

The Prevention or Delay of Type 2 Diabetes

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Diabetes is one of the most costly and burdensome chronic diseases of our time and is a condition that is increasing in epidemic proportions in the U.S. and throughout the world (1). The complications resulting from the disease are a significant cause of morbidity and mortality and are associated with the damage or failure of various organs such as the eyes, kidneys, and nerves. Individuals with type 2 diabetes are also at a significantly higher risk for coronary heart disease, peripheral vascular disease, and stroke, and they have a greater likelihood of having hypertension, dyslipidemia, and obesity (2–6).

There is also growing evidence that at glucose levels above normal but below the diabetes threshold diagnostic now referred to as pre-diabetes, there is a substantially increased risk of cardiovascular disease (CVD) and death (5,7–10). In these individuals, CVD risk factors are also more prevalent (5–7,9,11–14), which further increases the risk but is not sufficient to totally explain it.

In contrast to the clear benefit of glucose lowering to prevent or retard the progression of microvascular complications associated with diabetes (15–18,21), it is less clear whether the high rate of CVD in people with impaired glucose homeostasis, i.e., those with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or diabetes, is caused by elevated blood glucose levels or will respond to treatments that lower

blood glucose. Epidemiological studies have shown a clear relationship (19,20), whereas intervention trials in people with diabetes suggest, but have not demonstrated, a clear benefit of glycemic control (15,16,21,22). Additionally, there are no studies that have investigated a benefit of glucose lowering on macrovascular disease in subjects with only pre-diabetes (IFG or IGT) but not diabetes.

Although the treatment of diabetes has become increasingly sophisticated, with over a dozen pharmacological agents available to lower blood glucose, a multitude of ancillary supplies and equipment available, and a clear recognition by health care professionals and patients that diabetes is a serious disease, the normalization of blood glucose for any appreciable period of time is seldom achieved (23). In addition, in well-controlled so-called “intensively” treated patients, serious complications still occur (15–18,21), and the economic and personal burden of diabetes remains. Furthermore, microvascular disease is already present in many individuals with undiagnosed or newly diagnosed type 2 diabetes (11,24–28).

Given these facts, it is not surprising that studies have been initiated in the last decade to determine the feasibility and benefit of various strategies to prevent or delay the onset of type 2 diabetes. Two early reports (29,30) suggested that changes in lifestyle can prevent diabetes, but weaknesses in study design limited

their general relevance. Recently, however, four well-designed randomized controlled trials have been reported (31–35).

In the Finnish study (31), 522 middle-aged (mean age 55 years) obese (mean BMI 31 kg/m²) subjects with IGT were randomized to receive either brief diet and exercise counseling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects. A strong correlation was also seen between the ability to stop the progression to diabetes and the degree to which subjects were able to achieve one or more of the following: lose weight (goal of 5.0% weight reduction), reduce fat intake (goal of <30% of calories), reduce saturated fat intake (goal of <10% of calories), increase fiber intake (goal of ≥15 g/1,000 kcal), and exercise (goal of >150 min/week). No untoward effects of the lifestyle interventions were observed.

In the Diabetes Prevention Program (DPP) (32–34), the 3,234 enrolled subjects were slightly younger (mean age 51 years) and more obese (mean BMI 34 kg/m²) but had nearly identical glucose intolerance compared with subjects in the Finnish study. About 45% of the participants were from minority groups (e.g., African-American, Hispanic), and 20% were ≥60 years of age. Subjects were randomized to one of three intervention groups, which included the intensive nutrition and exercise counseling (“lifestyle”) group or either of two masked medication treatment groups: the biguanide metformin group or the placebo group. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years (range 1.8–4.6 years), a 58% relative reduction in the progression to diabetes was observed in the lifestyle group (absolute incidence 4.8%), and a 31% relative reduction in the progression of diabetes was observed in the metformin group (absolute incidence 7.8%) compared with control subjects (absolute incidence 11.0%).

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Abbreviations: CVD, cardiovascular disease; DPP, Diabetes Prevention Program; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NNT, number needed to treat; OGTT, oral glucose tolerance test; TRIPOD, Troglitazone in Prevention of Diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

On average, 50% of the lifestyle group achieved the goal of $\geq 7\%$ weight reduction, and 74% maintained at least 150 min/week of moderately intense activity. No serious side effects were seen in any group.

