Understanding and Identifying Pre-diabetes – Can We Halt the Diabetes Epidemic?

a report by
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Approximately 1.5 million people in the US develop diabetes each year, and are at risk of diabetic complications. Virtually all of these people had normal glucose metabolism at birth, and the vast majority (~95%) with type 2 diabetes experienced gradual progression towards the diabetic state over the ensuing decades of life. The term 'pre-diabetes' refers to impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), two intermediate metabolic states between normal glucose tolerance (NGT) and diabetes. IGT is defined by a plasma glucose level of 140–199mg/dl two hours following ingestion of a 75g oral solution; IFG is defined by a fasting plasma glucose value that lies between 100 and 125mg/dl.[1] Estimates from the Centers for Disease Control and Prevention (CDC)[2] indicate that in 1988–1994, among US adults 40–74 years of age 33.8% had IFG, 15.4% had IGT and 40.1% had pre-diabetes (IGT or IFG or both). More recent data are available for IFG, but not IGT: in 2003–2006, 25.9% of US adults 20 years of age or over and 35.4% of adults 60 years of age or over had IFG.[2] Applying this percentage to the entire US population in 2007, the CDC has estimated that there are approximately 57 million American adults 20 years of age or older with IFG, which means that at least 57 million American adults have pre-diabetes.[2] The risk factors identified for pre-diabetes overlap considerably with those for type 2 diabetes and include obesity, family history of diabetes, low high-density lipoprotein (HDL) cholesterol, high triglycerides, high blood pressure, history of gestational diabetes and ethnicity. The presence of these risk factors can be used to direct community screening efforts to identify persons with pre-diabetes, as recommended by the American Diabetes Association (ADA) (see *Table 1*).

Predictors of Progression to Type 2 Diabetes

The rate of progression from pre-diabetes to type 2 diabetes has been shown consistently to average ~10% annually in several prospective studies.[3–6] The collective data indicate that subjects with pre-diabetes assigned to placebo treatment rarely recover spontaneously from the pre-diabetic state. Thus, preventative interventions become a compelling public health priority. However, the optimal targeting of such interventions requires accurate knowledge of the triggers and predictors of progression from pre-diabetes to diabetes. Weight gain, insulin resistance and impaired insulin secretion predicted progression from pre-diabetes to diabetes in Pima Indians,[7] and may also be universal predictors in other populations. Weight gain predicted progression from NGT to IGT (5.2kg versus 2.6kg in non-progressors); progression from IGT to diabetes was associated with a further increase in weight (13kg versus 6kg in non-progressors over a five-year follow-up period). However, the greater rate of weight gain in the progressors did not occur in isolation, but was accompanied by ~30% worsening of insulin resistance and >50% decline in acute insulin secretory response to intravenous glucose.[7] Weight gain was identified as a predictor of incident diabetes in African-Americans in the Atherosclerosis Risk in the Community (ARIC) study.[8] An analysis of six prospective studies[9] on progression from IGT to diabetes revealed the following features: baseline FPG and the two-hour oral glucose tolerance test (OGTT) value were positively associated with diabetes risk; the rate of progression from IGT to type 2 diabetes was exponential among subjects in the top quartile of baseline FPG, but increased linearly with increasing two-hour OGTT glucose levels; incident diabetes occurred at higher rates in Hispanic, Mexican-American, Pima and Nauruan populations than among Caucasians; the degree of obesity, as measured by body mass index (BMI), predicted diabetes risk in the three studies with the lowest incidence rates of diabetes, but not in the studies that recorded the highest incidence of diabetes; and family history of diabetes did not predict the risk of progression from IGT to diabetes. The lack of correlation between a family history of diabetes and progression from IGT to diabetes suggests that familial/genetic factors may have exerted their maximal effects by the stage of IGT. With regard to racial/ethnic influences, data from the Diabetes Prevention Program (DPP) indicated that once pre-diabetes (IGT) has developed, the annual rate of progression to diabetes was similar (~10%) among African-Americans, Asian-Americans, Caucasians, Hispanics and Native Americans.[3]

