Perspectives in Diabetes
(How) Can We Prevent Type 2 Diabetes?

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In the past 6 years, several randomized controlled trials have been conducted to test the impact of behavioral and pharmacological interventions on rates of development of type 2 diabetes in high-risk groups (1–7). The studies have demonstrated that it is possible to reduce the number of people who develop diabetes by 25–62% over 3- to 6-year time frames. As a result, discussions on mitigating the growing public health problem of type 2 diabetes have expanded from a relatively narrow focus on disease treatment to a broader focus on disease prevention. Ultimately, the broader focus is relevant to prevention and early treatment, both aimed at stabilization or reversal of an otherwise progressive disease process. Optimal strategies for disease modification at the stages of pre-diabetes and early diabetes remain to be defined. However, existing information is sufficient to begin to sort out the relative effectiveness of interventions and to make some recommendations for clinical care. In this article, I discuss both the concept of and evidence for diabetes prevention in the context of the biology of type 2 diabetes. I also suggest an approach for clinical care that is based on a combination of knowledge about disease biology and the results of clinical trials.

HOW DO PEOPLE DEVELOP TYPE 2 DIABETES?

Hyperglycemia results from an insulin supply that is insufficient to meet the body's needs. Diabetes is hyperglycemia that exceeds the threshold where the risk of diabetic retinopathy is currently thought to begin. In type 2 diabetes, insufficient insulin supply occurs in a setting of increased insulin demands—chronic insulin resistance. Longitudinal studies of insulin secretion and insulin action in Pima Indians (8), Hispanic women with prior gestational diabetes (9), and Hispanic, white, and African-American participants in the Insulin Resistance

Atherosclerosis Study (10) reveal that abnormalities in insulin secretion and action are present long before type 2 diabetes develops. Moreover, both insulin resistance and failing insulin secretion are progressive over the course of years. Thus, type 2 diabetes develops from chronic and progressive loss of insulin secretion on a background of chronic and often progressive insulin resistance. These processes antedate the clinical diagnosis of diabetes, they cause the disease, and they continue to worsen after the diagnosis is made.

Clinical progression from normal glucose tolerance to diabetes takes years and logically involves an intermediate stage of impaired glucose levels (impaired glucose tolerance and/or impaired fasting glucose). Progression can occur in a few years (8,10) but may take much longer (11,12). An understanding of the relationship between clinical progression (based on circulating glucose levels) and biological progression (based largely on changes in the relationship between insulin supply and demand) is crucial to the understanding of diabetes prevention in the clinical and biological contexts. Our longitudinal studies in Hispanic women with previous gestational diabetes revealed an interesting pattern (9). Fasting glucose changed very little as β-cell compensation for insulin resistance, assessed as the disposition index based on acute insulin responses to intravenous glucose and minimal model measures of insulin resistance, fell from ~50% of normal to ~10–20% of normal. Further reductions in β-cell compensation were associated with more dramatic increases in fasting glucose. The pattern of change was similar for 2-h glucose levels from oral glucose tolerance tests, although there was a somewhat stronger "signal" of falling β-cell compensation reflected in rising 2-h glucose levels. These findings are consistent with the cross-sectional results of Ferrannini et al. (13). Figure 7 of that paper reveals that an ~70–75% reduction in β-cell sensitivity to glucose was associated with a relatively small increase in 2-h glucose levels, from ~5.6 to ~8.6 mmol/l (i.e., change from normal to impaired glucose tolerance). Loss of an additional 20–25% of β-cell sensitivity was associated with a much larger increase in 2-h glucose, to ~23 mmol/l. These two studies reveal that the signal provided by circulating glucose levels for the underlying deterioration in β-cell function starts out relatively weak (i.e., glucose changes little as β-cell function begins to fall). The signal becomes stronger (i.e., clinically detectable glucose changes begin to reflect the underlying loss of β-cell function) only when β-cell function is already quite bad. As a result, clinically detectable changes in glucose reflect falling β-cell function only relatively late in the course of progression to diabetes but perhaps early enough to be useful in clinical assessment of an individual's response to interventions designed to prevent diabetes. I will return to