Two other studies, each using a different class of glucose-lowering agent, have shown a reduction in progression to diabetes with pharmacological intervention. In the Troglitazone in Prevention of Diabetes (TRIPOD) study (35), 235 Hispanic women with previous gestational diabetes were randomized to receive either placebo or troglitazone (a drug now withdrawn from commercial sale in the U.S. but belonging to the thiazolidinedione class, of which two related drugs are currently available). After a median follow-up of 30 months, the annual incidence of type 2 diabetes in the two groups was 12.3 and 5.4%, respectively. Thus, troglitazone treatment was associated with a 56% relative reduction in progression to diabetes. Of note, after a washout period of >8 months, the preventive effects of the drug were still observed. Thus, it is possible that troglitazone may affect the natural history of glucose intolerance and may actually prevent diabetes in some people rather than just delaying its onset.

In the STOP-NIDDM trial (36,37), 1,429 participants with IGT were randomized in a double-blind fashion to receive either the α -glucosidase inhibitor acarbose or a placebo. The subjects had a mean age of 55 years and a mean BMI of 31 kg/m^2 . After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose-treated group compared with the placebo group. If this diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was observed in the acarbose group compared with the placebo group. The absolute risk reduction in the acarbose-treated group was 9%. The effect of acarbose was consistent among all age groups, BMI values and between both sexes.

With this background, we are now in the position to consider the practical implications of these studies and to discuss approaches toward the prevention of type 2 diabetes. The issues of concern are addressed below in a question-and-answer format and were developed by a joint workgroup of the American Diabetes Association and the National Institutes of Diabetes and Digestive and Kidney Diseases.

QUESTION 1: SHOULD WE ATTEMPT TO PREVENT DIABETES?

There are at least five conditions that should be met to justify initiating a program to prevent a disease. Ideally, these criteria should be applied to the prevention of diabetes-related morbidity and mortality rather than merely the diagnosis of diabetes.

First, the disease to be prevented should be an important health problem that imposes a significant burden on the affected population. Without question, diabetes satisfies this criterion.

Second, the early development and natural history of the disease should be understood sufficiently well to identify parameters that measure its progression to disease. Here, we have a great deal of data showing that the incidence of diabetes is strongly related to the hyperglycemic states IFG and IGT (38–41). Although there is evidence that other factors are independently associated with the development of diabetes, such as age, family history of diabetes, waist-to-hip ratio, BMI, blood pressure, and lipid levels, none taken singly is as good at discriminating who will progress to diabetes as measuring glucose levels. It should be noted, however, that when taken in the aggregate, these risk factors combined with plasma glucose levels are more predictive of future diabetes than are glucose levels by themselves (42).

Third, there should be a test to detect the predisease state that is safe, acceptable, and predictive. Two tests meet this criterion: measurement of fasting plasma glucose (FPG) and the 2-h value in the oral glucose tolerance test (OGTT). Both are widely available and have few untoward consequences, and a positive value in either is predictive of the development of diabetes.

Fourth, there should be safe, effective, and reliable method(s) to prevent or at least delay the disease from occurring. The results of the four prevention studies described above indicate that there are now interventions capable of at least delaying the onset of diabetes. In the Finnish study (31), the number needed to treat (NNT) for 1 year to prevent one case of diabetes was 22, and the NNT was 5 to prevent one case in 5 years. In the DPP (32), the NNT to prevent one case of diabetes in 3 years through lifestyle modification was 7, and the NNT for the same

period using metformin as the intervention was 14. None of the interventions were associated with any major harmful effects. These data suggest that the tested interventions are very safe and efficacious.

Although it is not a requirement to satisfy the fourth condition, it is also important to consider whether there are benefits to an intervention in addition to preventing the disease in question. In nearly all the diabetes prevention trials cited above, the average participant was overweight (BMI $>25 \text{ kg/m}^2$) and likely to be sedentary. Both of these characteristics are risk factors for other diseases, most notably CVD (43–45). Also, as reviewed above, IGT and perhaps IFG are independent risk factors for CVD. The changes in lifestyle that delayed the onset of diabetes consisted of modest weight loss and exercise and therefore may well have had a beneficial effect on health in addition to diabetes prevention.

Fifth, the effort to find individuals who are at high risk of getting the disease and the cost of the intervention(s) should not be burdensome and should be cost-effective. This condition has not yet been established. There is a convincing argument that opportunistic screening (i.e., screening during routine encounters with the health care system) is the most cost-effective way to find individuals at risk for diabetes (46). Although data from a modeling study suggest that it is appropriate to screen for individuals at high risk of developing diabetic complications (47), no studies have been published on the cost-effectiveness of screening to detect prediabetes (IFG or IGT) or to prevent or delay the diagnosis of diabetes. Of more importance, it is unknown whether intervention at the stage of pre-diabetes (IFG or IGT) is a cost-effective way to prevent or delay the complications of diabetes, which are more relevant to the patient, family, and society than is simply the diagnosis of diabetes.

