Dysglycemia/Prediabetes and Cardiovascular Risk Factors

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Obesity and diabetes are becoming a pandemic in developing and industrialized countries. Based on the current criteria, 24.1 million Americans have diabetes, and another 57 million have prediabetes. The term prediabetes *refers to people who have impaired fasting glucose (100-125 mg/dL), impaired glucose tolerance (2-hour postglucose load of 140-199 mg/dL), or both. Many persons with prediabetes already have microvascular disease consequences (eg, blindness, amputations, kidney failure) similar to those seen in patients with a diagnosis of diabetes. However, it is not established whether prediabetes should be considered a coronary heart disease risk equivalent. Whether dysglycemia is a surrogate for a more complex metabolic condition and/or directly increases cardiovascular disease (CVD) risk remains unclear. However, many studies have shown that hyperglycemia, through various mechanisms, can lead to premature atherosclerosis. In this regard, several diabetes prevention trials have shown that strategies that reduce the rate of conversion to diabetes can also modify CVD risk factors.*
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Key words: Prediabetes • Cardiovascular risk • Impaired fasting glucose • Impaired glucose tolerance • Dysglycemia

Dysglycemia is a qualitative term used to describe elevated blood glucose levels that do not meet the diagnosis of diabetes. In 2002, the American Diabetes Association (ADA) defined prediabetes as a condition in which blood glucose levels are elevated above the normal range but do not satisfy the criteria for the diagnosis of diabetes mellitus. Prediabetes is defined by the World Health Organization as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both. IFG, in turn, is defined as a fasting plasma glucose level equal or above 100 mg/dL up to 125 mg/dL, and IGT is defined as a 2-hour postprandial glucose (PPG) load level between 140 mg/dL and 199 mg/dL.[1]

Prevalence

The Australian Diabetes Study showed that the prevalence of IGT in adults aged 25 years and older was 10.6%, with a higher rate in women than men (11.9% vs 9.2%). The prevalence of IFG was 5.8%, with a higher rate in men than women (8.1% vs 3.4%). The overall prevalence of prediabetes in the Australian population was 16.4%.[1] In the US population, about 57 million people have prediabetes.[2] The number of prediabetic patients is dramatically increasing worldwide. It was estimated that in 2003, 314 million people developed prediabetes. By the year 2025, the number may reach 472 million (9% of the adult population) worldwide. In general, the prevalence of prediabetes is more common in men than in women, differs between regions, and increases with age. The prevalence of prediabetes is also higher in patients with other risk factors for prediabetes (eg, those with hypertension, obesity, dyslipidemia and/or the cardiometabolic syndrome, or relatives who have diabetes).[3]

Clinical Significance of Prediabetes

A meta-analysis of 20 studies published between 1979 and 1995 found an exponential relationship between the incidence of cardiovascular disease (CVD) events and plasma levels of fasting glucose or PPG, with a stronger association for PPG.[4] Furthermore, in the Funagata Diabetes Study in Japan, which followed patients with IGT/IFG for 7 years, IGT, but not IFG, was a risk factor for CVD.[5,6]

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study, which reviewed 13 epidemiologic studies, found that the mortality risk was increased by 1.5-fold in persons with IGT and by 1.2-fold in those with IFG when compared with normoglycemic persons. Subsequent analysis of the DECODE study showed that the relative mortality risk correlated with postload glucose values but not with fasting plasma glucose levels, even after adjusting for body mass index, blood pressure (BP), total cholesterol, and smoking. Furthermore, there was a linear increase in the hazard ratio for all-mortality causes as the 2-hour blood glucose increased from 95 mg/dL to 200 mg/dL.[2]

The Cardiovascular Health Study followed 4515 American men and women ages 66 and older for 8 years and found that the relative risk for CVD mortality was 1.22 in glucose intolerant subjects as compared with normoglycemic subjects.[4] An analysis of the National Health And Nutrition Examination Survey (NHANES) from 1999 to 2002 found an association between modest elevations in hemoglobin A_{1c} levels and peripheral arterial disease, even after adjusting for other variables.[6]

Data from the Baltimore Longitudinal Study on Aging indicated that there was no difference between persons with normal glucose tolerance and IFG in regard to baseline coronary heart disease (CHD) risk factors. However, CHD risk factors were significantly greater in those with IGT or IFG and IGT.[7] These findings suggest that the relative risk for CHD in persons with IGT is greater than in those with IFG. Indeed, persons with IGT (when compared with normoglycemic subjects) are at greater risk for death from all causes and have an increase in total and nonfatal myocardial infarction (MI) and stroke, regardless of whether they progress to diabetes or not.