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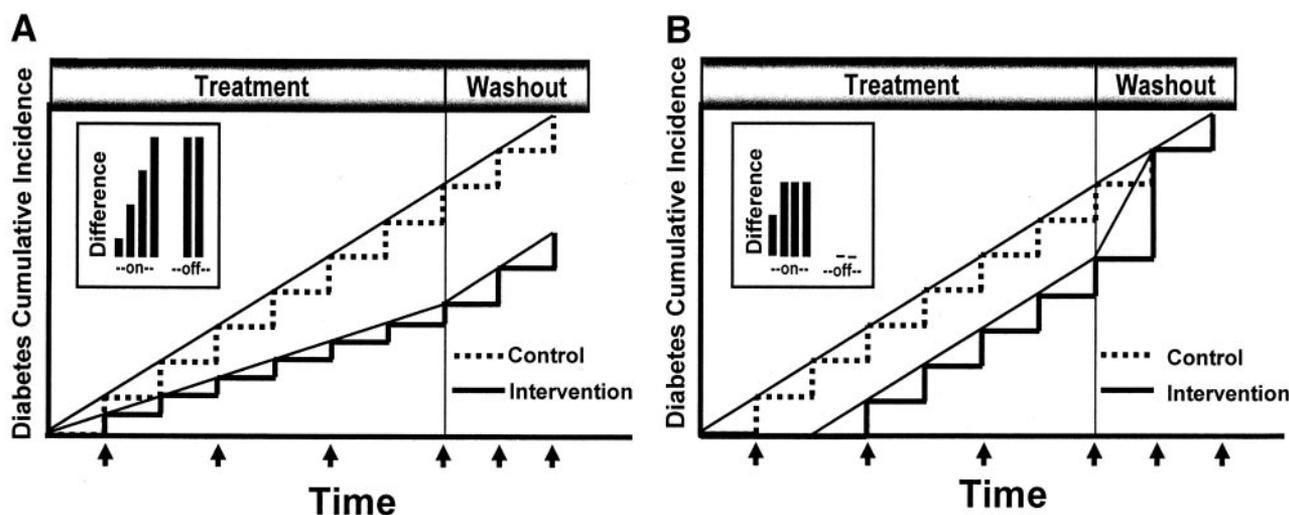
FIG. 1. Schematic representation of two interventions that would lead to a reduction in diabetes incidence rates in a clinical trial. Stepped lines represent cumulative incidence rates based on intermittent testing for diabetes. Straight lines are slopes of the cumulative incidence curves during and after treatment. Inserts depict the absolute risk reductions (fraction of cases in control − fraction of cases in intervention group) at intervals indicated by arrows along the *x*-axis. *A*: Intervention that slows rates of deterioration during treatment. Slopes are different during treatment and, following withdrawal of treatment, remain parallel. The difference in cumulative incidence rates achieved during treatment persists. *B*: Intervention that lowers glucose levels during treatment without altering their rate of deterioration. Slopes are parallel during treatment and, following withdrawal of treatment, cumulative incidence curves converge.

this point when I discuss potential clinical strategies for managing high-risk patients.

WHAT IS DIABETES PREVENTION?

