Prediabetes

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Pre-diabetes is a metabolic condition characterized by insulin resistance and primary or secondary beta cell dysfunction which increases the risk of developing type 2 diabetes mellitus.¹ It is used to describe the intermediate state of abnormal glucose metabolism in which blood glucose levels are higher than normal, but not yet in the range necessary for diagnosis of diabetes. The concept of prediabetes arose in 1950's when high perinatal mortality was reported in pregnancies before diagnosis of diabetes mellitus.² Prediabetes was included in the classification of glucose tolerance in the 1965 WHO Expert Committee Report on Diabetes Mellitus.

Diagnosis of Prediabetes

The term impaired glucose tolerance (IGT) was introduced by the National Diabetes Data Group (NDDG) in 1977 and later adopted by WHO. IGT is defined as a 2-hour blood glucose level of 140-199 mg/dl after a 75 gm oral glucose tolerance test (OGTT). The American Diabetes Association (ADA) in 1997 revised the diagnostic criteria for diabetes mellitus (DM) and other categories of glucose intolerance and recommended the recognition of a new category of impaired fasting glucose (IFG), defined as fasting blood glucose 110 to 125 mg/dl.³ Several studies in different ethnic groups disclosed that there was lack of agreement between IGT, a known risk factor for DM and cardiovascular disease, and IFG, the pathological significance of which was undetermined. Fasting plasma glucose 100mg/dl has been found to be closer to a two-hour cut-off of 140mg/dl in terms of the sensitivity for future diabetes. Thus, reducing the lower limit for IFG to 100mg/dl

yielded a group that identified the same proportion of the population as the IGT group as well as a similar number of future cases of diabetes. On the basis of these findings, the Expert Committee on Diagnosis and Classification of Diabetes Mellitus (2003) recommended that the lower limit for diagnosis of IFG be reduced from 110 to 100 mg/dl.⁴ The ADA in 2004 adopted the term 'prediabetes' to designate patients with increased risk of diabetes (IGT and IFG). Recognizing the continuous relationship between glycemia and risk of diabetes and its complications, the 2010 American Diabetes Association (ADA) guidelines now more formally refer to impaired fasting glucose (IFG) and IGT as "categories of increased risk of diabetes" with risks extending continuously even beyond the defined categories. Box 1 summarizes the categories of increased risk for diabetes.

Hemoglobin A1c (A1C) is a widely used marker of chronic glycemia and is now recommended to diagnose

Box 1. Categories of increased risk for diabetes (Prediabetes)

- **Impaired fasting glucose (IFG):**
FPG 100 mg/dl (5.6 mmol/l) to 125 mg/dl (6.9 mmol/l)
OR
- **Impaired Glucose tolerance (IGT):**
2-h PG in the 75-g OGTT 140 mg/dl (7.8 mmol/l) to 199 mg/dl (11.0 mmol/l)
OR
- **HbA1C 5.7–6.4%**

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diabetes, with a threshold of $\geq 6.5\%$.⁵ The Expert Committee noted that those with A1C levels above the laboratory "normal" range but below the diagnostic cut point for diabetes (6.0 to < 6.5%) are at very high risk of developing diabetes. Indeed, incidence of diabetes in people with A1C levels in this range is more than 10 times that of people with lower levels.⁶⁻⁹ Prospec-

tive studies indicate that people within the A1C range of 5.5–6.0% have a 5-year cumulative incidence of diabetes that ranges from 12 to 25%,⁶⁻⁹ which is appreciably (three- to eightfold) higher than incidence in the U.S. population as a whole.¹⁰ Analyses of data from the National Health and Nutrition Examination Survey (NHANES) indicate that the A1C value that most accurately identifies people with IFG or IGT falls between 5.5 and 6.0%. Among the nondiabetic adult population, an FPG of 110 mg/dl (6.1 mmol/l) corresponds to an A1C of 5.6%, while an FPG of 100 mg/dl (5.6 mmol/l) corresponds to an A1C of 5.4%. Compared to the fasting glucose cutpoint of 100 mg/dl (5.6 mmol/l), an A1C cutpoint of 5.7% is less sensitive but more specific and has a higher positive predictive value to identify people at risk for later development of diabetes. A large prospective study found that a 5.7% cutpoint has a sensitivity of 66% and specificity of 88% for the identification of subsequent 6-year diabetes incidence.¹¹