Pre-diabetes and Cardiovascular Risk

Epidemiological studies, including the Paris Prospective Study[10] and EPIC-Norfolk,[11] have shown that levels of glycaemia in the pre-diabetes range confer an increased risk of cardiovascular disease (CVD) morbidity and mortality. Patients who progress to type 2 diabetes manifest additional risk for atherosclerotic disorders, resulting in increased burden of CVD, stroke and peripheral vascular diseases compared with subjects without diabetes. More than 75% of deaths in people with diabetes are attributable to CVD. The accumulation of cardiometabolic risk factors predisposes to the increased CVD risk in type 2 diabetes. Most patients with pre-diabetes have cardiometabolic risk factors, including upper body obesity, hypertriglyceridaemia, decreased HDL cholesterol levels, dysglycaemia, hypertension and expression of pro-inflammatory cytokines, among others.[12] In the Paris Prospective Study,[10] a pre-diabetes status at baseline conferred a

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doubling of the 10-year risk of CVD mortality. In the EPIC-Norfolk study,[11] the relationship between glycated haemoglobin (HbA$_{1c}$) and CVD mortality was evident as a continuum of risk, beginning well before the glycaemic threshold for the diagnosis of diabetes is reached. These data indicate that macrovascular disease manifests during the pre-diabetic stage, which strengthens the rationale for early preventative interventions.

Halting the Epidemic of Diabetes

Lifestyle Intervention

Several randomised controlled studies have demonstrated the efficacy of lifestyle intervention in preventing progression from pre-diabetes to type 2 diabetes.[3–5] The lifestyle interventions applied in these studies generally involved a modest weight loss (~5–<10%) through dietary modification and increased physical activity. The dietary modification involved reduction in caloric consumption, selective reduction in saturated fat calories and increased intake of complex carbohydrates. The physical activity component involved accrual of an additional 150–240 minutes per week of voluntary, moderate-intensity (~55% maximum oxygen uptake [VO$_2$ max]) physical activity above routine levels.[3–5] The primary outcome measure was the rate of progression from IGT to type 2 diabetes during a defined period (approximately three to six years) of observation. Investigators in the Da Qing Study[4] enrolled 577 Chinese adults (mean age 45 years, mean BMI 26kg/m^2) who had IGT at baseline. The subjects were randomised by clinic to a control group or to one of three active treatment groups: diet only, exercise only or diet plus exercise. The follow-up schedule was approximately every two weeks during the initial three months and quarterly thereafter. The cumulative incidence of diabetes at six years was 67.7% in the control group compared with 43.8% in the diet group, 41.1% in the exercise group and 46.0% in the diet-plus-exercise group. Cox's proportional hazards analysis, adjusted for differences in baseline BMI and fasting glucose, showed that the diet, exercise and diet-plus-exercise interventions resulted in 31, 46 and 42% reductions in risk of developing diabetes, respectively, compared with the control group. Surprisingly, the Da Qing study failed to show an additive effect of diet plus exercise on the primary end-point. In the Finnish Diabetes Prevention Study,[4] 522 middle-aged IGT subjects (172 men and 350 women, mean age 55 years, mean BMI 31kg/m^2) were randomly assigned to either an intervention or a control group. Each subject in the intervention group received individualised lifestyle counselling aimed at inducing ~5% weight loss and increasing physical activity by ~210 minutes per week. The mean weight loss by the end of the second year was ~3.5kg in the intervention group and ~0.8kg in the control group. The cumulative incidence of diabetes after four years was 11% in the intervention group and 23% in the control group, a significant 58% reduction in diabetes incidence. The lifestyle intervention arm of the DPP enrolled 1,079 subjects with IGT (out of the 3,234 participants enrolled in the study) drawn from all ethnic and racial groups in the US population.[3] The goals for the participants assigned to the intensive lifestyle intervention were to achieve and maintain a weight reduction of at least 7% of initial bodyweight through modest caloric restriction (500–700 fewer calories per day) and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 minutes per week. After an average follow-up period of 2.8 years, the participants randomised to lifestyle intervention showed a 58% reduction in the incidence of diabetes compared with placebo.[3] The beneficial effect of lifestyle intervention was seen in all age, gender, racial and ethnic subgroups of the DPP participants. Furthermore, reversion to NGT occurred in ~30% of subjects in the lifestyle intervention arm compared with ~18% in the control arm. Thus, caloric restriction and increased physical activity not only

