News and Views from the Literature

Diabetes Mellitus

An Update on Diagnostic Criteria for Diabetes and the Metabolic Syndrome

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[*Rev Cardiovasc Med.* 2004;5(3):182–185]

Coronary artery disease is the leading cause of mortality and morbidity in patients with diabetes mellitus. We are now witnessing an obesity-driven epidemic of diabetes and have recently become familiar with the existence and relevance of prediabetic conditions, including the insulin resistance syndrome, and their association with cardiovascular risk. It is not uncommon that the first presentation of a patient with undiagnosed diabetes or the insulin resistance syndrome is an acute cardiovascular event, such as an acute coronary syndrome, stroke, or heart failure. It is therefore important that in the course of a busy day in the clinic we not gloss over laboratory data, such as an elevated hemoglobin HbA_{1c} or random or fasting glucose level, that point to an abnormality of glucose metabolism. This would result in a later diagnosis of diabetes and prediabetic conditions and a missed opportunity to intervene earlier to reduce cardiovascular risk. The 2 articles reviewed below deal with new issues relevant to the diagnosis of diabetes mellitus and prediabetic conditions, as well as the implications of the metabolic syndrome in terms of the future risk of developing diabetes.

Follow-Up Report on the Diagnosis of Diabetes Mellitus

Expert Committee on the Diagnosis and Classification of Diabetes Mellitus
Diabetes Care. 2003;26:3160–3167.

Since the 1997 Expert Committee report, new clinical data related to the diagnosis of diabetes and prediabetic conditions have accumulated that have implications for these recommendations. These data have raised a series of questions.

Should the cut-off point of fasting plasma glucose (FPG) of 126 mg/dL or higher and/or the cut-off point for 2-hour plasma glucose (PG) of 200 mg/dL or higher for the diagnosis of diabetes be changed? The selection of glucose levels for FPG and 2-hour PG was based on their association with the risk for developing retinopathy. Recent data suggest that the incidence of retinopathy increases at an FPG level of 126 mg/dL or higher. The European Diabetes Epidemiology Group DECODE study (Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe) reported that a 2-hour PG cut-off level of approximately 180 mg/dL provides diagnostic power similar to that of an FPG level of 126 mg/dL. The DECODE investigators found that among the 1517 people with diabetes studied, 40% met the fasting criterion only and 31% met the 2-hour PG criterion only. In the United States, the Third National Health and Nutrition Examination Survey (NHANES) found that in previously undiagnosed diabetic adults aged 40–74 years, 44% met

Table 1
Diagnostic Thresholds for Diabetes and Lesser Degrees of Impaired Glucose Regulation

	Test	
Category	**FPG**	**2-Hour PG**
Normal	< 100 mg/dL	< 140 mg/dL
Impaired fasting glucose	100–125 mg/dL	—
Impaired glucose tolerance	—	140–199 mg/dL
Diabetes	≥ 126 mg/dL	≥ 200 mg/dL

PG, plasma glucose; FPG, fasting PG. Reproduced with permission from the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2003;26:3160–3167.

both the FPG and 2-hour PG diagnostic criteria, 14% met the FPG but not the 2-hour PG criterion, and 41% met the 2-hour PG but not the FPG criterion. The NHANES investigators' recommendations were to maintain the 1997 consensus recommendations for diagnostic thresholds for diabetes and lesser degrees of impaired glucose regulation (Table 1).

Should the lower limit for impaired fasting glucose be reduced from 110 mg/dL? The predictive powers of either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) for the future development of diabetes varies from population to population studied. In most cases, the sensitivity of IGT is greater, but in some cases the IFG might be more specific. Because IGT is more common, it identifies larger numbers of dysglycemic people who will develop diabetes. The differences in sensitivity and specificity might be related to how IFG and IGT have been defined. After evaluating the ability of various baseline levels of FPG to predict diabetes in a variety of populations, the Expert Committee stated that the current lower limit of 110 mg/dL was too high and that a cut-off point of 100 mg/dL would optimize the specificity and sensitivity to predict future diabetes.

Should the HbA_{1c} level be included as a criterion for the diagnosis of diabetes? The use of the HbA_{1c} test has advantages and disadvantages for the diagnosis of diabetes. The advantages include the following:

1. It measures the average glycemic index for a time scale of weeks; therefore, it is indicative of the chronic state of hyperglycemia, whereas the hyperglycemia measured by the FPG or 2-hour PG is transitory.
2. The sample takes no advanced preparation and can be done during any part of the day.
3. In reference laboratories, the precision of the HbA_{1c} is similar to that observed with the measure of plasma glucose.
4. It provides in 1 test the ability to diagnose diabetes and to follow the efficacy of treatment.
5. A threshold level of HbA_{1c} has been associated with retinopathy and, when a level 2 standard deviations above the mean measure is used, it has a specificity of 98% and sensitivity of 66%.

