major eligibility criterion (Saito et al. 2011) and none that used nonglycemic risk factors alone. Therefore, there is little information on the effectiveness of preventive interventions in persons who do not have IGT.

The randomized clinical trials of preventive interventions have tested a variety of lifestyle changes involving some combination of dietary change and increased physical activity, various drugs aimed at preventing increasing glucose concentrations or decreasing weight, or combinations of diet, physical activity, and drugs.

Lifestyle Modification Interventions, With or Without Drug Arms

Several randomized clinical trials formally tested whether modifying recognized risk factors for T2DM, namely, lifestyle modification directed at weight loss and/or increased physical activity or exercise, could prevent or delay T2DM.

Da Qing Randomized Clinical Trial of Lifestyle Modification (1997)

The Da Qing study was a cluster-randomized two-by-two factorial clinical trial evaluating four combinations of diet and exercise interventions given for 6 years (Pan et al. 1997). Participants had IGT by 1985 World Health Organization (WHO) criteria (WHO 1985). Interventions were randomly assigned by clinic (33 clusters). The four intervention arms included a program of dietary modification, exercise, both, or neither (the control group). The dietary intervention included increased consumption of vegetables, reduced alcohol, and simple carbohydrates, and, if BMI $\geq$25 kg/m^2, limited total energy intake. The exercise-only intervention was to increase physical activity by at least 20 min per day of brisk walking or equivalent activity. The 6-year cumulative incidence of diabetes was 48% in the diet-only group, 41% in the exercise-only group, 46% in the diet plus exercise group, and 68% in the control group. The incidence rates in cases/100 person-years were 8.3, 5.1, 6.8, and 13.2 in the same four groups.

The interventions lasted 6 years, after which active treatment and formal follow-up were discontinued. Follow-up data were obtained by examination and record review 23 years after randomization. The four randomized groups were collapsed into a comparison of the control group (8 clusters) with the pooled three groups with diet, exercise, or both interventions (25 clusters). Annual incidence rates decreased during long-term follow-up, probably because of less frequent glucose tolerance testing or earlier development of diabetes in the persons at highest risk. Over the entire 23-year period, diabetes incidence rates in the combined intervention groups (diet, exercise, or both) were 0.55 (95% CI = 0.40–0.76) times the incidence rate in the control group (Li et al. 2014).

The study also reported effects on retinopathy, nephropathy, and death rates. Twenty years after randomization, the pooled intervention groups had a 47% reduction in severe retinopathy (hazard ratio = 0.53, 95% CI = 0.29–0.99) (Gong et al. 2011). The hazard ratio for nephropathy was 1.05, 95% CI = 0.16–7.05, which was inconclusive because of the wide confidence interval. The all-cause mortality rates during 23 years of follow-up were reduced by 54% in women, with no effect in men (Li et al. 2014). Limitations of this study included the cluster randomization and variable schedules of follow-up over time.

The Finnish Diabetes Prevention Study (DPS) (2001)

The Finnish DPS (Tuomilehto et al. 2001) was a randomized clinical trial of 522 overweight or obese, middle-aged adults (mean age 55 years) with IGT according to the 1985 WHO criteria (WHO 1985). Participants were randomly assigned to a lifestyle (diet and exercise) intervention or a control group. The lifestyle intervention participants were instructed to reduce fat intake and increase consumption of fiber, whole grains, vegetables, and low-fat dairy products, with a goal of losing at least 5% of body weight. They were also encouraged to participate in moderate-intensity exercise for at least 30 min per day. End-of-study data were available from 92% of the participants after an average follow-up of 4 years. The intervention and control groups lost an average of 4.2 kg and 0.8 kg in the first year of the study. Diabetes incidence was 58% lower in the lifestyle intervention group (32 cases/1000 person-years) than in the control group (78 cases/1000 person-years).

The lower diabetes incidence in the lifestyle group persisted during 9 additional years of follow-up after the end of the intervention (for 13 years after randomization). During the total follow-up, the adjusted hazard ratio for diabetes (intervention group vs. control group) was 0.61 (95% CI = 0.48–0.79) (Lindström et al. 2013), suggesting that the active intervention had somewhat persistent effects. The corresponding hazard ratio during the postintervention follow-up was 0.67 (95% CI = 0.48–0.95).

Compared with the control group, the lifestyle intervention group had a nonsignificantly lower mortality rate (hazard ratio = 0.57, 95% CI = 0.21–1.58) after 10 years of follow-up, but similar cardiovascular morbidity (hazard ratio = 1.04, 95% CI = 0.72–1.51) (Uusitupa et al. 2009). These results suggested a mortality benefit, but with a sample of only 522 persons and resulting wide confidence intervals, the mortality results were inconclusive.