In the context of the biology of type 2 diabetes—rising glucose levels that are driven by falling β-cell compensation for bad and often worsening insulin resistance—diabetes prevention requires stabilization (or even improvement) in β-cell function and glucose levels. If an at-risk person's β-cell function stops falling and his or her glucose levels stop rising, then that person does not develop diabetes. In the context of clinical trials, development of diabetes is treated as a yes-no variable, defined by the side of the glucose diagnostic threshold on which each subject ends up. In this context, there are two fundamental ways in which cumulative incidence rates of diabetes can be reduced during a period of intervention that is short compared with the time frame of diabetes development. One way is through real modification of the biology of type 2 diabetes. If an intervention slows the rate of falling β-cell compensation and rising glucose, fewer individuals will "cross the line" to diabetes in the course of a 3- to 6-year trial. Such slowing will delay the onset of diabetes. If the slowing is marked, then the delay can be very long. If the intervention halts deterioration in some subjects, then those people stop progressing to diabetes and real prevention can occur. The other fundamental method of reducing new cases of diabetes during a 3- to 6-year trial is simply to lower the glucose levels in the intervention group at the beginning of therapy. Even in the absence of an impact on the rate of deterioration, fewer people will cross the line to diabetes during the trial. The underlying deterioration is masked because the primary outcome is glucose of a certain level (above the diabetes threshold) rather than a change in glucose. Fewer people cross the diabetes threshold because they are initially moved farther from it, not because they deteriorate more slowly.

These two scenarios in their pure forms will look different in clinical trials, where the primary outcome is reported as diabetes cumulative incidence rates or diabe-

tes-free survival rates. Examples of the different expected cumulative incidence patterns during and after treatment appear in Fig. 1. An intervention that slows metabolic deterioration (Fig. 1A) will yield lower annual diabetes incidence rates on an ongoing basis. Thus, the slopes of the diabetes cumulative incidence curves will differ throughout treatment. Each year, there will be a larger and larger difference between intervention and control groups in the fraction of people with diabetes (Fig. 1A, insert). When treatment is stopped, the underlying biology of diabetes will likely resume in the intervention group. Subjects will start to develop new cases of diabetes at the same rate as the nonintervention group, so the cumulative incidence curves will become parallel. However, the fraction of people with diabetes in the intervention group will remain lower than the fraction in the control group, reflecting the slowing or arrest in deterioration that was achieved during treatment (slowing or stopping of the diabetes "clock").

Contrast this pattern with the pattern expected from an intervention that simply lowers glucose levels without affecting the rate of deterioration (Fig. 1B). Such an intervention will result in parallel cumulative incidence curves after a delay in the development of the first case of diabetes in the intervention group. There will be a relatively constant difference in the fraction of people with diabetes (Fig. 1B, insert). When the intervention is stopped, glucose levels will rise quickly in the intervention group to reflect what has happened to β-cell function during treatment. Cumulative incidence curves will move toward each other and, if the washout period is long enough, will actually converge.