Epidemiology

It is estimated that the world wide prevalence of diabetes will increase from 6.0% in 2007 to 7.3 % in 2025, the age group of 20 – 79 years and the number of diabetic subjects will correspond to 246 and 380 millions respectively. The corresponding prevalence of impaired glucose tolerance (IGT) in the same age group would be 8% and the number with IGT will be 418 millions in 2025.¹² In a study from Kashmir valley, the data of 5083 apparently healthy individuals, who were given OGTT, were analyzed applying ADA criteria. The prevalence of prediabetes in this study population was 26.5%; IFG occurred in 985 (19.5%) subjects and IGT in 167 (3.3%), while 194 (3.8%) subjects had both IFG and IGT.¹³

Pathophysiology of Prediabetes

The state of prediabetes is heterogenous with respect to the nature of metabolic defect, the pattern of hyperglycemia, and the cardiovascular risk. Pathogenesis of prediabetes is similar to type 2 DM. It involves complex interplay of two basic defects; insulin resistance and B-cell failure, the magnitude of which is less as compared to overt type 2 DM.¹⁴ Individuals with isolated IFG and isolated IGT show similar impairments in insulin action, but those with isolated IFG have a more pronounced defect in early insulin secretion and, in addition, increased endogenous glucose output. In IGT, the glycemic excursions after each meal are high and the early insulin responses to meals tend to be lower than normal, but the second phase is delayed and prolonged. Postchallenge hyperglycemia, including IGT, is characterized by greater skeletal muscle (peripheral) insulin resistance and compensatory hyperinsulinemia than IFG.¹⁰ More severe metabolic abnormalities are present in individuals with combined IFG and IGT.¹⁰ Little difference has been observed between individuals with IFG and IGT in terms of lipid levels or BP, although levels tend to be higher than normal subjects in both

cases. IGT and IFG are not equivalent metabolically, and it is therefore not surprising that there are differences in their prevalence and in the people categorized as having one or the other. In most populations, IGT is more prevalent than IFG. Furthermore, there is some degree of overlap between the categories but the majority of people with IGT do not have IFG, and the majority with IFG do not have IGT.

Individuals who meet criteria for IGT or IFG may be euglycaemic in their daily lives as shown by normal or near-normal glycated hemoglobin levels. IGT is often associated with the metabolic syndrome. Hyperglycemia is seldom an isolated metabolic abnormality and is often the consequence of abdominal obesity followed by insulin resistance, and is therefore commonly accompanied by an atherogenic dyslipidemia profile as well as by altered fibrinolysis and inflammatory markers.

Relationship with diabetic complications

Prediabetes is associated with a significant degree of risk for both macrovascular and microvascular pathology. IGT has been found to result in complications traditionally attributed to diabetes. These complications include primarily macrovascular (myocardial infarction and stroke), and microvascular disease (retinopathy, microalbuminuria, and polyneuropathy). The retinopathy said to be linked to the prediabetic states have all been of background diabetic retinopathy. IFG has been associated with elevated risk of retinopathy but not with microalbuminuria or peripheral neuropathy. The thresholds associated with microvascular and macrovascular clinical events are different. Data from the Diabetes in Egypt Project found that patients in the fasting glucose range of 98 to 108 mg/dl had a 4% prevalence of diabetic retinopathy, compared with 13% prevalence among patients in the fasting glucose range of 108 to 130 mg/dl.¹⁵