The US Diabetes Prevention Program (DPP) (2002)

The US Diabetes Prevention Program (DPP) was a large prevention randomized clinical trial testing both a lifestyle and a drug intervention (DPP 2002). The trial enrolled 3234 nondiabetic, overweight or obese, mostly middle-aged adults with IGT and FPG values of 95 mg/dl (5.3 mmol/l) to <126 mg/dl (7.0 mmol/l). There were minor variations in eligibility criteria by clinical center, race, and time. The three randomly assigned interventions were an intensive lifestyle modification program, metformin (850 mg twice a day), and placebo. The metformin and placebo groups received printed material containing standard lifestyle recommendations. The participants were racially/ethnically diverse, with 45% recruited from racial/ethnic and age groups at particularly high risk of diabetes (African Americans, Hispanic Americans, American Indians, and Asian Americans). Mean age at baseline was 51 years and mean BMI was 34 kg/m^2.

The main goal of the intensive lifestyle intervention was 7% loss of body weight over 24 weeks with long-term maintenance. Participants were instructed engage in at least 150 min of moderate-intensity physical activity (such as brisk walking) per week and to eat a low-fat, reduced-calorie diet. 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 a mean follow-up of 2.8 years.

The initial phase of the trial was stopped in 2001, before the planned end-date, on the advice of the data and safety monitoring board because of the clear benefits of both interventions on development of diabetes. The lifestyle intervention led to a 58% reduction (95% CI = 48–60%) in diabetes incidence, based on annual OGTTs and mid-year FPG levels, compared with placebo plus standard lifestyle recommendations (DPP 2002). Diabetes risk reduction was related to the amount of weight lost (DPP 2006).

The metformin arm experienced a 31% lower diabetes incidence, compared with placebo, during the mean follow-up of 2.8 years. This was accompanied by a modest weight loss of 1.7 kg, compared with a 0.3 kg gain in the placebo group. An estimated 64% of the beneficial effect of metformin on diabetes risk was attributed to weight loss (DPP 2007). Improved estimated insulin sensitivity was also associated with reduced diabetes risk (DPP 2005b).

In a secondary analysis of history of gestational diabetes, women reporting a history of gestational diabetes were compared with women who had given birth at least once but had no history of gestational diabetes. The women with prior gestational diabetes had an especially high risk of developing diabetes in the DPP. Metformin was more effective in these women (50% reduction in incidence compared with placebo) compared to its insignificant 14% risk reduction in parous women without a history of gestational diabetes. By contrast, the lifestyle intervention had similar benefits in those with a history of gestational diabetes (53% reduction compared with placebo) or without such a history (49% reduction) (DPP 2008).

In addition to the 3234 participants randomly assigned to the placebo, metformin, or lifestyle interventions, 585 were randomly assigned to the thiozolidenedione drug troglitazone. This study arm was terminated early when the potential hepatic toxicity of troglitazone became known (DPP 2005a). During the average of 0.9 years of its

use in DPP, troglitazone reduced the incidence of diabetes by 75% compared with placebo – the largest risk reduction of all the DPP interventions among the subset of participants randomized when troglitazone was being used in the DPP. Whether the reduction in incidence would have persisted, had troglitazone therapy been continued, could not be determined. Other randomized clinical trials of thiazolidinediones, however, have been effective in diabetes prevention (see below).

Following unmasking and publication of the primary DPP results (DPP 2002), all participants, regardless of randomized study group, were offered a group-implemented lifestyle intervention because the lifestyle intervention had been the most effective intervention in the DPP. Placebo was discontinued, and unmasked metformin was continued as a study intervention in the original metformin group during the long-term follow-up study, named the Diabetes Prevention Program Outcomes Study (DPPOS) (DPP 2009). Eighty-eight percent of the surviving DPP cohort enrolled in DPPOS.

During the DPPOS, annual diabetes incidence rates in the former placebo and metformin groups fell to approximately equal those in the former lifestyle group, but the cumulative incidence of diabetes remained lowest in the former lifestyle group. Despite the convergence of annual incidence rates during long-term follow-up, the large difference in rates during the active intervention phase resulted in persistent differences between treatment groups during follow-up. During a mean follow-up of 15 years since DPP randomization, diabetes incidence was reduced by 27% in the lifestyle intervention group (hazard ratio = 0.73, 95% CI = 0.65–0.83; $p < 0.0001$) and by 18% in the metformin group (hazard ratio = 0.82, 0.72–0.93; $p = 0.001$), compared with the placebo group. At year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group (DPP 2015a).