The cost of identifying individuals with pre-diabetes (IFG or IGT) and then intervening to prevent diabetes has implications other than financial. Individuals can react negatively to whatever label they are given, and some may be discriminated against in the workplace or by insurers. Any intervention can, of course, promote anxiety and be socially disruptive. Finally, hazards resulting from the use of medications are always possible.

In summary, our knowledge of the early stages of hyperglycemia that portend the diagnosis of diabetes, and the recent success of major intervention trials, clearly show that individuals at high risk can be identified and diabetes delayed, if not prevented. The cost-effectiveness of intervention strategies is unclear, but the huge burden resulting from the complications of diabetes and the potential ancillary benefits of some of the interventions suggest that an effort to prevent diabetes may be worthwhile.

QUESTION 2: WHO ARE POTENTIAL CANDIDATES FOR SCREENING AND INTERVENTION?

Most of the diabetes prevention trials required that subjects have IGT (defined as an FPG level <140 mg/dl and a 2-h OGTT value between 140 and 199 mg/dl) as the main enrollment criterion (Table 1). Only the DPP (33) also required an FPG value less than the current cut point for diabetes (i.e., <126 mg/dl but >95 mg/dl), and, thus, all of the other trials enrolled some subjects who would be classified as having diabetes by the current FPG criteria. Well over one-third of the participants in the DPP also had IFG. Only the DPP enrolled large numbers of ethnic minorities, and their demographic characteristics were similar to Caucasians in the study (34).

Choice of screening test

No studies have examined the usefulness of the A1C test to predict future diabetes. Three studies have examined whether the FPG test or 2-h OGTT is a better predictor of future diabetes. In each study, a fasting and 2-h OGTT value was obtained at

baseline and follow-up. The cumulative incidence of diabetes over 5–6 years was low (4–5%) in those individuals starting with a normal fasting and normal 2-h OGTT value, intermediate (20–34%) in those with IFG and a normal 2-h OGTT or IGT and a normal FPG, and highest (38–65%) in those with combined IFG and IGT. There was virtually no difference in the rate of progression to diabetes if a person had IFG or IGT. In the U.S., Harris et al. (48) reported that some individuals with a normal FPG level will have IGT or diabetes if a 2-h OGTT is performed, but fewer people with a normal 2-h OGTT will have IFG or diabetes if an FPG test alone is done. These observations have been confirmed repeatedly in virtually every population that has been studied.

Thus, using the current definitions of IFG, IGT, and diabetes (49), the 2-h OGTT appears to identify more people who have impaired glucose homeostasis and, thus, more people who will progress to diabetes. However, Gabir et al. (39) pointed out that the differences in the proportion of subjects with IGT or IFG “reflect the fact that they represent different proportions of the glucose distributions rather than that FPG or the 2-h OGTT value per se are inherently different in their sensitivity, specificity, or predictive power.” It has been suggested, therefore, that if the cut point of IFG were lowered to around 100 mg/dl, the FPG and 2-h OGTT would have similar sensitivity and positive predictive values, although it should be noted that they would not necessarily include the same individuals (39). Regarding the tests themselves, the FPG test is more convenient to patients, more reproducible, less costly, and

easier to administer than the 2-h OGTT (49–51).

For all the above reasons, the FPG test or 2-h OGTT can be used to screen for pre-diabetes (IFG or IGT). Alternatively, some investigators have proposed logistic regression models using multiple risk factors, from which a “risk score” can be created (42). If this work can be confirmed and the sensitivity, specificity, and predictive value is acceptable, such an approach would have great advantages and utility.

Age considerations and screening frequency

No study has explicitly addressed the age at which screening should begin, the optimal frequency of screening, or other indications for screening. In the Finnish, DPP, and STOP-NIDDM trials, participants were much older and heavier than the population initially screened, suggesting that individuals >45 years of age and who are substantially overweight are most likely to have IGT (or IFG). In a cross-section of U.S. adults tested between 1988 and 1994 (52), the prevalence of IFG or undiagnosed diabetes in people 40–74 years of age was 14.5%; the prevalence of IGT or undiagnosed diabetes (by 2-h OGTT) in people from the same population was 22%. The prevalence of IFG or undiagnosed diabetes (by FPG) increases greatly between age 20 and 39 years and age 40 and 49 years and reaches a peak in people aged 60–74 years. The prevalence of IFG, IGT, or undiagnosed diabetes in those >45 years of age and who are overweight (BMI >25 kg/m²) are 9.3, 12.8, and 7.3%, respectively (M.I. Harris, personal communication).