IGT also increases the risk of microvascular complications, such as neuropathy, retinopathy, and proteinuria.[8] As an example, the prevalence of polyneuropathy is 28.0% in the diabetic subjects, 13.0% in those with IGT, 11.3% in those with IFG, and 7.4% in those with normal glucose tolerance.[9] In another study, it was found that retinopathy consistent with diabetic retinopathy was detected in 12.6% of subjects with diabetes and 7.9% of subjects with prediabetes.[10]

In this context, an offspring of the Framingham study of 3370 subjects with a mean age of 54 years and no diabetes was followed for 4 years. During this time, 118 CVD events occurred. Subgroup analysis showed that fasting glucose, PPG, and hemoglobin A_{1c} values were all significantly correlated with the onset of CVD events, with PPG having the highest risk. Finally, a 20-year follow-up of women in the Nurses' Health Study showed that nonfatal MI or stroke increased significantly prior to diagnosis of diabetes during follow-up.[11]

Pathogenesis and Detection

The pathogenesis of prediabetes, as in type 2 diabetes, is linked to tissue insulin resistance causing elevated blood glucose levels despite secondary high insulin levels.[1,12] Some suggest that IFG is associated with hepatic insulin resistance and that IGT is associated predominantly with skeletal muscle insulin resistance.[1,13] Prediabetes can be detected with a fasting glucose test and a 2-hour PPG test following a 75-gm glucose load (Figure 1).

Insulin Resistance

The San Antonio Heart Study found that there was a significant association between baseline homeostasis model assessment of insulin resistance quintile (which reflects the level of insulin resistance) and the risk for CVD events, even after

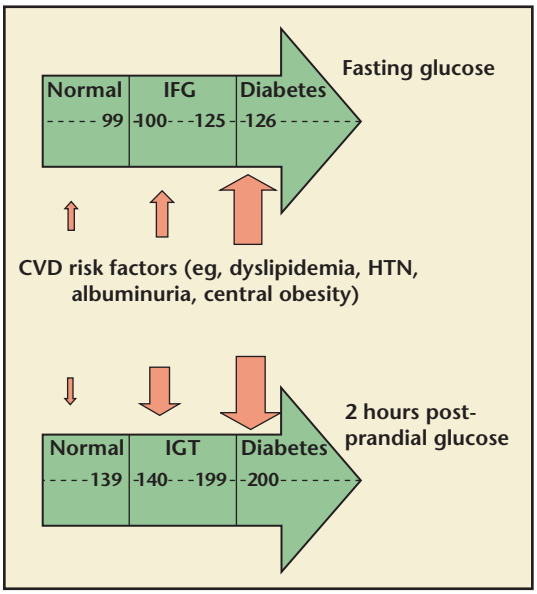

Figure 1. *Prediabetes can be detected with a fasting glucose test and a 2-hour post-prandial glucose test following a 75-gm glucose load. IFG, impaired fasting glucose; CVD, cardiovascular disease; HTN, hypertension; IGT, impaired glucose tolerance.*

adjusting for levels of low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and systolic BP, smoking, alcohol consumption, and exercise.[11,14] These findings suggest that insulin resistance in the prediabetic state is associated with increased CVD risk, which is partially independent of other established risk factors.[11]

The predilection for CVD in insulin-resistant individuals likely reflects both small- and large-vessel disease. Small-vessel complications can be attributed to tissue ischemia caused by a failure of reactive vasodilation, which is mediated by nitric oxide (NO). Large-vessel complications, such as MI and stroke, are potentiated by inflammatory atherogenesis and defects of thrombolysis that allow clot formation.