Other effects seen in the active intervention phase persisted during the DPPOS. For example, over 10 years since randomization, women with a history of gestational diabetes assigned to placebo had a 48% higher risk of developing diabetes compared with women without a history of gestational diabetes who reported at least one delivery. In women with a history of gestational diabetes, the lifestyle and metformin interventions reduced progression to diabetes compared with placebo by 35% and 40%, respectively. Among the women without a history of gestational diabetes, the lifestyle intervention reduced the progression to diabetes by 30%, and metformin did not significantly reduce the progression to diabetes (DPP 2015b).

Eligibility for DPP enrollment was based on fasting and 2-h postload plasma glucose concentration, in addition to BMI and other factors. HbA_{1c} was measured but not used in determining eligibility or defining the primary outcome of diabetes. All DPP participants were judged to be at high risk of developing diabetes by virtue of elevated fasting and 2-h glucose concentrations and BMI $\geq$24 kg/m^2. Nevertheless, baseline HbA_{1c} was an additional predictor of diabetes. After excluding the few participants with $HbA_{1c} > 6.5\%$ at study entry, treatment effects were evaluated in a post hoc analysis with an alternate diabetes definition of $HbA_{1c} \geq 6.5\%$. Metformin and lifestyle interventions were both effective, compared with placebo, in preventing this outcome, and their effects did not differ significantly from each other (DPP 2015c).

Extended follow-up in the DPPOS examines diabetes incidence and long-term outcomes of diabetes and its complications (DPP 2009, 2015a), although incidence of cardiovascular events and mortality rates have not yet been reported. After an average of 15 years since randomization, DPP participants were evaluated for a composite microvascular/neuropathy outcome defined by the average prevalence of diabetic retinopathy, nephropathy, and neuropathy (DPP 2015a). Retinopathy was assessed by central grading of retinal photographs, nephropathy by albuminuria or estimate glomerular filtration rate, and neuropathy by light touch sensation. There were no significant treatment effects overall, but significant sex by treatment interactions, such that in women only, the composite prevalence of complications was ~22% lower in the lifestyle intervention group than in the placebo or metformin treatment groups. Those who had not developed diabetes had a 28% lower prevalence of complications than those who had developed diabetes.

Additional evidence for long-term benefit comes from the 10-year cost-effective analysis of the DPP interventions. Costs of delivering the interventions and costs of medical care outside of the study were estimated from participant reports of hospitalizations, outpatient visits, and drug costs. The lifestyle intervention was estimated to be cost-effective (costing $10,037 per quality adjusted life year gained over the placebo group), and the metformin intervention was estimated to save costs (DPP 2012). Such an analysis may reflect aspects of health that are not captured by the study's assessments of diabetes and its complications.

Lifestyle Intervention in Japanese Men with IGT (2005)

A lifestyle intervention randomized clinical trial was conducted Japanese men with IGT who were recruited at health screening examinations. The mean BMI was 24 kg/m^2, lower than in European and US trials. They were randomly assigned in an approximately 4:1 ratio to a standard intervention group ($n = 356$) or to an intensive weight loss group ($n = 102$) and followed for 4 years. Diabetes incidence was defined by at least two consecutive FPG concentrations of at least 140 mg/dl (7.8 mmol/l), i.e., not by an OGTT as was done in most other diabetes prevention trials. Diabetes incidence was reduced by 67% by the weight loss intervention (Kosaka et al. 2005). Although these results are consistent with those of other lifestyle intervention trials, this study is difficult to compare with the others because of different inclusion criteria and outcome definition.

The Indian Diabetes Prevention Program (IDDP, 2006)

The IDPP extended the findings of US DPP by (1) enrolling 531 Asian Indians who were younger and had lower BMI, on average, then volunteers in the DPP, and (2) testing a lifestyle intervention and metformin as in the DPP, but including a combined lifestyle and metformin intervention group (Ramachandran et al. 2006). At study entry, participants (420 men and 111 women) had mean age of 46 years and mean BMI was 26 kg/m^2. The metformin dose (250–500 mg twice per day) was substantially lower than the dose of 850 mg twice per day used in the DPP. Study volunteers were followed an average of 30 months, during which time cumulative incidence rates of diabetes were 55.0% (control group), 39.3% (lifestyle

modification group), 40.5% (metformin group), and 39.5% (lifestyle modification plus metformin group). The relative risk reductions were 28.5% (95% CI 20.5–37.3, $p = 0.018$) in the lifestyle modification group, 26.4% (95% CI 19.1–35.1, $p = 0.029$) in the metformin group, and 28.2% (95% CI 20.3–37.0, $p = 0.022$) in the lifestyle modification plus metformin group, compared with the control group. Thus, both the lifestyle modification and metformin interventions reduced diabetes incidence, but their effects were not additive. The risk reductions were lower than in the DPP, perhaps because the interventions were less intense.