All told, these data suggest that pre-diabetes (IFG or IGT) is much more likely to be detected in overweight middle-aged individuals than in younger lean individuals. Finally, in a subset analysis of the DPP results (32), there was a trend toward greater success of the lifestyle intervention among the elderly than among those <45 years of age, providing further support for initiating screening at middle-age when the intervention to be implemented is more effective.

In summary, the current evidence suggests that opportunistic screening to detect pre-diabetes (IFG or IGT) should be considered in individuals ≥45 years of age, particularly in those with a BMI ≥25 kg/m². Screening should also be considered for

Table 1—Eligibility criteria and characteristics of participants with IGT in major diabetes prevention trials

Study	Eligibility criteria			Actual participants		
	Age	BMI	FPG (mg/dl)	Mean age	Mean BMI	Mean FPG (mg/dl)
Malmö (29)	47–49	NS	NS	47–49	>25	NG
Da Qing (30)	NS	NS	NS	44	>25	NG
Finnish (31; J. Tuomilehto, personal communication)	40–65	≥25	NS	55	31	110
DPP (33,34)	≥25	≥24	95–125	51	34	106
TRIPOD (35)	NS	NS	NS	35	30	94
STOP-NIDDM (36,37)	40–70	25–40	101–139	55	>31	101–139

NG, not given; NS, not specified or relevant to eligibility.

people who are <45 years of age and are overweight if they have another risk factor for diabetes (Table 3). Asian-Americans should be considered for screening at lower levels of BMI (e.g., 23 kg/m²). There are no data that support screening of children for IFG or IGT, although there are recommendations for screening children for diabetes (53).

Screening should be performed using either the FPG test or 2-h OGTT. It is preferable that the FPG test be given in the morning because afternoon values tend to be lower (54). Although it is clear that the 2-h OGTT will detect more cases of glucose intolerance and undiagnosed diabetes than the FPG test at current cut points, the proportion who progress to diabetes from pre-diabetes (IFG or IGT) is similar. Given the age-related incidence of diabetes and the rate of progression to diabetes in normoglycemic middle-aged subjects, repeat testing in 3-year intervals seems reasonable.

The case for screening is strengthened by the fact that screening will not only detect cases of IFG or IGT, but also cases of undiagnosed diabetes. Thus, policies to identify individuals for whom it is appropriate to initiate a diabetes prevention strategy will also identify individuals who should receive treatment for diabetes. Furthermore, because individuals with IFG, IGT, or undiagnosed diabetes are at high risk for CVD, their identification should herald increased surveillance and treatment for hypertension, dyslipidemia, and tobacco use.

QUESTION 3: HOW SHOULD DIABETES PREVENTION BE PERFORMED?

The strategies shown to be effective in preventing diabetes relied on lifestyle modification or glucose-lowering drugs that have been approved for treating diabetes. The DPP is the only study in which a comparison of the two was made, and lifestyle modification was nearly twice as effective in preventing diabetes (58 vs. 31% relative reductions, respectively). However, the greater efficacy of metformin in younger, very obese individuals compared with older, less overweight subjects suggests that this pharmaceutical intervention may be effective only in particular subsets of patients.

Lifestyle modification

In the two well-controlled studies that included a lifestyle intervention arm, substantial efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. In the Finnish study, weight loss averaged 9.2 lb at 1 year, 7.7 lb after 2 years, and 4.6 lb after 5 years (31,53); the exercise component of the intervention called for "moderate exercise" of 30 min/day. In the DPP (33), the lifestyle group lost ~12 lb at 2 years and 9 lb at 3 years (mean weight loss for the study duration was about 12 lb or 6% of initial body weight). In both of these studies, most of the participants were obese (BMI >30 kg/m²).

Although in both studies diabetes could be delayed or prevented with only modest changes in weight and activity, considerable effort from well-trained staff was needed to achieve these behavioral changes. In the Finnish study (31), the intervention group had seven sessions with a nutritionist during the first year of the study and one session every 3 months thereafter. They also received individualized guidance on increasing physical activity, and over 50% of the participants in the first year of the study received supervised progressive individually tailored physical training sessions. Free membership to an exercise club was offered.

In the DPP (32,33), participants in the lifestyle arm met with a case manager 16 times over the first 6 months and then generally monthly thereafter. They made telephone contact at least monthly. Group courses on exercise and weight loss lasting 4–6 weeks were offered every 3 months. Also, two supervised exercise sessions were offered each week. Moreover, anyone having difficulty achieving or maintaining the study's goals for loss or exercise were offered incentives, such as exercise tapes or equipment, free enrollment in exercise facilities, free low-calorie foods, more structured eating plans, and home visits for encouragement and counseling.