Table 1: Criteria for Testing for Pre-diabetes and Diabetes in Asymptomatic Adult Individuals

1. Testing should be considered in all adults who are overweight (BMI ≥25kg/m^2) and have additional risk factors:
   - physical inactivity;
   - first-degree relative with diabetes;
   - members of a high-risk ethnic population (e.g. African-American, Latino, Native American, Asian-American and Pacific Islander);
   - women who delivered a baby weighing >9lb or were diagnosed with GDM;
   - hypertension (140/90mmHg or on therapy for hypertension);
   - HDL cholesterol level <35mg/dl (0.90mmol/l) and/or a triglyceride level >250mg/dl (2.82 mmol/l);
   - women with polycystic ovarian syndrome (PCOS);
   - IGT or IFG on previous testing;
   - other clinical conditions associated with insulin resistance (e.g. severe obesity and acanthosis nigricans); and
   - history of CVD.

2. In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at 45 years of age.

3. If results are normal, testing should be repeated at least at three-year intervals, with consideration of more frequent testing depending on initial results and risk status.

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Table 2: Controlled Trials to Prevent Progression from Pre-diabetes to Diabetes

Study (Intervention)	Number of Subjects	Study Population	Risk Reduction
Da Qing (diet + exercise)	577	Chinese, mean age 45 years, BMI 26	31–46% after six years
STOP-NIDDM (acarbose)	1,429	IGT adults, mean age 55 years, mean BMI 31	25% after 3.3 years
Finnish DPS (diet + exercise)	522	IGT adults, mean age 55 years, mean BMI 31	58% after 3.2 years
DPP (diet + exercise, or metformin)	3,234	IGT adults, mean age 51 years, mean BMI 34	Metformin 31%, lifestyle 58% after 2.8 years
Xendos (orlistat + diet + exercise)	3,305	Swedish, BMI >30, mean age 43 years, 21% with IGT	Entire group 37%, IGT subgroup 45% after 4 years
DREAM (rosiglitazone)	5,269	IGT and/or IFG subjects, mean age 54.7 years, BMI 30.9	62% after approximately three years

prevented progression from IGT to diabetes, but were also effective in restoring NGT in a substantial proportion of subjects with initial IGT.[3]

Drug Intervention

Table 2 summarises some intervention studies to halt the progression from pre-diabetes to type 2 diabetes. In the DPP, subjects with pre-diabetes assigned to metformin treatment experienced ~30% reduction in the rate of progression to diabetes.[3] Acarbose[13] and orlistat[14] have also been reported to significantly reduce progression to diabetes, but, like metformin, the efficacy of these medications was weaker than that of lifestyle intervention. In contrast, rosiglitazone has been reported to reduce progression by >60%, which approximates to the effect of lifestyle modification alone.[6] Preliminary data presented at the ADA Annual Scientific meeting in June 2008 indicate that another thiazolidinedione drug, pioglitazone, was highly effective in preventing progression to diabetes. In general, drug-mediated prevention of diabetes is plagued with risks from the adverse effects of the specific drugs, medication costs, the need for long-term medication and consequent adherence problems. Furthermore, current

experience indicates that these medications may need to be administered indefinitely, as there is a high likelihood of glycaemic rebound following their cessation.[15] Based on these limitations, the prospects of a drug-based strategy for diabetes prevention in the general population seems quite uncertain. The occurrence of glycaemic rebound following withdrawal of medication[15] indicates that the drug interventions tested so far have not fundamentally altered the underlying pathobiology of pre-diabetes. The ideal drug for diabetes prevention should be well-tolerated, match or exceed the efficacy of lifestyle intervention, repair the pathophysiological defects that underlie pre-diabetes and return the patient to pristine glucose metabolism. Such a drug should exert a durable effect that outlasts the period of medication exposure. The latter property would allow the medication to be withdrawn after a defined period of intervention, without the risk of immediate or short-term relapse of pre-diabetes. Moreover, the cost of such a drug must not be prohibitive, given the large number (>57 million) of people with pre-diabetes who may be eligible for treatment. Although no currently approved drug meets all of the stated criteria, it may be possible to design a drug or combination of agents that can meet most of the desired criteria. A compound that improves insulin sensitivity through induction of significant weight loss, while concomitantly improving beta-cell function through cellular augmentation or regeneration, could have a durable effect in reversing the natural history of pre-diabetes. The emerging drugs in the superfamily of incretins, incretin analogues and incretin mimetics offer some glimmer of hope, and need to be tested alone and in combination with other proven agents in future diabetes prevention studies.