Lifestyle Intervention in Japanese Men with Impaired Fasting Glucose (2011)

A Japanese randomized clinical trial enrolled 641 overweight Japanese participants (72% were men) in a lifestyle intervention trial (Saito et al. 2011). This was the only randomized clinical trial discussed in this chapter in which IGT was not an eligibility criterion. Eligibility was based on elevated FPG (100–125 mg/dl or 5.5–6.9 mmol/l, defined as IFG), similar to the FPG eligibility criteria of the DPP, but IGT was not required. OGTTs were performed to exclude diabetes at entry and to define the diabetes outcome. The median age was 49 years and the mean BMI was 27 kg/m^2. Subjects were randomized to lifestyle intervention ($n = 311$) or a control group ($n = 330$). The intensive lifestyle intervention reduced diabetes incidence by 44% compared with standard care (i.e., hazard ratio = 0.56, 95% CI = 0.36–0.87).

The hazard rate reduction was greater among subgroups at higher baseline risk as determined either by IGT, FPG $\geq$ 110 mg/dl (6.1 mmol/l), or $HbA_{1c} \geq 5.6\%$ by the Japan Diabetes Society method (approximately 6.0% by the National Glycohemoglobin Standardization Program, NGSP, method). These high-risk subgroups contained fewer than half the participants but the majority of the outcome events (baseline NGSP-equivalent HbA_{1c} was $\geq$6.0% in 29% of the participants who experienced 57% of the outcomes). In those with NGSP-equivalent $HbA_{1c} \geq 6.0\%$, the hazard rate was reduced by 76%, the greatest relative risk reduction of any subgroup presented. There was no risk reduction among the subjects with isolated IFG (i.e., IFG with normal 2-h glucose and HbA_{1c}), although the effect estimate was very imprecise in this lower-risk group that experienced only 22 outcome events. Therefore, in addition to IFG, other glycemic measures such as elevated HbA_{1c} or IGT were needed to identify persons at high enough risk to show a treatment effect. These results are consistent with suggestions that HbA_{1c} could be used to identify persons for prevention interventions (International Expert Committee 2009) or to further stratify risk among persons selected by other criteria (DPP 2015c). They also confirm that intervention effects are hard to establish or nonexistent in persons without multiple risk factors.

Pharmacologic Interventions

Two of the lifestyle intervention trials described above – the Diabetes Prevention Program and the Indian Diabetes Prevention Program – included metformin

treatment arms. The following clinical trials evaluated only drugs for diabetes prevention. Although many included lifestyle intervention advice for all study participants, lifestyle intervention was not a study variable and was not evaluated in these trials.

Early UK and Swedish Prevention Studies Using Drugs (1979–1982)

The modern history of T2DM prevention began with three randomized clinical trials of drug therapy from the 1960s to 1980s. They began before the current definitions were established for IFG, IGT, and diabetes, so these terms used to describe these trials have slightly different definitions that those used today. These trials examined drugs then in common use to treat T2DM.

In the Whitehall study, 204 men with IGT were randomly assigned either the biguanide phenformin or placebo (Jarrett et al. 1979). The study definition of IGT was complicated, making it difficult to compare with other studies. It required a screening blood glucose 6.1–11.0 mmol/l followed by a 50 g OGTT performed in the afternoon with peak blood glucose >10 mmol/l and at least one of the following: 2-h blood glucose 6.7–11.0 mmol/l, two values >10.0 mmol/l, or mean 2-h glucose from the screening test, and the OGTT >6.7 mmol/l. 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% confidence interval, CI = 0.4–1.8).

The Bedford study randomly assigned 241 men and women with IGT to the sulfonylurea tolbutamide or placebo and to two dietary groups in a 2 by 2 factorial design (Keen et al. 1974, 1982). IGT was defined by a 50 g OGTT with the 2-h plasma postload capillary glucose of 6.7–11.1 mmol/l. The study drugs were tolbutamide 0.5 g twice daily or matching placebo. One diet group was taught to restrict carbohydrate intake to 120 g/day. The other group received only brief advice to limit table sugar. During 10 years, 15% of subjects worsened to diabetes, but there were no effects of either the drug or diet interventions.