Keeping in mind the modest lifestyle goals of either study (5% reduction in body weight and 150 min moderate exercise/week in the Finnish Study and 7% weight reduction and 150 min/week self-reported moderate physical activity in the DPP) and the fact that the participants were already motivated to join a clinical

trial, it is discouraging that the substantial levels of effort described above were only partially successful in achieving the desired objectives. In the Finnish study, only 43% achieved the weight reduction goal, and 36% of subjects increased their physical activity. In the DPP, only 50% reached the weight loss goal, and 74% reached the exercise goal. In both studies, some weight was regained despite the continuation of intensive strategies.

Although many other weight loss strategies have been described, all have been difficult to accomplish and maintain (55–59). Without question, however, many individuals have achieved and maintained appropriate lifestyle changes, and some have done so without health care system interventions. But even so, better strategies are needed to help people lose weight and keep it off and exercise more often. Moreover, the U.S. health care system is not structured to provide or reimburse for regular lifestyle counseling (56,57). Also, the current absence of published data demonstrating the cost-effectiveness of early intervention to prevent diabetes-related complications will dampen support for widespread implementation of costly intervention policies.

On the other hand, because there is strong epidemiologic evidence that physical activity and weight loss are of medical benefit, not just for preventing diabetes but also for improving cardiovascular health and quality of life (56,57), health care policymakers and health care systems should aggressively explore low-cost ways to promote physical activity and weight loss. At the same time, cost-effective patient education and counseling interventions should continue to be developed and tested.

Pharmacological interventions

Three diabetes prevention trials used pharmacological therapy, and all have reported a significant lowering of the incidence of diabetes. The biguanide metformin reduced the risk of diabetes by 31% in the DPP (32), the α -glucosidase inhibitor acarbose reduced the risk by 32% in the STOP-NIDDM trial (37), and the thiazolidinedione troglitazone reduced the risk by 56% in the TRIPOD study (35). Whereas all the drugs clearly delayed the onset of diabetes, the TRIPOD data, after a drug washout period, suggested that troglitazone may have had a

true preventive action as well. Although metformin and acarbose may also have a preventive action, the incidence of diabetes after discontinuation of the drug has not yet been determined.

In the DPP, metformin was about half as effective as diet and exercise in delaying the onset of diabetes overall, but it was nearly ineffective in older individuals (≥ 60 years of age) or in those who were less overweight (BMI < 30 kg/m²). Conversely, metformin was as effective as lifestyle modification in individuals age 24–44 years or in those with a BMI ≥ 35 kg/m². Thus, the population of people in whom treatment with metformin has equal benefit to that of a lifestyle intervention is only a small subset of those who are likely to have pre-diabetes (IFG or IGT).

It is unknown whether other glucose-lowering drugs will delay or prevent diabetes or even whether other agents in the α -glucosidase inhibitor or thiazolidinedione classes will be equally effective as those already tested. This is being actively investigated. Also, as with any prescription pharmacological agent, all of these drugs require regular monitoring, and each has been linked to undesirable side effects that preclude their use in some patients. These side effects must be taken into consideration, especially when the drugs are being used to prevent or delay diabetes rather than to treat it. There are also data to suggest that ACE inhibitors (60) may lower the risk of developing diabetes, but more studies are necessary before these drugs can be recommended for preventing diabetes.

Lifestyle or medication?

The greater benefit of weight loss and physical activity strongly suggests that lifestyle modification should be the first choice to prevent or delay diabetes. Modest weight loss (5–10% of body weight) and modest physical activity (30 min daily) are the recommended goals. Because this intervention not only has been shown to prevent or delay diabetes, but also has a variety of other benefits, health care providers should urge all overweight or sedentary individuals to adopt these changes, and such recommendations should be made at every opportunity.

Drug therapy to prevent or delay diabetes appears to be much less beneficial for a variety of reasons. First, when compared directly with lifestyle modification, at least metformin was considerably less

efficacious overall, and the advantage of lifestyle modification was even greater in older or less overweight patients (32). The relative risk reduction using acarbose appears similar to that of metformin, although the study participants were very different. Second, all glucose-lowering drugs require monitoring, have been associated with significant adverse side effects, and are contraindicated in some individuals. Third, none of the glucose-lowering agents tested or commercially available have been studied with regard to protection against CVD or have any other clinical benefit to nondiabetic individuals. Even in people with diabetes, there is only one glucose-lowering agent (metformin) for which there is any outcome data to suggest possible effectiveness in reducing the incidence of macrovascular disease (16,22). Finally, prescribing a medication to delay the onset of diabetes, which is also used to treat diabetes, will increase a patient's total years of drug exposure and may increase the likelihood of untoward drug effects.