Obviously, either of these scenarios would result in lower glucose levels during the intervention, an effect that could have important health benefits. However, therapies that do not alter the biology of progression cannot prevent diabetes, they can only delay it. Moreover, the duration of delay is limited by the degree to which glucose levels can be moved away from the diabetes threshold at the start of therapy. Small initial glucose reductions result in short-
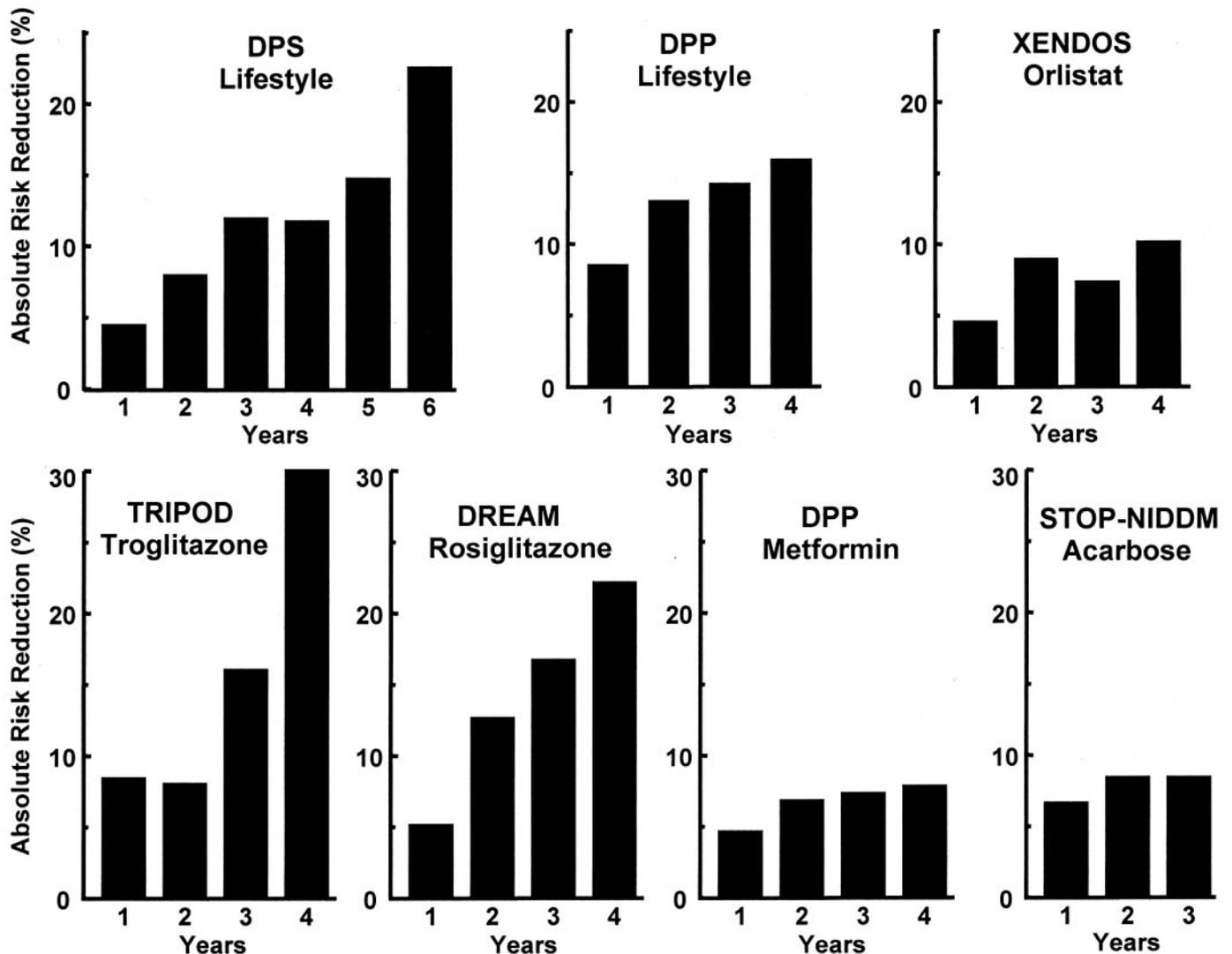
FIG. 2. Annual absolute risk reductions in intervention groups compared with control groups during treatment in six studies using six different interventions for diabetes prevention in high-risk individuals. Interventions appear below study acronyms. Plots were made using data from the figures in the publications describing the primary trial results (1–6).

term diabetes delay. Larger reductions result in hypoglycemia. No such limitations are operative for therapies that modify diabetes biology. If they are effective enough, they can stop progression toward diabetes and truly prevent the disease. Even short of such a dramatic effect, they can greatly slow progression to diabetes, resulting in long-term delay in the development of diabetes. This distinction would be simply semantic if it were impossible to fully arrest the underlying disease biology. However, as detailed later in this article, we proved in the Troglitazone in Prevention of Diabetes (TRIPOD) Study that such arrest is possible. Thus, diabetes prevention is possible, and our focus needs to be on developing and implementing true disease-modifying interventions.

WHAT DO CLINICAL TRIALS REVEAL?