The third major study of this era was conducted in 147 men with IGT in Malmöhus County, Sweden (Sartor et al. 1980; Knowler et al. 1997). Diabetes and IGT were classified by an OGTT with a load of 30 g glucose per square meter of body surface area among men initially identified by having glycosuria. Diabetes was diagnosed if the 1-h postload capillary blood glucose was 11.1 mmol/l or more, the 2-h glucose was 8.6 mmol/l or more, and the 3-h glucose was 5.8 mmol/l or more. If these criteria were not met, but at least one of the following values was found – 1-h glucose 8.9 mmol/l or more, 2-h glucose 6.7 mmol/l or more, or 3-h glucose 4.7 mmol/l – subjects met the glycemic eligibility criteria, which here for simplicity are termed "IGT." All study participants were instructed to limit dietary carbohydrate and lipid and, if overweight, total energy intake. They were also randomly assigned to tolbutamide (0.5 mg three times per day), matching placebo, or neither drug nor placebo. The original report from the trial was interpreted as showing prevention by tolbutamide, based on an analysis of a very small number, 23, of those thought to have continued taking tolbutamide throughout, among whom none developed

diabetes. This conclusion was not based on the currently adopted "intention-to-treat" principle, i.e., analysis by assigned treatment group regardless of adherence. When analyzed later by intention-to-treat, 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) (Knowler et al. 1997).

Long-term mortality rates were ascertained after the end of the trial, which was possible because of the availability of national vital statistics in Sweden. 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) (Knowler et al. 1997). While these effects were not statistically significant in this small randomized clinical trial, they were among the first to suggest that drug treatment of IGT might have health benefits beyond reducing hyperglycemia progression to diabetes.

None of these three early studies established whether diabetes could be prevented; their findings were inconclusive, largely owing to the small sample sizes. Whether pharmacologic prevention of T2DM was possible remained unknown until the 2000s.

Randomized Clinical Trials with Orlistat (2000; 2004)

Diabetes prevention has been tested with weight loss drugs, because overweight and obesity are major risk factors for T2DM. Drugs that affect weight, but do not have a known direct effect on plasma glucose concentration, were hypothesized to prevent diabetes development. Several randomized clinical trials have been performed in obese adults using the weight-loss drug orlistat, an intestinal lipase inhibitor. Three such trials were discussed in a pooled analysis (Heymsfield et al. 2000). Compared with placebo, orlistat was reported to reduce 2-year cumulative diabetes incidence by 61% (7.6% in the placebo group vs. 3.6% in the orlistat group) among those with IGT at randomization. Owing to its gastrointestinal side effects, however, only 69% of the subjects completed the 2-year study. The high drop-out rate, which could be associated with drug effects or side effects, makes it difficult to interpret these results.

A subsequent 4-year randomized clinical trial of orlistat reported a 37% reduction in diabetes incidence (Torgerson et al. 2004). As with earlier orlistat studies, a low percentage of participants completed the trial (52% of the orlistat group and 34% of the placebo group), making it difficult to estimate the effects of the drug. Although orlistat may be beneficial in some persons, the high discontinuation rate owing to side effects limits its widespread use for diabetes prevention.

Troglitazone in Prevention of Diabetes (TRIPOD) Study of Women with Previous Gestational Diabetes (2002)

Troglitazone was compared with placebo in 266 nondiabetic Hispanic women with previous gestational diabetes, about 70% of whom had IGT at entry into the randomized clinical trial called TRIPOD. Troglitazone reduced the development of diabetes by 55% over 2.5 years (Buchanan et al. 2002). As in the DPP, the drug was discontinued before planned study-end because of the potential for liver toxicity. The

preventive effect of troglitazone was attributed to improved insulin sensitivity, with resulting lower demand for insulin secretion, thus protecting the beta cells.

Acarbose in the Study to Prevent Noninsulin-Dependent Diabetes Mellitus (STOP-NIDDM)) (2002)

The α-glucosidase inhibitor acarbose was investigated as a diabetes prevention drug because of its lowering postprandial hyperglycemia, which is characteristic of IGT. The STOP-NIDDM randomized clinical trial tested acarbose in preventing diabetes in high risk adults. (Chiasson et al. 2002). This randomized clinical trial included 1429 subjects with IGT and IFG (FPG $\geq$ 5.6 mmol/l or 100 mg/dl and $<$7.0 mmol/l or 126 mg/dl) who were randomized to acarbose gradually titrated to 100 mg 3 times a day or placebo (Chiasson et al. 2002). Incident diabetes was defined by plasma glucose $\geq$11.1 mmol/l (200 mg/dl) at 2 h in a 75 g OGTT. Over a 3.3-year follow-up period, acarbose led to a 25% reduction in the incidence of diabetes. Weight loss contributed to the decreased risk of diabetes, but the acarbose effect persisted after adjustment for age, sex and BMI. Acarbose was associated with reversion of IGT to normal glucose tolerance [hazard ratio = 1.42 (95% CI: 1.24–1.62). Approximately one-quarter of the cohort (including 31% of the acarbose group) did not complete the study, the drop-out rate in acarbose-treated patients attributed to gastrointestinal side effects (flatulence, diarrhea, and abdominal cramps) that may limit its applicability for diabetes prevention in general practice. The STOP-NIDDM trial also studied treatment effects beyond the development of diabetes.