Therefore, when all factors are considered, there is insufficient evidence to support the use of drug therapy as a substitute for, or routinely used in addition to, lifestyle modification to prevent diabetes. Until there are studies showing that drugs will delay or prevent the complications of diabetes, or until the cost-effectiveness of using pharmacological agents has been established, we do not recommend the routine use of these agents to prevent diabetes.

The lifestyle intervention used in the DPP appeared to prevent or delay the onset of diabetes for ~ 3 years. Although not designed to determine directly whether there was also CVD benefit, both the Finnish study and the DPP reduced the magnitude of some CVD risk factors. Lifestyle intervention appears to be very safe, and, therefore, regular monitoring for untoward effects is unnecessary. Because ~ 3 –5% of the lifestyle cohort and 6–11% of the control group in the studies developed diabetes per year, which mirrors the rate of progression in other studies (38–40), monitoring for the development of diabetes every 1–2 years in patients who have pre-diabetes (IFG or IGT) seems warranted. In the absence of data on the cost-effectiveness of lifestyle intervention regimens that will reduce diabetes-related complications, the nature and frequency of patient-provider encounters to support

behavior modification are not yet known. However, low-cost ways to reinforce lifestyle goals are greatly encouraged, and low-cost community-based programs to increase physical activity and avoid unhealthful lifestyle choices offer potential benefits for people who are at risk for diabetes.

QUESTION 4: HOW DO STRATEGIES TO PREVENT DIABETES DIFFER FROM THOSE TO TREAT DIABETES?

At first thought, it might appear that performing an FPG test or OGTT to determine whether a patient has pre-diabetes (IFG or IGT) and then prescribing weight loss and/or exercise in “positive” individuals is no different from using the same tests to screen for diabetes and initiating the same treatment in those with diabetes. One might say that the only difference is that the cut point for intervention has been lowered and that, conceptually, “prevention” is no different from “treatment” (i.e., we are starting treatment for diabetes earlier). In many ways, such a conclusion is true. Finding and treating IFG or IGT has the same motivation as finding and treating diabetes—both are intended to reduce the complications of diabetes and risk factors for CVD. Pre-diabetes (IFG or IGT) can be thought of as an early stage of diabetes because a high proportion of individuals who have either of these conditions will go on to develop the disease. Thus, policies for diabetes prevention can appropriately be thought of as early interventions in the natural history of progression to type 2 diabetes.

But there are also important differences between preventing diabetes and treating diabetes. First, people with diabetes will receive additional tests and procedures (e.g., foot examination, dilated eye examination, A1C measurement, urine protein) to detect complications of hyperglycemia that are not relevant to people with pre-diabetes (IFG or IGT). Second, patients with diabetes are at greater risk for some acute complications (e.g., hypoglycemia, increased infections) as well as microvascular complications that have not been documented in individuals with pre-diabetes (IFG or IGT). Both patient self-monitoring and careful monitoring by a provider for some diabetes-related conditions are not as important in pre-diabetes (IFG or IGT) as they

Table 2—Synopsis of recommendations to prevent or delay diabetes

- Individuals at high risk for developing diabetes need to become aware of the benefits of modest weight loss and participating in regular physical activity. (A)
- Screening: based on current screening guidelines for diabetes (49), men and women ≥ 45 years of age, particularly those with a BMI ≥ 25 kg/m²*, are candidates for screening to detect pre-diabetes (IFG or IGT). Screening should be considered in younger individuals with a BMI ≥ 25 kg/m²* who have additional risk factors (Table 3). (B)
- In individuals with normoglycemia, rescreening at 3-year intervals is reasonable. (C)
- How to screen: screening should be carried out only as part of a health care office visit. Either an FPG test or 2-h OGTT (75-g glucose load) is appropriate, and positive test results should be confirmed on another day. (B)
- Intervention strategy: patients with pre-diabetes (IFG or IGT) should be given counseling on weight loss as well as instruction for increasing physical activity. (A)
- Follow-up counseling appears important for success. (B)
- Monitoring for the development of diabetes should be performed every 1–2 years. (E)
- Close attention should be given to, and appropriate treatment given for, other CVD risk factors (e.g., tobacco use, hypertension, dyslipidemia). (A)
- Drug therapy should not be routinely used to prevent diabetes until more information is known about its cost-effectiveness. (E)

*May not be correct for all ethnic groups.

are in people with diabetes. Third, the goals for blood pressure and lipid management for people who have diabetes are more rigorous than for people who have pre-diabetes (IFG or IGT). Whether similar goals are warranted for people with pre-diabetes (IFG or IGT) remains to be determined. Finally, individuals labeled “diabetic” are more likely to be subject to possible social and economic discrimination. The ability to recommend and monitor a therapeutic regimen without having a disease label placed on an individual may be advantageous.