Insulin resistance, free fatty acids (FFA), and inflammatory cytokines released from fat cells appear to be even more important than hyperglycemia in causing chronic endothelial damage. This may explain why some patients with insulin resistance can develop CVD even while they are still normoglycemic.[8] Vascular endothelial dysfunction is a major feature of all dysglycemic complications and it develops, in large part, as a consequence of acquired defects of bioavailable NO, which plays a major protective role against atherosclerosis (by causing vasodilation and inhibition of platelets adhesion).

Vascular NO is produced by endothelial NO synthase in response to insulin and other stimuli, including acetylcholine, bradykinin, and mechanical shear stress. NO diffuses locally to vascular smooth muscle cells to mediate arterial vasodilation.

Increased production of vascular reactive oxygen species (ROS) also plays an important role in the pathogenesis of vascular disease in persons with prediabetes. These ROS, in addition to being directly injurious, also bind to NO and convert it into peroxynitrite, which also damages the vascular endothelial cells. Dysglycemia is associated with increased ROS production which, in turn, decreases NO available for vasodilation. Hyperglycemia leads to increased aldose reductase activity that converts excess glucose to sorbitol, which is then metabolized by sorbitol dehydrogenase to fructose (polyol pathway). Sorbitol and fructose, to a greater extent than glucose, react nonenzymatically with proteins, lipids, and nucleic acids, and produce advanced glycation end products, which further induce ROS generation that consumes bioavailable NO. Insulin resistance, in part due to its adverse effects on NO bioavailability, is associated with increases in mitogenic signaling that lead to vascular smooth cell proliferation.[8] Thus, these insulin resistance–related abnormalities in NO bioavailability likely contribute to the increased propensity of vascular disease in persons with prediabetes.

Systemic inflammation also plays a key role in the pathogenesis of vascular disease associated with dysglycemia. In this context, data from the Insulin Resistance Atherosclerosis Study indicate that chronic subclinical inflammation is a component of the prediabetic state and is associated with insulin resistance, as indicated by the fact that levels of C-reactive protein, fibrinogen, and plasminogen activator inhbitor-1 were significantly greater in subjects who converted to diabetes than in subjects who did not convert.[11]

The Association of Dysglycemia and the Cardiometabolic Syndrome

The cardiometabolic syndrome is a constellation of risk factors, metabolic in origin, that are accompanied by increased risk for CVD and type 2 diabetes.[13] The National Cholesterol Education Program Adult Treatment Panel III definition of the syndrome is presented in Table 1.

Centrally deposited (visceral) adipose tissue particularly predisposes to the cardiometabolic syndrome. Visceral fat is predisposed to

Table 1
Clinical Identification of the Cardiometabolic Syndrome

Three or More of the Following Risk Factors:

Risk Factor	Defining Level
1. Abdominal obesity	
Men	Waist circumference > 40 inches
Women	Waist circumference > 35 inches
2. Triglycerides	≥ 150 mg/dL
3. HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
4. Blood pressure	≥ 135/≥ 80 mm Hg
5. Fasting glucose	≥ 110 mg/dL

Data from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[26]

macrophage infiltration and produces numerous inflammatory cytokines called adipokines that have various adverse actions on vascular, renal, hepatic, and skeletal muscular tissue. Visceral fat cells are less able to take up FFAs than peripheral adipose cells, which results in elevated FFAs and increased fat infiltration of the liver and skeletal muscle. This increase in fat infiltration contributes to the reduced metabolic signaling in these tissues. In this context, elevated FFAs inhibit insulin-stimulated peripheral tissue glucose uptake while promoting the development of metabolic dyslipidemia. Metabolic dyslipidemia is characterized by low plasma levels of HDL cholesterol, high plasma triglycerides, and elevated small, dense LDL cholesterol.[15] Increased inflammatory adipokines also promote systemic inflammation and thrombosis, increase oxidant stress, and contribute to hypertension and accelerated atherogenesis in association with the cardiometabolic syndrome. However, even after adjusting for known risk factors in cardiometabolic syndrome, including visceral adiposity, hyperglycemia still remains a risk factor for CVD in prediabetic persons.

Accordingly, patients with IGT or the cardiometabolic syndrome have been shown to be at a significantly increased risk of CVD mortality and should probably be treated as a CHD or diabetes mellitus equivalent.[2,16] According to this approach, treatment strategies should incorporate the BP and lipid goals currently established for patients with diabetes.