The acarbose arm had a 49% reduction in cardiovascular events [15 vs. 32 subjects; hazard ratio = 0.51 95% CI: 0.01–0.95); p = 0.03] (Chiasson et al. 2003). This difference from the placebo group was statistically significant, but based on few events. Acarbose also slowed the progression of carotid intimal medial thickness, a measure of subclinical atherosclerosis measured in a subset of the cohort (n = 132) (Hanefeld et al. 2004). Beneficial effects on several CVD risk factors (waist circumference, blood pressure and plasma triglycerides) were also reported (Chiasson et al. 2003). Altogether, these observations suggest that acarbose treatment may reduce the risk of cardiovascular events.

Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM, 2006)

Based on a suggestion that angiotensin-converting-enzyme inhibition might reduce diabetes risk (Yusuf et al. 2001), ramipril, a drug in this class, and the thiazolidinedione rosiglitazone were studied for diabetes prevention in DREAM (DREAM 2006a, b). Rosiglitazone is in the same thiazolidinedione class as troglitazone which, in previous randomized clinical trials, led to substantial reductions in diabetes incidence rates, before the drug was withdrawn from the market because of toxicity (as described above). DREAM tested ramipril and rosiglitazone in a 2 by 2 factorial design in 5269 participants with IFG, IGT, or both. IFG was defined by FPG 110 to $<$126 mg/dl and IGT by 2-h plasma glucose 140 to $<$200 mg/dl in an OGTT. For ramipril, the hazard ratio for developing diabetes was 0.91 (95% CI = 0.80–1.03). The incidence of diabetes was reduced by 62% by rosiglitazone (hazard ratio = 0.38,

95% CI = 0.33–0.44), and 50% of rosiglitazone-treated patients reverted to normoglycemia, compared with 30% of placebo-treated patients. There was no synergistic effect of the drugs in participants who were randomly allocated to both ramipril and rosiglitazone, i.e., the effect of each drug was the same in the presence or absence of the other drug.

Side effects, including weight gain (rosiglitazone-treated patients gained 2.2 kg more than placebo-treated patients) and edema, were observed with rosiglitazone. The frequency of congestive heart failure was also increased in the rosiglitazone group (hazard ratio = 7.03, 95% CI = 1.60–30.9), based on few cases (0.5% in the rosiglitazone group and 0.1% in the rosiglitazone-placebo group) in this generally healthy population (DREAM 2006b).

The Voglibose Randomized Clinical Trial (2009)

Voglibose, another α-glucosidase inhibitor, was studied in a randomized clinical trial in Japanese adults with IGT and at least one other diabetes risk factor (Kawamori et al. 2009). The diabetes outcome was defined by $HbA_{1c} \geq 6.5\%$ and, on two occasions, either FPG $\geq$7.0 mmol/l, 2-h plasma glucose $\geq$11.1 mmol/l, or random plasma glucose $\geq$11.1 mmol/l. The study was terminated before its planned end because of efficacy. After approximately 1-year of follow-up, the diabetes hazard rate ratio (voglibose vs. placebo) was 0.60 (95% CI = 0.43–0.82). Participant acceptance was greater than with acarbose in the STOP-NIDDM trial; 86% of the voglibose group and 83% of the placebo group completed the trial. Voglibose appeared to be moderately well tolerated and reduced the incidence of diabetes, at least for the short term. Because follow-up was terminated after about 1 year, long-term acceptance and efficacy of this medicine for diabetes prevention remain uncertain.

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcome Research (NAVIGATOR) Trial (2010)

This randomized clinical trial employed a 2 by 2 factorial design using the short-acting insulin secretagogue nateglinide (NAVIGATOR 2010a) and the angiotensin receptor blocker valsartan (NAVIGATOR 2010b) in 9306 participants with IGT, FPG from 95 to <110 mg/dl, and CVD or CVD risk factors. The mean age was 64 years and mean BMI was 30.5 kg/m^2. Nateglinide (60 mg three times daily) did not reduce the cumulative incidence of diabetes during the 5-year follow-up compared with placebo (hazard ratio = 1.07, 95% CI = 1.00–1.15) and was associated with increased frequency of hypoglycemic events (19.6% with nateglinide vs. 11.3% with placebo, $p < 0.001$) and slightly greater weight (+ 0.35 kg, $p = 0.001$) over the course of the study. Valsartan (160 mg once daily) was associated with a small reduction in diabetes incidence compared with placebo (hazard ratio = 0.86, 95% CI = 0.80–0.92). There was no significant interaction between the effects of the two drugs. About 80% of the participants completed the trial.