QUESTION 5: WHAT ADDITIONAL RESEARCH IS NEEDED?

The results of the prevention studies reviewed above suggest that additional research needs to be done to capitalize fully on our ability to prevent type 2 diabetes. The following are some of the health services research questions that should be answered.

- What is the cost-effectiveness of a DPP-like lifestyle intervention? Are there more cost-effective strategies, and how would they affect the morbidity and mortality associated with diabetes?
- What is the cost-effectiveness of using drugs to prevent diabetes?

- What is the most effective way to identify individuals who are at high risk for unrecognized IFG or IGT (pre-diabetes)?
- Are there intervention programs that require fewer resources than what was provided in the DPP or Finnish studies but still achieve comparable weight reduction and increased physical activity?
- Are there efficient interventions that will achieve greater degrees of weight reduction and physical activity than those achieved in the prevention studies?
- What programs will *sustain* the success-

ful achievement of weight reduction and physical activity?

- What is the most effective way to combine public awareness, professional education, and health systems policy to ensure identification of individuals with pre-diabetes (IFG or IGT) and the achievement of a sustained lifestyle modification?
- Are there effective lifestyle interventions that can be implemented outside of the health care system?

CONCLUSIONS — There is now substantial evidence that type 2 diabetes

Table 3—Risk factors for type 2 diabetes

- Age ≥ 45 years
- Overweight (BMI ≥ 25 kg/m²*)
- First-degree relative with diabetes
- Habitual physical inactivity
- Member of a high-risk ethnic population (e.g., African-American, Latino, Native American, Asian-American, Pacific Islander)
- Previously identified pre-diabetes (IFG or IGT)
- History of GDM or delivery of a baby weighing > 9 lbs
- Hypertensive ($\geq 140/90$ mmHg)
- HDL cholesterol level ≤ 35 mg/dl (0.90 mmol/l) and/or a triglyceride level ≥ 250 mg/dl (2.82 mmol/l)
- PCOS
- History of vascular disease

*May not be correct for all ethnic groups.

can be prevented or delayed. Individuals at high risk of developing diabetes (those with pre-diabetes) can be identified easily. It is not yet known whether the successful interventions will cost-effectively reduce the morbidity and mortality associated with diabetes. Diabetes prevention policies that focus on lifestyle modification, specifically modest weight loss and increased physical activity, are also very likely to have additional health benefits. Public health messages, health care professionals, and health care systems should all encourage behavior changes to achieve a healthy lifestyle. Further research is necessary to understand better how to facilitate effective and efficient programs for the primary prevention of type 2 diabetes. Nonetheless, it is possible to recommend some prevention policies, as are shown in Table 2.

References

- King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 21:1414–1431, 1998
- Reaven GM: Banting Lecture: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1988
- DeFronzo RA, Ferrannini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–194, 1991
- Turner RC, Millns H, Neil HA, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS 23). *BMJ* 316:823–828, 1998
- The DECODE Study Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
- Eastman RC, Cowie CC, Harris MI: Undiagnosed diabetes or impaired glucose tolerance and cardiovascular risk. *Diabetes Care* 20:127–128, 1997
- Saydah SH, Loria CM, Eberhardt MS, Brancati FL: Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care* 24:447–453, 2001
- Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events: a meta-regression analysis of published data from 20 studies of 95,783 individuals followed for 124 years. *Diabetes Care* 22:233–240, 1999
- Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyorala M, Forhan A, Eschwege E: High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men: 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 21:360–367, 1998
- Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E: Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care* 22:45–49, 1999
- Harris MI: Undiagnosed NIDDM: clinical and public health issues. *Diabetes Care* 16:642–652, 1993
- Wei M, Gaskill SP, Haffner SM, Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. *Diabetes Care* 21:1167–1172, 1998
- Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
- Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Mortality from coronary heart disease and stroke in relation to degree of glycaemia: the Whitehall study. *Br Med J (Clin Res Ed)* 287:867–870, 1983
- UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
- UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352:854–865, 1998
- Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
- Reichard P, Nilsson BY, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 329:304–309, 1993
- Moss SE, Klein R, Klein BE, Meuer SM: The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 154:2473–2479, 1994
- Khaw KT, Wareham N, Luben R,ingham S, Oakes S, Welch A, Day N: Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European prospective investigation of cancer and nutrition (EPIC-Norfolk) *BMJ* 322:15–18, 2001
- The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
- Turner RC, Cull CA, Frighi V, Holman RR: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49): UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 281:2005–2012, 1999
- Rajala U, Laakso M, Qiao Q, Keinänen-Kiukaanniemi S: Prevalence of retinopathy in people with diabetes, impaired glucose tolerance, and normal glucose tolerance. *Diabetes Care* 21:1664–1669, 1998
- Harris MI, Klein R, Welborn TA, Knudman MW: Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
- Kohner EM, Aldington SJ, Stratton IM, Manley SE, Holman RR, Matthews DR, Turner RC: UKPDS: diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. *Arch Ophthalmol* 116:297–303, 1998
- Turner R, Cull C, Holman R: United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 124:136–145, 1996
- Klein R, Klein BE, Moss SE: Prevalence of microalbuminuria in older-onset diabetes. *Diabetes Care* 16:1325–1330, 1993
- Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmo feasibility study. *Diabetologia* 34:891–898, 1991
- Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and