Management of Prediabetes

Once type 2 diabetes develops, cardiovascular and renal disease may continue to progress despite efforts to maintain plasma glucose levels in the normal range. At this stage, the progressive decline in glucose tolerance and consequent hyperglycemia is primarily due to a loss of β cell function. A preventative approach might be to begin aggressive glucose lowering, BP control, and LDL cholesterol treatment in individuals with IFG, IGT, or both before the diagnosis of overt diabetes or the development of CVD and microvascular complications.[17]

Lifestyle Intervention

Several randomized, prospective studies of subjects with prediabetes have shown beneficial effects of lifestyle intervention in preventing type 2 diabetes. For example, in the Diabetes Prevention Program, goals for the lifestyle intervention group included weight loss of 7% and moderate physical activity (brisk walking for a total of 150 minutes weekly). Although not all subjects achieved these goals, there was a 58% relative risk reduction in progression to diabetes in the lifestyle-intervention group compared with the control group.[18] Development of hypertension was also significantly decreased with intensive lifestyle intervention. Triglyceride levels fell in all treatment groups, but they decreased more with intensive lifestyle intervention. Although intensive lifestyle intervention significantly increased HDL cholesterol levels, total and LDL cholesterol levels remained similar among treatment groups. Lifestyle intervention also reduced levels of other CVD risk factors, such as C-reactive protein, compared with both placebo and, to a lesser degree, metformin. Finally, the incidence of cardiometabolic syndrome was reduced by 41% in the lifestyle group and by 17% in the metformin group compared with the placebo group.[6]

Using a similar lifestyle strategy in the Finnish Diabetes Prevention Study, after 3.2 years of follow-up, lifestyle intervention of people at high risk for diabetes was shown to prevent or postpone the onset of type 2 diabetes.[19] In addition to the lower risk for developing diabetes, almost all CVD risk factors were significantly reduced. At the end of the follow-up period, BP, plasma insulin, and serum triglyceride level were all

much lower in the intervention group than in control subjects.[6]

From these data, we can conclude that lifestyle modification is an important strategy that has a significant effect on lowering CVD risk factors as well as on the progression to new onset diabetes. In reality, lifestyle modification is a difficult task to achieve and maintain, and pharmacological intervention is often required.[20]

Pharmacologic Therapies in Prediabetic Patients

Metformin combined with standard lifestyle advice was one treatment tested in the Diabetes Prevention Program study. Metformin treatment was effective in reducing the incidence of new-onset diabetes compared with placebo (31% reduction), but it was not as effective as intensive lifestyle intervention (58% reduction). The Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) found that treatment with acarbose (an intestinal α glucosidase inhibitor) reduced the incidence of type 2 diabetes by 36% over a mean follow-up of 3.3 years as well as lowered BP.[19] A substudy of STOP-NIDDM found that acarbose slowed the progression of carotid vessel intima-media thickening (IMT) in prediabetic subjects as compared with placebo.[21]

In contrast to metformin, sulfonylurea medications do not prevent the conversion to type 2 diabetes or reduce the risk for CVD. In the Malmohus County Study, subjects who followed diet regulation with or without tolbutamide (a sulfonylurea) for a period of 10 years had a decrease in the incidence of diabetes that could not be attributed to tolbutamide. Despite the widespread use of sulfonylurea medications in the treatment of type 2 diabetes, their effect on CVD morbidity and mortality remains controversial.[17]

The role of thiazolidinediones in the treatment of prediabetes is unclear and in a state of evolution. For example, in the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study, rosiglitazone was found to reduce the risk of new-onset type 2 diabetes and to increase reversion to normal glucose tolerance when administered in addition to lifestyle modification.[20] No effect was found in terms of CVD events, although there was increased risk for heart failure in the subjects treated with rosiglitazone.[6] The use of both angiotensin-converting enzyme (ACE) inhibitors and angiotensin type 1 receptor blockers (ARBs) has been shown retrospectively to prevent or delay the incidence of type 2 diabetes. These studies include Heart Outcomes Prevention Evaluation (HOPE) (ramipril), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (lisinopril), the Losartan Intervention for Endpoint Reduction (LIFE) trial, and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.[17] In the prospective, randomized DREAM trial, among people with IFG or IGT, the use of the ACE inhibitor ramipril for 3 years did not significantly reduce the incidence of diabetes or death.[22] Ramipril treatment did, however, decrease glucose levels and lower hepatocellular enzyme levels, which suggests improvements in glucose metabolism. Mechanisms by which ACE inhibitors and ARBs may improve insulin metabolic signaling could include improved blood flow in the skeletal muscle microcirculation, which improves insulin and glucose delivery to the insulin-sensitive tissues.[3] These drugs may also interrupt the direct negative effects of angiotensin II on insulin metabolic signaling in skeletal muscle and liver tissue.