Natural History of Prediabetes

Overall, prediabetes confers about a six fold increased risk of diabetes compared with normal glucose tolerance; about 3%–10% of people per year with prediabetes develop diabetes. In the Diabetes Prevention Program, in subjects who had IGT, with or without IFG, there was about a 10% annual rate of progression to diabetes in the control group.¹⁶ Other studies have shown similar or somewhat lower rates for progression from IGT or IFG to diabetes. The combination of IFG and IGT confers a greater risk of diabetes than either category alone. In most populations studied, the rates of conversion from IFG and IGT to diabetes are similar, with IGT having greater sensitivity but less specificity than IFG in predicting diabetes risk. Each category has a similar positive predictive value. Many people with prediabetes (a quarter or more) may revert long term to having normal glucose tolerance, and after a protracted follow-up, only about 50% of people with IGT or IFG will develop diabetes. The Baltimore Longitudinal Study observed

815 individuals over 6-20 years with regular oral glucose tolerance tests.¹⁷ At baseline, about 60% had normal glucose tolerance, 33% had prediabetes, and 8% had diabetes. Of those with normal glucose tolerance at baseline, progression to IGT occurred in 10 times more participants than to IFG (39% versus 4%). Those with an elevated 2-hour plasma glucose level either alone or with an elevated fasting plasma glucose level progressed more rapidly to diabetes; 22% subjects with prediabetes progressed to diabetes at 10 years. IGT was a stronger predictor of progression than IFG. In the control groups of various intervention studies, rates of progression to diabetes are 6%-11% per year. This progression from normal to abnormal glucose tolerance thus occurs gradually, over years, allowing ample opportunity for prevention.

Impact on cardiovascular disease

Numerous reports have documented that CVD risk is increased in prediabetes by 10% to 40% compared with populations with normal glucose regulation.^{18,19} Increased rates of the cardiovascular risk factors found in people with type 2 diabetes such as increased serum triglyceride levels, decreased HDL cholesterol levels, hypertension and central adiposity are more common in adults with prediabetes compared with those with normal glucose tolerance, but less so than in people with type 2 diabetes. When other known CVD risk factors, such as hypertension and lipid abnormalities, are adjusted for statistically, IGT, but possibly not IFG, remains an independent CVD risk factor. An increasing plasma glucose level in IGT is associated with a greater risk of cardiovascular death. Endothelial dysfunction characterized by a decrease in the bioavailability of endothelial nitric oxide (NO), seems to be an initiating event in individuals with IGT and T2DM. Insulin resistance plays a significant role in the development of atherosclerosis. In vascular endothelium, the phosphatidylinositol 3-kinase (PI3-kinase)-dependent insulin signaling pathway regulates the production of NO via stimulation of endothelial nitric oxide synthase (eNOS) activity. Signaling via the PI 3-kinase pathway is impaired in states of insulin resistance in all insulin sensitive tissues, including endothelial cells, thus leading to reduced production of NO and attenuation of its beneficial vascular effects. Signaling via the mitogen-activated protein kinase (MAP-kinase) pathway mediates the growth-promoting effects of insulin and remains intact in insulin-resistant states. In the setting of resistance in the PI 3-kinase pathway, there is compensatory hyperinsulinemia, and thus promotion of mitogenesis (cell proliferation) and vasoconstriction, factors that promote atherosclerosis.^{20,21} Adipose tissue is a rich source of proinflammatory mediators that may directly contribute to vascular injury and atherosclerosis. These mediators include leptin, TNF- α , interleukin (IL)-6, resistin, and many others. C-reactive protein (CRP) an inflammatory marker has been shown to predict diabetes and CVD. Treatment of postprandial glycemia led to reduced CRP levels, improvement in

endothelial dysfunction and reduced progression of IGT to diabetes.²²

Management of Prediabetes

Conventionally hyperglycemia is treated when it is clinically overt. However, this approach has two drawbacks—i) at least on an average 6-8 years are lost by the time clinically manifest DM occurs, which in turn will cause extensive vascular damage and ii) achieving and maintaining long-term intensive glycemic control at the stage of overt diabetes is difficult and often unsuccessful. Prediabetes must be recognized and treated, not only because it portends the possible development of type 2 diabetes but also because it can be associated with the metabolic syndrome, which carries a high risk for cardiovascular disease. The modifiable risk factors for the development of diabetes mellitus include physical inactivity, obesity, hypertension, dyslipidemia and prediabetes. Major diabetes prevention trials have primarily targeted these modifiable risk factors.