Recently published diabetes prevention trials have identified three potentially useful general approaches to masking, delaying, or preventing type 2 diabetes: *1*) intensive lifestyle modification or orlistat, which reduces body weight and, presumably, body fat; *2*) thiazolidinedione drugs, which reduce the impact of excess body fat on

insulin action and may have some direct β-cell protective effects (14); and *3*) metformin or acarbose, which reduces rates of glucose appearance in the circulation (from liver and gastrointestinal tract, respectively). These interventions have all reduced the number of new cases of diabetes during 3–6 years of treatment, but differences in the patterns of diabetes development suggest that some of the interventions really modify the underlying disease processes that lead to diabetes, while others mostly mask those processes. Figure 2 summarizes the differences, using plots of the difference between control and intervention groups, in the fraction of people with diabetes annually during six of the trials.

The Finnish Diabetes Prevention Study (DPS) demonstrated in Finns and the U.S. Diabetes Prevention Program (DPP) confirmed in several ethnic groups that intensive lifestyle interventions designed to reduce caloric intake and increase physical activity reduce the risk of diabetes in people with impaired glucose tolerance (1,4). Each study reported a 58% relative risk reduction in the lifestyle intervention group. In both studies, there was initial weight loss, with subsequent weight gain. Weight in both

studies remained lower in the intervention group than in the control subjects. Both studies yielded increasing differences in the fraction of people with diabetes during the intervention (Fig. 2), consistent with a slowing of metabolic deterioration. The DPS recently reported results from poststudy observation (15). Subjects in the former intervention group maintained slightly lower weights and somewhat greater levels of physical activity compared with subjects in the control group. The former group experienced small but statistically significant continued protection from diabetes as well. The Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study (5) reported that orlistat added to a lifestyle intervention increased initial weight loss and provided a 37% relative risk reduction for diabetes compared with lifestyle alone in obese people with normal or impaired glucose levels. Most of the risk reduction was in the subgroup of ~20% of the cohort that entered the trial with impaired glucose tolerance. Differences in the cumulative incidence of diabetes at annual evaluations did not provide a clear pattern of increase (Fig. 2).

Thiazolidinediones have produced relative risk reductions in the range of 55–62% (as high as 75% if one considers the brief troglitazone arm of the DPP [16]). The TRIPOD Study demonstrated a 55% relative risk reduction in Hispanic women with prior gestational diabetes (2). Diabetes cumulative incidence rates diverged throughout treatment and did not converge at all during 8 months of observation after treatment was stopped. Women who did not develop diabetes during treatment had stable glucose levels and stable β-cell function over a 4.5-year period, including the 8-month washout. β-Cell protection persisted during an additional 3.5 years of treatment in the Pioglitazone in Prevention of Diabetes (PIPOD) Study (17). These two studies provide proof that falling β-cell function can be arrested for relatively long periods of time, albeit in only a subset of treated subjects, establishing the potential for true diabetes prevention. In both studies, the mechanism for prevention appeared to be a reduction in insulin secretory demands that resulted from amelioration of chronic insulin resistance. The recently completed Diabetes REduction Assessment with rosiglitazone and ramapril Medication (DREAM) Study (6) provided larger scale confirmation of the results of the TRIPOD and PIPOD studies in men and women with either impaired glucose tolerance or impaired fasting glucose. The relative risk reduction for diabetes during 4 years of treatment with rosiglitazone was 62%. The cumulative incidence of diabetes in the intervention and control groups diverged throughout the study (Fig. 2). During a 2- to 4-month washout period, new cases of diabetes occurred at rather high, albeit identical, rates in the two groups so that cumulative incidence rates remained parallel (reported at the International Diabetes Federation meeting in December 2006). Ramipril had no significant impact on the risk of diabetes in the DREAM Study (7). Finally, the U.S. DPP had a troglitazone arm that was terminated after ~11 months of treatment (16). The relative reduction for diabetes during this short time was 75% compared with the placebo group. During ~3 years of follow-up after discontinuation of treatment, new cases of diabetes occurred at the same rate in the control and intervention groups, so that cumulative incidence rates did not converge. Taken together, these four studies provide solid evidence for slowing or arrest of metabolic deterioration by thiazolidinediones. However, as demonstrated clearly in the

TRIPOD Study, protection did not occur to equal degrees in all treated subjects.