The NAVIGATOR trial had extended follow-up to evaluate treatment effects on CVD. Neither drug, alone or in combination with the other, affected a composite primary outcome of CVD death, nonfatal MI, or stroke, revascularization or hospitalization for angina or congestive heart failure, nor on a "core" composite that

excluded revascularization and angina (NAVIGATOR 2010a, b), despite lower blood pressure with valsartan than with placebo. The lack of prevention of CVD events does not support the hypothesis of a CVD benefit from reducing post-challenge (or postprandial) hyperglycemia with an insulin secretagogue.

The Canadian Normoglycemia Outcomes Evaluation (CANOE) Trial of the Combination of Rosiglitazone and Metformin (2010)

The CANOE randomized clinical trial tested the efficacy of a combination of submaximal doses of two drugs, metformin (500 mg twice daily) and rosiglitazone (2 mg twice daily) vs. placebo on diabetes incidence in 207 persons with IGT (Zinman et al. 2010). In the placebo group, mean age was 55 years and mean BMI was 32 kg/m^2. In the rosiglitazone plus metformin group, mean age was 50 years and mean BMI was 31 kg/m^2. After a median follow-up of 3.9 years, the 2-drug treatment resulted in a relative risk reduction for diabetes of 66% (95% CI = 41–80) and 80% regressed to normoglycemia, compared with 52% in the placebo group ($p = 0.0002$). The low-dose combination therapy was reportedly well tolerated, without excessive weight gain. The efficacy and tolerability of this low dose combination, compared with larger doses of the individual agents, suggest that low dose combinations may lead to similar benefit with greater tolerability.

The Actos Now for the Prevention of Diabetes (ACT NOW) Trial of Pioglitazone (2011)

Another thiazolidinedione drug, pioglitazone, was tested in the ACT NOW randomized clinical trial for the prevention of diabetes (DeFronzo et al. 2011). Six-hundred-two adults with IGT were enrolled. Mean age was 52 years, and mean BMI was 34 kg/m^2. Participants were randomized to treatment with pioglitazone 30 mg per day or placebo with median follow-up of 2.4 years. The study was completed by only 70% of the pioglitazone group and 76% of the placebo group. Pioglitazone led to a 72% reduction in diabetes incidence compared with placebo (hazard rate ratio = 0.28, 95% CI = 0.16–0.49). This study replicated the large effects of the thiazolidinedione drugs troglitazone and rosiglitazone on reducing diabetes incidence. Pioglitazone was associated with weight gain and edema, as are other drugs of this class.

The SEQUEL Secondary Analysis of a Study of Phentermine-Topiramate for Weight Loss (2012)

As with the previous randomized clinical trials of orlistat, a weight loss drug (see above), it was hypothesized that another weight loss drug would prevent diabetes. CONQUER was a randomized clinical trial of combinations of phentermine and topiramate compared with placebo for weight loss (Garvey et al. 2012). SEQUEL was secondary analysis of a subset of centers and participants in CONQUER with additional follow-up for diabetes incidence. Diabetes was lower in the active treatment groups compared with placebo, and the diabetes risk reduction was associated with the amount of weight loss. SEQUEL was a secondary analysis of a subset of participants in the CONQUER weight loss study, but it is not clear how this subset represents all those randomized in the original randomized clinical trial. Loss to

follow-up was not well described. A strategy of carrying forward the last observation was used to impute a substantial fraction of values, but there was not a clear description of the frequency of missing data or the characteristics of participants with missing outcome data. Loss to follow-up in such studies is not likely to be random but rather due to frustration with lack of weight loss or drug side effects.

A Randomized Clinical Trial of Liraglutide in Weight Management (2017)

Liraglutide, a glucagon-like peptide-1 analogue, was evaluated in a 56-week randomized clinical trial of 3731 nondiabetic adults with BMI $\geq$30 kg/m^2 or $\geq$27 kg/m^2 if they also had dyslipidemia or hypertension (Pi-Sunyer et al. 2015). The study was extended for 2 additional years in the subset of participants with prediabetes by American Diabetes Association criteria (American Diabetes Association 2010). During the 3 years of follow-up since randomization, the diabetes incidence rate was reduced by 79% (hazard ratio = 0.21, 95% confidence interval = 0.13–0.34) in this subgroup, although 50% of the participants were lost to follow-up (Le Roux et al. 2017). In a sensitivity analysis making various assumptions to impute missing data, the diabetes incidence rate was estimated to be reduced by 66% (hazard ratio = 0.34, 95% confidence interval = 0.22–0.53).