- Diabetes Study. *Diabetes Care* 20:537–544, 1997
31. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
 32. Diabetes Prevention Research Group: Reduction in the evidence of type 2 diabetes with life-style intervention or metformin. *N Engl J Med* 346:393–403, 2002
 33. The Diabetes Prevention Program: Design and methods for a clinical trial in the prevention in type 2 diabetes. *Diabetes Care* 22:623–634, 1999
 34. The Diabetes Prevention Program Research Group: The Diabetes Prevention Program: baseline characteristics of the randomized cohort. *Diabetes Care* 23:1619–1629, 2000
 35. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic β -cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002
 36. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M: The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data: Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. *Diabetes Care* 21:1720–1725, 1998
 37. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, for the STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
 38. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CD, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn Study. *JAMA* 285:2109–2113, 2001
 39. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, Knowler WC: The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. *Diabetes Care* 23:1108–1112, 2000
 40. Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, Hemraj F, Fareed D, Tuomilehto J, Alberti KG: Impaired fasting glucose or impaired glucose tolerance: what best predicts future diabetes in Mauritius? *Diabetes Care* 22:399–402, 1999
 41. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701–710, 1997
 42. Stern MP, Williams K, Haffner SM: Identification of individuals at high risk of type 2 diabetes: do we need the oral glucose tolerance test. *Ann Intern Med*. In press
 43. Donahue RP, Orchard TJ: Diabetes mellitus and macrovascular complications: an epidemiological perspective. *Diabetes Care* 15:1141–1155, 1992
 44. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH: The disease burden associated with overweight and obesity. *JAMA* 282:1523–1529, 1999
 45. U.S. Department of Health & Human Services: *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996
 46. Engelgau MM, Narayan KM, Herman WH: Screening for type 2 diabetes. *Diabetes Care* 23:1563–1580, 2000
 47. CDC Diabetes Cost-Effectiveness Study Group: The cost-effectiveness of screening for type 2 diabetes. *JAMA* 280:1757–1763, 1998
 48. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS: Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 20:1859–1862, 1997
 49. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 26:S5–S20, 2003
 50. Stolk RP, Orchard TJ, Grobbee DE: Why use the oral glucose tolerance test? *Diabetes Care* 18:1045–1049, 1995
 51. Mooy JM, Grootenhuys PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996
 52. Harris MI, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, Wiedmeyer HM, Byrd-Holt DD: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination Survey 1988–1994. *Diabetes Care* 21:518–524, 1998
 53. American Diabetes Association: Type 2 diabetes in children and adolescents. *Diabetes Care* 23:381–389, 2000
 54. Troisi RJ, Cowie CC, Harris MI: Diurnal variation in fasting plasma glucose: implications for diagnosis of diabetes in patients examined in the afternoon. *JAMA* 284:3157–3159, 2000
 55. Wing RR, Goldstein MG, Acton KJ, Birch LL, Jakicic JM, Sallis JF Jr, Smith-West D, Jeffery RW, Surwit RS: Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. *Diabetes Care* 24:117–123, 2001
 56. National Institutes of Health: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obes Res* 6 (Suppl. 2):51S–209S, 1998
 57. NIH Consensus Development Panel on Physical Activity and Cardiovascular Health: Physical activity and cardiovascular health. *JAMA* 276:241–246, 1996
 58. The Writing Group for the Activity Counseling Trial Research Group: Effects of physical activity counseling in primary care: the Activity Counseling Trial: a randomized controlled trial. *JAMA* 286:677–687, 2001
 59. Wee CC, McCarthy EP, Davis RB, Phillips RS: Physician counseling about exercise. *JAMA* 282:1583–1588, 1999
 60. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G: Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 342:145–153, 2000