Lifestyle Modification plus Medication

It is conceivable that at-risk persons who are suboptimally adherent to lifestyle modification may benefit from adjunctive medication. However, the additive effect of lifestyle intervention and medications in the population with pre-diabetes has not been well-studied. Carefully designed new clinical trials are needed to test the efficacy of combination interventions, using lifestyle and selected medications, on the outcome of pre-diabetes.

Primary Prevention of Cardiovascular Disease in Pre-diabetes

The DPP investigators assessed the effects of lifestyle intervention, metformin and placebo on CVD risk factors among IGT subjects.[16] Compared with the placebo and metformin arms, subjects assigned to lifestyle intervention showed decreased blood pressure, increased HDL cholesterol levels, lower triglycerides levels and a reduced need for antihypertensive and lipid-lowering medications during approximately three years of follow-up. Also, lifestyle intervention reduced the crude incidence of hypertension by 33% in the DPP lifestyle group.[16,17] Increased physical activity and dietary modification constitute the cornerstone of non-pharmacological intervention for diabetes prevention. These lifestyle measures also help decrease cardiometabolic risk. Regular physical activity improves insulin action, blood pressure and lipid levels and decreases

obesity, among other benefits. Notably, the pro-atherogenic visceral fat compartment is quite sensitive to physical activity, and decreases in waist circumference often occur early during lifestyle change.[18] The recommended goal for most people is 30–60 minutes of moderate-intensity aerobic exercise repeated three or more times per week. Programmes should be tailored to the physical condition of individual patients, and should always include warm-up and cool-down periods. Cardiac screening is advisable for patients 35 years of age or over, especially if they have been sedentary. Dietary practices that restrict saturated fat intake, with augmentation of dietary fibre, fruits and vegetables, offer distinct metabolic and cardiovascular benefits.[19] Fat intake should be limited to ~30% of total calories (saturated fat should be <7%) and transfatty acids should be eliminated.[20] The Mediterranean diet, based on generous servings of fruits, vegetables and nuts, improves cardiometabolic risk profile and decreases morbidity and mortality.[21–23] However, in the DPP,[16] the level of low-density lipoprotein (LDL) cholesterol was not significantly altered by lifestyle intervention (although a reduction in the more atherogenic small, dense LDL particles was observed), which indicates that adjunctive therapy with a statin drug may be necessary for selected high-risk patients.[24] Previously, the STOP-NIDDM study group had reported a large effect of acarbose treatment in reducing clinical CVD events[25] among subjects who initially had pre-diabetes. However, such an effect has not been reported by the other medication-based diabetes prevention studies.[3,6,14]

Conclusion

Dietary modification, regular physical activity, smoking cessation and other lifestyle changes have been shown to exert favourable effects on glycaemia, blood pressure, bodyweight, fat distribution and lipid and lipoprotein profiles, among other metabolic and psychological benefits. Lifestyle interventions have also been demonstrated to be effective in the primary prevention of type 2 diabetes. These consistent metabolic and cardiovascular benefits make the implementation of lifestyle intervention a public health imperative. The ADA[1] has suggested criteria for screening individuals at risk of pre-diabetes. Persons who test 'positive' for pre-diabetes should receive lifestyle intervention similar to that used in the DPP.[3] In the DPP, the benefits of lifestyle change were observed universally across all age and BMI groups, whereas the effect of metformin was restricted to young obese persons.[3,26] The reported epigenetic effects of lifestyle intervention on the expression of pro-inflammatory and glucoregulatory genes[27,28] provide exciting novel insights into behavioural modulation of disease genes. Although several medications have been reported to reduce progression to diabetes, for the millions of people with pre-diabetes lifestyle modification is the compelling option because of its minimal toxicity and superb efficacy compared with medications. ■

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