Lifestyle modification

Intensive lifestyle changes have demonstrated reduction in progression from prediabetes to diabetes, and weight reduction with dietary intervention and exercise appears to be the most cost effective option. Modest weight reduction (5 to 10%) forms the cornerstone in the treatment as well as prevention of diabetes mellitus. Dietary recommendations should include use of complex carbohydrates having low glycemic index, and reduced total fat and saturated fat intake to < 30% and < 10% of total daily calories, respectively. Exercise improves insulin sensitivity, induces weight loss, controls hypertension, and makes lipid profile less atherogenic, thus resulting in favorable effects on cardiovascular risk factors. Based on several landmark clinical trials, a planned, regular exercise programme is favored first line non-pharmacologic option in persons at high risk of developing diabetes.

The Diabetes Prevention Program (DPP) randomized 3234 subjects with prediabetes to one of four groups - intensive lifestyle intervention, metformin, troglitazone, and placebo.¹⁶ Patients were counseled to reduce fat intake and consume fewer calories. The target weight loss was at least 7% of total body weight. Patients were also counseled on the need for physical activity, with a goal of at least 150 minutes per week. Troglitazone therapy was stopped after about 10 months because one patient developed fatal liver failure. The study was discontinued prematurely because the results showed compelling evidence of superiority of lifestyle changes in preventing diabetes. At 2.8 years, patients treated with lifestyle intervention had a highly significant 58% reduction in the rate of new-onset type 2 diabetes as compared to placebo. The reduction was consistent among both sexes and all ethnic groups. The number needed to treat (NNT) for 3 years of intervention with lifestyle modification was 6.9. In contrast,

patients randomized to metformin 850 mg twice a day had a 31% reduction in new-onset diabetes. In the follow-up at 10 years in the U.S. Diabetes Prevention Program Outcome Study (DPPOS) a sustained 34% reduction in the rate of conversion to diabetes was reported.²³

The Finnish Diabetes Prevention study (DPS), randomized 522 overweight subjects with IGT to intervention group (weight reduction, diet modification and exercise) or control group.²⁴ The cumulative incidence of diabetes at 4 years was 11% in the intervention group and 23% in the control group. Lifestyle modifications were directly associated with a 58% reduction in incidence of DM; the NNT to prevent one case of DM in 4 years was 8. Subjects who did not lose weight but achieved the targets for exercise (at least 4 hours per week) also had significantly decreased incidence of diabetes.

The Indian Diabetes Prevention Programme was a community based randomized controlled study in 531 subjects (421 men and 110 women) who had persistent IGT on two GTT tests.²⁵ Their age (mean 45.9 ± 5.7 years) and BMI (25.8 ± 3.5 kg/m²) were significantly lower than in DPP and in DPS cohorts. In a median followup period of 30 months, a high rate of conversion to diabetes was noted (18.3 %/year). The relative risk reduction with interventions was 28.5%. LSM and metformin were equally effective in reducing the incidence of diabetes (cumulative diabetes incidence 39.5% vs 55% in controls) and there were no additional benefits by combining both.

Pharmacologic interventions

Using drugs that improve insulin sensitivity as early as possible in the course of diabetes seems likely to help modify disease progression, especially if combined with medical nutrition therapy and physical activity.

Metformin

Metformin is the most widely used insulin sensitizer for new-onset diabetes mellitus in overweight or obese individuals. It suppresses hepatic glucose production and inhibits free fatty acid production, thus reducing insulin resistance and improving peripheral glucose uptake. In the DPP study, after 3 years of treatment, metformin at a dose of 850 mg twice a day failed to show its superiority over lifestyle modification in preventing onset of diabetes.¹⁶ Its low cost, reasonably safe side-effect profile and tolerability has made metformin an attractive agent in the drug therapy of prediabetes.