It is known that β-blockers and thiazide diuretics may negatively influence glucose metabolism. It is possible that the lower incidence of new-onset diabetes with ACE inhibitors and ARBs in some studies could just reflect the higher incidence of diabetes in the comparator group (treated with β-blockers or thiazide diuretics) rather than indicate a true reduction in risk attributable to the use of the ACE inhibitors or ARBs. Thus, our understanding of the extent that ACE inhibitors or ARBs positively influence glucose metabolism is still evolving.[17]

Drugs used in the treatment of obesity and dyslipidemia may also have an effect on the development of new-onset diabetes. In this context, patients treated with orlistat (a gastrointestinal lipase inhibitor) plus lifestyle modification over a 4-year period lost more body weight and had fewer cases of new-onset diabetes than those treated with lifestyle modification alone.[17] The effects of statins on the development of diabetes have been inconclusive. One study showed that pravastatin treatment reduced the risk of developing diabetes in men (ages 45-64 years) by 30%.[23] However, another study showed little, if any, protective effect of statins on the development of type 2 diabetes.[24] In the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, there was a trend toward an increase in new-onset diabetes with rosuvastatin therapy.[25]

Because people with prediabetes have a similar overall cardiometabolic syndrome risk as those with type 2 diabetes, the American College of Endocrinology consensus statement on the diagnosis and management of prediabetes (published in

July 2008) recommended intensive lifestyle management as the preferred treatment of persons with prediabetes and CVD risk factors. This approach was recommended in light of safety issues and based on the strong evidence of the efficacy of lifestyle approaches in improving blood glucose and reducing CVD risk factors. Additionally, prediabetic persons should receive the same antiplatelet therapy and aim for the same lipid and hypertension targets as patients with diabetes.

Pharmacologic therapy with metformin and/or acarbose may be considered in addition to lifestyle strategies. Strong evidence shows that these drugs are safe and cost-effective, and that they reduce the development of diabetes from prediabetes.[2]

Conclusions

Epidemiologic data support the idea that blood glucose is an independent risk factor for CVD. The relationship between hyperglycemia and the development of CVD is graded and continuous, and it starts even when blood glucose is in the so-called "normal range." Thus, it is important to screen high-risk patients as early as possible for dysglycemia and the cardiometabolic syndrome. Early detection should promote an earlier intervention, resulting in a greater impact on the risk reduction for CVD, as well as for new-onset diabetes. Lifestyle modification with moderate weight loss (5%-7%) is an effective intervention strategy when it can be achieved and maintained. If pharmacologic intervention is needed, metformin or acarbose should be considered to reduce the risk that new-onset diabetes, and its attendant CVD complications, will develop. In prediabetic patients, management of blood glucose—in addition to treatment of hypertension and achievement of goal lipid levels as recommended for patients with diabetes—will likely reduce the incidence of CVD. ■

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Main Points

- There is an exponential relationship between the incidence of cardiovascular disease (CVD) events and plasma levels of fasting glucose or postprandial glucose load, with a stronger association for the latter.
- Mortality risk is increased in persons with impaired glucose tolerance (IGT) and impaired fasting glucose as compared with normoglycemic persons.
- Centrally deposited (visceral) adipose tissue predisposes to the cardiometabolic syndrome.
- Patients with IGT or cardiometabolic syndrome have been shown to be at a significantly increased risk of CVD mortality and should probably be treated as if they had coronary heart disease or diabetes mellitus.
- Several randomized, prospective studies of subjects with prediabetes have shown beneficial effects of lifestyle intervention in preventing type 2 diabetes.
- Drugs used in the treatment of obesity and dyslipidemia may also delay development of new-onset diabetes.

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