The disadvantages of the HbA_{1c} test for the diagnosis of diabetes include the following:

1. Different glycated Hb fractions are measured in different laboratories, which results in poor standardization.
2. A chemical preparation to create uniform calibration standards has only recently been developed.
3. HbA_{1c} levels can be affected by a variety of conditions, including hemoglobinopathies, pregnancy, uremia, and hemolytic anemia.

The conclusion of the committee was that the HbA_{1c} test be used as a measure of the effectiveness of diabetes treatment and not be added to the group of tests for the definitive diagnosis of diabetes.

What is the value of the 2-hour oral glucose tolerance test (OGTT) in addition to the FPG test? Both the FPG test and the OGTT provide data associated with the microvascular and macrovascular complications of hyperglycemia; however, the tests are not interchangeable. An abnormal FPG level does not identify everyone with an abnormal 2-hour PG level, and vice versa.

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The 2-hour OGTT was originally developed to detect an abnormality of glucose metabolism in patients with normal FPG levels. It can be performed in the fasting or nonfasting state. Most longitudinal observational studies have found that an elevated 2-hour PG level (less than the cut-off level for diabetes) is a better predictor of all-cause mortality and cardiovascular events than is an elevated FPG level. However, many flaws have been found in these trials. The 2-hour PG level is a marker for early-stage insulin resistance and might be useful for identifying patients who might be at high risk for cardiovascular events and eligible

for aggressive risk-reduction therapy. The FPG test is more reproducible, less complicated to perform in a clinic, and less expensive. The consensus of the committee was that the evidence "precludes definitively declaring either test more advantageous than the other."

The OGTT offers the advantage that it can provide a measure of fasting glucose *and* a 2-hour PG value. It is clear that all-cause mortality is increased in people with a normal FPG level who meet the diabetic cut-off point for the 2-hour PG level; however, whether or not treating these patients leads to reduced mortality is not known.

The Metabolic Syndrome as a Predictor of Type 2 Diabetes: The San Antonio Heart Study

Lorenzo C, Okoloise M, Williams K, et al.
Diabetes Care. 2003;26:3153–3159.

The metabolic syndrome, otherwise referred to as the insulin resistance syndrome, is present in nearly 50% of older individuals in the United States. The increasing prevalence of the metabolic syndrome is driven by increases in body mass index (BMI), particularly in US youths. Subjects who fulfill the criteria for the metabolic syndrome are at an increased risk of cardiovascular disease, independent of the classic coronary risk factors, and warrant aggressive risk-factor-modification therapy, including the treatment of dyslipidemia and hypertension. Exercise and diet have been shown to reduce insulin resistance. Treatment with glitazones has been shown to not only improve insulin sensitivity but also to have positive effects on lipid profiles, blood pressure, and the distribution of fat. Both rosiglitazone and pioglitazone have been found to reduce C-reactive protein levels in diabetics. Rosiglitazone has also been found to reduce the levels of plasminogen activator inhibitor-1, implicated as part of the hypercoagulable state of metabolic syndrome, as well as levels of matrix metalloproteinase 9, which has been implicated in predisposing to coronary plaque rupture. Whether interventions based on reversing insulin resistance lead to a reduction of cardiovascular risk is currently under investigation. In the meantime, the knowledge that the metabolic syndrome increases cardiovascular risk and predisposes to the development of diabetes should prompt cardiologists to be aware of this condition.

The purpose of the study by Lorenzo and colleagues was to compare the "ability of the National Cholesterol Education Program (NCEP) definition of metabolic syndrome versus a modified definition of the 1999 World Health Organization (WHO) definition that excludes the 2-hour PG requirement and impaired glucose tolerance (IGT) to predict incident diabetes in the San Antonio Heart Study." (NCEP and WHO criteria for the metabolic syndrome are listed in Table 2.) A total of 1734 subjects completed a 7- to 8-year follow-up examination; patients with diabetes at baseline were excluded. Patients who developed diabetes during the follow-up period were older, had a family history of diabetes, and at baseline had greater mean BMI (31.3 vs 27.2) and waist circumference, along with higher FPG, 2-hour PG, triglyceride levels, systolic and diastolic blood pressures, and fasting insulin levels and lower levels of high-density lipoprotein cholesterol. Of the subjects who developed diabetes, 45% had IGT at baseline (7% with IFG), 49% met the NCEP definition, and 41% met the WHO definition. Of those patients who did not develop diabetes, 7% had IGT at baseline (1% with

Table 2
Criteria for the Metabolic Syndrome

NCEP ATP III (Syndrome present if at least 3 criteria are met)

1. Abdominal obesity
   Men: > 40 in
   Women: > 35 in
2. Triglycerides ≥ 150 mg/dL
3. HDL Cholesterol
   Men: < 40 mg/dL
   Women: < 50 mg/dL
4. Blood pressure ≥ 130/85 mm Hg
5. Fasting glucose ≥ 110 mg/dL