Role of Genetics in Diabetes Prevention

The complex field of genetic susceptibility to T2DM is described in another chapter. Most of the discoveries of diabetes susceptibility genes have come from large case-control studies, but several prevention randomized clinical trials have evaluated gene variants as predictors of outcomes within the trials and of potential modifiers of treatment effect. Some results of genetics studies within the DPP are described elsewhere (Florez et al. 2006; Hivert et al. 2011; Jablonski et al. 2010; Hivert et al. 2016). A general conclusion is that preventive interventions that are effective in general are also effective regardless of known genetic susceptibility factors for diabetes. Some exceptions have been described, and more are likely to be discovered in the future, in that gene variants associated with drug actions may modify the effects of those drugs, including on diabetes prevention. For example, variants in the *SLC47A1* gene, that is involved in metformin metabolism, modified the metformin effect in the DPP (Jablonski et al. 2010).

In summary, in prevention of type 2 diabetes, the beneficial effects of lifestyle interventions and of some medicines overcome genetic risk.

Discussion

Population-wide approaches to preventing T2DM (e.g., changes in food availability, transportation, and occupational and leisure physical activity) have the potential of lowering diabetes risk in the largest numbers of people. This conclusion is

speculative, however, because such interventions are difficult to implement and evaluate, generally requiring methods other than the randomized clinical trials that are considered the best methods for evaluating individual-based interventions. By contrast, individual-based interventions in high-risk persons have been well studied with varying degrees of success. Most have shown risk reductions with lifestyle interventions and some drugs, such as metformin, α-glucosidase inhibitors, and thiazolidinediones. These interventions can prevent or delay T2DM over the short term, i.e., several years, but there is less evidence for longer term prevention of diabetes, its complications, or mortality. That is, evidence of benefits of preventive interventions beyond glycemia is limited.

How should high-risk persons be identified for prevention interventions? (Knowler 2011). The high-risk approach is based on enrollment of persons with strong risk factors and the assumption that such risk factors can be affected by the intervention. Obesity, sedentary behavior, insulin resistance, and elevated glycemia (but below diagnostic levels) are easily identifiable with available tests and are potentially modifiable with diet, exercise, drugs, or combinations of each. Other risk factors such as genetic susceptibility or history of gestational diabetes in currently nondiabetic women are not modifiable, but may help in selecting high-risk person with other modifiable risk factors. Risk factors such as drug treatment for other conditions (e.g., statins for dyslipidemia) could be removed by discontinuing such treatment, but the balance between potential risks and benefits of such action is usually not obvious. Most of the published prevention randomized clinical trials have selected persons with IGT, requiring performance of an OGTT. Some trials also required overweight or obesity or elevated FPG for eligibility. All were performed only in adults, so there remains a lack of data on children and adolescents, who are also at risk of T2DM, especially in some US minority groups.

The OGTT required for detection of IGT is inconvenient, time-consuming, and often infeasible in large-scale screening programs. The American Diabetes Association defines “pre-diabetes” by elevated levels (but not meeting diabetes diagnostic criteria) of either FPG, 2-hour post-load glucose (i.e., IGT), or HbA1c, i.e., IGT is not required (American Diabetes Association 2010). There is limited evidence that interventions shown effective in persons with IGT will also benefit persons with other high-risk characteristics (including “prediabetes”) but without IGT. The most informative randomized clinical trials in this regard were the lifestyle intervention in Japanese men with impaired fasting glucose and DREAM, described above. In the Japanese lifestyle trial, prevention was very effective in men without IGT but with elevated FPG and HbA1c (Saito et al. 2011). In DREAM, rosiglitazone was nearly equally effective in persons with isolated IFG (i.e., without IGT), isolated IGT, and both IFG and IGT in combination (DREAM 2006b). Replication of these finding is needed before concluding whether IGT is necessary as an eligibility criterion for preventive interventions for T2DM. Elevated HbA1c may be as good at predicting T2DM and subsequent complications as is IGT (McCance et al. 1994; Vijayakumar et al. 2017; Warren et al. 2017), and it has been suggested as a suitable measure for identifying persons for preventive intervention (International Expert Committee

2009). Effectiveness of interventions for preventing T2DM in high-risk persons identified only by HbA1c, however, has not been evaluated to my knowledge.

In summary, lifestyle interventions and several different drugs can prevent T2DM in high-risk persons in the short term, i.e., for at least several years. There is less evidence that these interventions can prevent diabetes in the long term or reduce risk of diabetes complications, including mortality. Applying results of prevention randomized clinical trials to large numbers of people or on a population level remains a major challenge, but one that should be undertaken.

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