Metformin in the DPP (4) and acarbose in the STOP-NIDDM Study (3) yielded 31 and 25% relative risk reductions, respectively, compared with placebo groups in men and women with impaired glucose levels. In both studies, cumulative incidence curves diverged little after the initial year of treatment (Fig. 2), consistent with similar rates of metabolic deterioration in the two treatment groups in each study. During 2–4 weeks posttreatment observation in the DPP, the rate of new cases of diabetes was twice as high in the former metformin group as in the former placebo group (18). Similarly, during 3 months of posttreatment observation in the STOP-NIDDM Study, the rate of new cases of diabetes was 45% higher in the former acarbose drug group (3). Nonetheless, the fraction of people with diabetes at the end of the washout remained lower in the active drug group. These results suggest a significant component of "masking" of deterioration by glucose lowering that was limited to the period of treatment with metformin or acarbose. Some real disease modification may have occurred as well.

What are the take-home messages from these analyses? First, interventions that either reduce body weight and fat or that block the impact of obesity on insulin resistance provide the best evidence for modification of the biological processes that lead to type 2 diabetes. These findings point to some component of obesity and insulin resistance as the driving force behind the progressive β-cell failure that attends the development of hyperglycemia. The findings provide little evidence in support of glucose toxicity as an important cause of β-cell dysfunction before the development of diabetes. Second, based on data from the TRIPOD and PIPOD studies, stabilization of β-cell function and glucose levels for relatively long periods of time is possible. Thus, β-cell failure is not "hardwired" in people at risk for type 2 diabetes. It can be stopped, at least for several years, in some individuals. Third, and perhaps most important, none of the interventions tested to date have been fully and uniformly effective in preventing diabetes. These three messages have significant implications for the development and implementation of clinical approaches to diabetes prevention.

WHAT ARE THE IMPLICATIONS FOR CLINICAL CARE?

Clinical trials reveal what can work, on average, in relatively large cohorts of people. Clinical care is delivered one patient at a time. Thus, clinicians need to know more than the average effect of an intervention in a clinical trial. They need to know whether the intervention works in each of their patients. The six trials described above do not really address this additional need. However, the biology of type 2 diabetes provides a potentially useful clinical approach in monitoring success. That biology is progressive over time, and it is characterized by declining β-cell compensation for insulin resistance. This decline is, in turn, manifested by increasing glucose levels. Fasting glucose levels may not change much as β-cell function declines (9), although increasing fasting glucose is generally a sign of deterioration. Postchallenge glucose levels are more informative about changing β-cell function (9), but they are harder to collect and poorly reproducible. Average glycemia (e.g., A1C) holds promise as a clinically useful marker of disease stability or progression. For example, women who developed diabetes in the TRIPOD

Study had a 35% loss of β-cell compensation for insulin resistance over a 2-year period. This loss of β-cell function was attended by a 0.5% increase in A1C (T.A.B., unpublished observation). In other words, changing A1C, rather than any specific level of A1C, provided an index of changing β-cell compensation for insulin resistance. Clearly, this observation in a relatively small cohort under clinical trial conditions will require confirmation in larger studies and in clinical care settings. If broader testing confirms the utility of A1C monitoring in detecting progression toward or to diabetes, the test may become a standard for evaluation of response to interventions aimed at diabetes prevention and disease modification. If not, development of other clinical approaches for monitoring β-cell compensation should be a priority in the field of diabetes prevention and early treatment.