World Health Organization (syndrome present if [1] or [2] plus 2 or more of the other criteria are met)

1. Impaired fasting glucose (FPG 110–126 mg/dL) or impaired glucose tolerance (2-hour OGTT 140–200 mg/dL) or diabetes
2. Insulin resistance, defined as lower 25th percentile by euglycemic, hyperinsulinemic clamp test or above the 75th percentile by homeostasis model assessment
3. Increased arterial blood pressure (≥ 160/90 mm Hg)
4. Increased plasma triglycerides (≥ 150 mg/dL) and/or decreased HDL (< 35 mg/dL for men and < 39 mg/dL for women)
5. Central obesity (waist-to-hip ratio > 0.9 for men and > 0.85 for women) and/or BMI > 30 kg/m^2
6. Microalbuminuria (urinary albumin-to-creatinine ratio ≥ 20 mg/g)

NCEP ATP, National Cholesterol Education Program Adult Treatment Panel; HDL, high-density lipoprotein; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; BMI, body mass index.

IFG), 14% met the NCEP definition, and 12% met the WHO definition of metabolic syndrome.

IGT and the NCEP definition had a higher sensitivity than the modified WHO definition (51.9%, 52.8%, and 42.8%, respectively). IGT had a higher positive predictive value than the NCEP and WHO definitions (43.0%, 30.8%, and 30.4%, respectively). Combining the NCEP and IGT definitions increased sensitivity to 70.8% and had a positive predictive value of 29.7%. When the NCEP definition of an abnormal fasting glucose level was lowered to 5.4 mmol/L (100 mg/dL) or higher, it performed even better, with a sensitivity of 62% and positive predictive accuracy of 31%.

The authors concluded that the metabolic syndrome predicts diabetes independently of other factors; that the NCEP definition of metabolic syndrome predicts incident diabetes better than the modified WHO definition; and that a further lowering of the definition of IFG to 5.4 mmol/L or higher further improves the prediction of diabetes by the metabolic syndrome. ■

Atherosclerosis

Conventional Risk Factors and Cardiac Events—Debunking an Old Myth About Prevalence

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[*Rev Cardiovasc Med.* 2004;5(3):185-186]

Major Risk Factors as Antecedents of Fatal and Nonfatal Coronary Heart Disease Events

Greenland P, Knoll MD, Stamler J, et al.

JAMA. 2003;290:891-897.

This analysis evaluated subjects from the Chicago Heart Association Detection Project, the Multiple Risk Factor Intervention Trial, and the Framingham Heart Study, who had documented cardiac events (n = 20,995). At least 1 conventional risk factor (cigarette smoking, hypertension, diabetes, or hypercholesterolemia [cholesterol > 240 mg/dL]) was present in 91.1% of those who experienced a fatal coronary heart disease (CHD) event. This analysis did not take obesity, sedentary lifestyle, the dysmetabolic syndrome, high-density lipoprotein cholesterol, or low-density lipoprotein cholesterol, into account. If these variables had been considered, virtually all of those with fatal CHD events would have had at least 1 modifiable cardiac risk factor. Furthermore, these data antedate the acceleration of the U.S. obesity pandemic.

The "take-home message" from this study is that virtually all patients with cardiac events have longstanding, modifiable, and potentially reversible cardiac risk factors. Because modern technologies (ie, coronary revascularization) have been largely unsuccessful in halting and reversing the CHD epidemic, more emphasis must be placed on novel approaches such as primary prevention. This will require attacking conventional risk factors and their underlying environmental causes—diets high in sugars, fats, and simple carbohydrates for the majority who are overweight or obese; cigarette smoking; hypertension; and physical inactivity.

Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease

Khot UN, Khot MB, Bajzer CT, et al.

JAMA. 2003;290:898-904.

With methods similar to those employed by Greenland and coworkers, this analysis combined patient data for ST-segment elevation myocardial infarction (STEMI), unstable angina (UA) /non-STEMI, and percutaneous coronary intervention from 14 clinical trials (n = 122,458). Presumably, not all subjects in this sample had CHD, especially in the UA/non-STEMI group, where, typically, ~20% are found to have normal coronary arteries at angiography. Taking this limitation into consideration, the investigators found at least 1 conventional risk factor was present in 82.6% of subjects. Although hyperlipidemia was classified differently from trial to trial, and could not be distilled into a single number, the other likely risk factors had similar definitions in all of the epidemiological studies, though they were not specifically stated in the article. Importantly, the investigators noted that if obesity was considered as a risk factor, then ~90% of cases would have had at least 1 risk factor. Again, the current obesity pandemic would lead us to believe that, in this analysis of primarily non-fatal CHD events, virtually all such patients have modifiable or reversible risk factors that can be addressed with weight reduction and