Thiazolidinediones

The thiazolidinediones (TZDs), PPAR- γ agonists, act as insulin-sensitizing agents and decrease peripheral insulin resistance. These drugs reduce endogenous insulin requirement and stress on the pancreatic β -cells, thus preserving their function. This group of drugs has been extensively evaluated in prediabetes. Troglitazone, the first TZD was evaluated for prevention of DM in women with prior gestational diabetes mellitus in the Troglitazone in Prevention of Diabetes (TRI-

POD) study.²⁶ This study demonstrated a 56% reduction in relative risk of progression of prediabetes to diabetes as compared to placebo at 1.5 years of follow-up. The drug was discontinued in the year 2000 because of reports of hepatic toxicity. In a subsequent study, the PIPOD study, 95 eligible women who had completed the TRIPOD study and had post trial HbA1c <7% were enrolled.²⁷ Participants received pioglitazone in the dose of 30 mg/day, later increased to 45 mg/day in addition to dietary advice and prescribed exercise for a period of 3 years. New-onset diabetes occurred only 4.6% per year with pioglitazone for 3 years and 6 months of post drug washout as compared to the rate of 12.1% per year observed during placebo treatment in the TRIPOD study. In the DREAM trial Rosiglitazone at 8 mg daily for 3 years was shown to decrease the incidence of DM by 60% as well as induce regression to normoglycemia by 70% to 80% compared with placebo.²⁸ Mean weight gain of 2.2 kg occurred in patients randomized to rosiglitazone. At present the controversies associated with use of TZDs limit their use in prevention of diabetes.

Enteric enzyme inhibitors

Inhibition of both α -glucosidase and lipase has been studied in the setting of prediabetes, examining the impact of relative malabsorption on diabetes incidence. The α -glucosidase inhibitors decrease postprandial glucose levels by delaying carbohydrate absorption from the gut. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) evaluated the efficacy of these agents in prevention of diabetes.²⁹ This study included 700 patients with IGT and fasting blood glucose between 100 and 139 mg/dl with BMI 25 to 40 kg/m². Acarbose was given at a starting dose of 50mg/day and increased to a maximum of 100 mg thrice daily or to maximum tolerated dose. After a mean follow-up of 3.3 years, acarbose reduced the relative risk of developing DM by 25% as compared to placebo. Because of lack of systemic adverse effects acarbose may play an important role in the prevention of diabetes in patients who can tolerate the gastrointestinal side effects. Orlistat, a lipase inhibitor blocks fat absorption, resulting in weight loss either through steatorrhea or through behavior modification of eating behavior. In the double-blind, prospective XENDOS study, 3305 obese subjects (BMI ≥ 30 kg/m²), were randomized to lifestyle changes plus either orlistat 120mg or placebo, three times daily over 4 years.³⁰ Orlistat was shown to reduce the incidence of T2DM by 37.3% compared to placebo in 694 patients with IGT. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $p < 0.001$).

Other drugs

Nateglinide is a non-sulfonylurea secretagogue which stimulates rapid short-duration secretion of insulin. In a multicentre, randomized, placebo-controlled trial, nateglinide,

in lower doses of 30mg or 60mg was proved to be safe and effective in reducing postprandial hyperglycemia in patients with IGT. Statins (HMG Co A-reductase inhibitors) apart from the lipid-lowering action exhibit anti-inflammatory, anti-atherosclerotic, renoprotective and glucose lowering effects. In the WOSCOPS study, the use of pravastatin after adjustment for other risk factors was found to result in a 30% reduction in the development of diabetes.³¹

Several studies in hypertensive high cardiovascular risk patients have reported reduction in the incidence of DM by inhibition of renin-angiotensin system (RAS). Both angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have shown this effect in trials where diabetes prevention was not specified as primary outcome. ACEIs and ARBs enhance insulin sensitivity and therefore benefit patients with abnormal glucose metabolism.³²