What interventions should be used? At present no pharmacological agent is approved for diabetes prevention in the U.S. Moreover, results from two studies, the TRIPOD Study (19) and ADOPT (A Diabetes Outcome Progression Trial) (20), indicate that disease modification is possible with pharmacological agents even after diabetes develops. These facts point to lifestyle interventions as the most appropriate initial approach in high-risk individuals (e.g., those with impaired glucose levels or a history thereof, as in gestational diabetes) (21). A recent American Diabetes Association consensus statement (21) also suggested that metformin can be used for diabetes prevention in individuals aged <60 years with BMI ≥35 kg/m^2. That recommendation was primarily based on cost and safety considerations rather than on evidence for real disease modification or long-term reductions in morbidity or mortality. Monitoring success of the initial intervention is not straightforward. For example, the amount of weight an individual has to lose and/or the amount of exercise she/he has to do to stabilize the disease process cannot be determined a priori. The best we can do is to implement the intervention and then monitor for the primary goal of treatment, stability, or improvement of glucose levels or markers thereof. Rising glycemia indicates an inadequate response to the lifestyle intervention. When glycemia reaches the threshold for diabetes, pharmacologic interventions aimed at disease modification can be added. To date, drugs that modify fat-induced insulin resistance (i.e., thiazolidinediones) have provided the strongest evidence for disease modification. Drugs that primarily lower glucose appearance rates (metformin and acarbose) provide less evidence for disease modification. Combination therapies and the effects of most antiobesity drugs and incretin-based treatments remain to be tested.

Three other points deserve consideration for clinical care. First, not all impairments of glucose levels or tolerance are linked to insulin resistance. Thus, particularly in lean individuals, other etiologies (e.g., autoimmunity) should be considered. Second, responses to treatment in the existing clinical trials have varied by some potentially useful clinical characteristics. Intensive lifestyle modification in the DPS had its greatest effect to reduce diabetes risk in people who met program goals. Intensive lifestyle modification in the DPP was most effective in people with the lowest 2-h glucose levels at baseline. Metformin in the DPP was somewhat more effective in younger people, people with relatively high BMI, and people with relatively high fasting glucose. Troglitazone in the TRIPOD Study worked best in people who were the most obese, insulin resistant, and hyperinsulinemic. Similarly, rosiglitazone in the DREAM Study was most effective in people with relatively high BMI and waist circumference. Third, all of the pharmacological interventions have adverse effects. Gastrointestinal side effects may limit compliance with metformin, acarbose, and orlistat. Metformin may cause lactic acidosis in people with renal dysfunction or congestive heart failure. Thiazolidinediones can cause weight gain through a combination of fluid retention and increased body fat. Fluid retention may be manifest as congestive heart failure in a small but important subset of patients. Thiazolidinediones have also been associated with a small risk of fractures in the appendicular skeleton (humerus, hand, foot) in postmenopausal women with established type 2 diabetes. These adverse effects, combined with the overall impact of the interventions on diabetes risk, the evidence for disease modification, and costs should be used to guide selection of interventions in individual patients.

SUMMARY

Type 2 diabetes is a progressive disease. It develops over years as a result of declining pancreatic β-cell compensation for chronic and often worsening insulin resistance. Preventing type 2 diabetes requires modification of the underlying disease biology to slow, stop, or reverse the decline in β-cell compensation. Data from six randomized trials reveal several interventions that reduce the number of high-risk people who develop diabetes during relatively short periods of treatment. Interventions that reduce body fat or that mitigate the effect of excess fat to cause insulin resistance provide the greatest risk reduction and the best evidence for real disease modification. At least two studies indicate that disease modification is possible soon after glucose levels enter the diabetes range. These findings, combined with the fact that falling β-cell compensation leads to rising glycemia, provide a rationale for an intervention strategy that begins with lifestyle modification and progresses to pharmacological therapy aimed at reducing insulin resistance if lifestyle approaches fail to prevent glucose from rising to the diabetes range. Our knowledge base in this field is still quite rudimentary, and we have no information about truly long-term (i.e., for decades) prevention of type 2 diabetes. Even for the short to intermediate term, additional work is needed to determine optimal application of the general strategy described above, to examine combination approaches to prevention, and to test new interventions as they become available. Such work should focus on disease modification, not just cases of diabetes, as a major outcome.

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