Antiobesity medications

Because of the effects of obesity on insulin resistance, weight loss is an important therapeutic objective for overweight or obese individuals who are at risk for diabetes. Weight reduction via medications and surgery has also been shown to help prevent and treat diabetes. Anti-obesity drugs not only produce weight loss but also improve blood glucose levels in patients with diabetes. Orlistat and rimonabant have been evaluated in obese patients with prediabetes. Orlistat promotes weight loss by reducing dietary fat absorption from intestines and has modest weight reducing efficacy with unpleasant gastrointestinal side effects that limit its use in many patients.³⁰ Rimonabant, a selective cannabinoid-1 receptor blocker, is a weight-reducing agent that appeared to have promising effects on weight loss and metabolic risk factors. Due to concerns of depression with suicidal tendencies it has not been approved by US FDA as yet for use in obesity. The RIO (Rimonabant in Obesity) program comprising four double-blind trials compared rimonabant, 5 to 20 mg daily, with placebo in more than 6600 individuals over 1 to 2 years.³² In addition to significant weight loss (6.9 kg for 10 mg rimonabant compared with 1.7 kg for placebo; $p < 0.001$) and reduction in waist circumference, rimonabant significantly decreased fasting plasma insulin, 1- and 2-hour plasma glucose and insulin concentrations during a 75gm OGTT

Bariatric surgery

Bariatric surgical procedures affect weight loss by limiting calorie intake as a result of mechanical obstruction or by impairing nutrient absorption through intestinal bypass. Significant weight loss is seen in most subjects able to tolerate the procedures. These procedures also result in significant incretin hormone changes with remarkable increases in glucagon-like peptide 1 well before weight loss occurs. The Swedish Obese Subjects (SOS) study followed obese subjects who underwent gastric surgery with matched obese subjects for up to 10 years.³³ Of the 4,047 obese patients, surgery resulted in a 23% weight loss after 2 years; the rate of new-onset

diabetes was reduced by 32-fold in the group of patients undergoing bariatric surgery compared with control group treated with standard therapies. This effect was consistent, although less pronounced in 1703 subjects followed up to 10 years. In another study, 608 subjects were followed for 14 years after gastric surgery. The weight reduced from a preoperative mean of 304 lb to 192 lb in one year, 205 lb in 5 years and 206.5 lb at 10 years; while 82% of diabetic subjects attained normal levels of blood glucose and HbA1c, 98.7% of those with IGT attained normal glucose levels.

Recommendations for Prediabetes screening

ADA has proposed screening recommendations for prediabetes to be done as part of a health care visit in individuals with age ≥ 45 years especially those who are overweight and, in individuals who are < 45 years and overweight in presence of other risk factors such as first degree relative with diabetes, history of gestational diabetes, high risk ethnicity, hypertension, dyslipidemia, polycystic ovarian syndrome and habitual inactivity.³⁴ If the results are normal, it is recommended to repeat the screening tests every three years. People with prediabetes are at high risk of developing diabetes and cardiovascular disease and are the ideal target population for prevention programs. The demonstration that type 2 DM is preventable raises hope for the possibility of concomitant prevention of CVD morbidity and mortality and progression to future DM associated with prediabetes. At the same time, screening and proper treatment of the other risk factors for atherosclerosis are also recommended, such as smoking, hypertension, and dyslipidemia.

When to treat prediabetes

The decision to initiate therapy for prediabetes should be undertaken with the full understanding of provider and patient that any therapy requires a long-term commitment.

Ongoing monitoring of metabolic status and potential therapeutic side effects are required with treatment modification undertaken if goals are not achieved or intolerable side effects are encountered. There are no clear cut recommendations regarding when to start treating patients with prediabetes. However, it is never too early to educate individuals who are overweight and at risk for diabetes about weight maintenance or weight reduction and physical activity. If they smoke, they should be encouraged to quit and referred to a smoking cessation program. Patients should be treated aggressively for CVD risk, particularly if they have the metabolic syndrome, dyslipidemia, or hypertension. The appropriate intervention for people with prediabetes who are overweight or obese should be intensive lifestyle intervention, aiming to achieve a minimum of 5 to 7% body weight loss, with reduced total fat and saturated fat intake, optimal dietary fiber intake, and 150

minutes of physical activity per week. It is recommended that a minimum 6 months of lifestyle intervention be tried before pharmacotherapy is considered. Pharmacotherapy particularly with metformin should be recommended for very-high-risk individuals (those with a history of GDM, the very obese, and/or those with more severe or progressive hyperglycemia). Other options include acarbose, orlistat or thiazolidinedione.

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