Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 7, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.08.080

STATE-OF-THE-ART PAPER

Pre-Diabetes, Metabolic Syndrome, and Cardiovascular Risk

Scott M. Grundy, MD, PHD

Dallas, Texas

Pre-diabetes represents an elevation of plasma glucose above the normal range but below that of clinical diabetes. Pre-diabetes can be identified as either impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). The latter is detected by oral glucose tolerance testing. Both IFG and IGT are risk factors for type 2 diabetes, and risk is even greater when IFG and IGT occur together. Pre-diabetes commonly associates with the metabolic syndrome. Both in turn are closely associated with obesity. The mechanisms whereby obesity predisposes to pre-diabetes and metabolic syndrome are incompletely understood but likely have a common metabolic soil. Insulin resistance is a common factor; systemic inflammation engendered by obesity may be another. Pre-diabetes has only a minor impact on microvascular disease; glucose-lowering drugs can delay conversion to diabetes, but whether in the long run the drug approach will delay development of microvascular disease is in dispute. To date, the drug approach to prevention of microvascular disease starting with pre-diabetes has not been evaluated. Pre-diabetes carries some predictive power for macrovascular disease, but most of this association appears to be mediated through the metabolic syndrome. The preferred clinical approach to cardiovascular prevention is to treat all the metabolic risk factors. For both pre-diabetes and metabolic syndrome, the desirable approach is lifestyle intervention, especially weight reduction and physical activity. When drug therapy is contemplated and when the metabolic syndrome is present, the primary consideration is prevention of cardiovascular disease. The major targets are elevations of cholesterol and blood pressure. (J Am Coll Cardiol 2012;59:635–43) © 2012 by the American College of Cardiology Foundation

The prevalence of type 2 diabetes is increasing in the United States and worldwide. Because of many complications and the high costs of diabetes, its prevention and its complications demand more attention. The major complications of diabetes are cardiovascular diseases (CVD)—both microvascular disease and macrovascular disease. The leading risk factor for type 2 diabetes is a condition called *pre-diabetes*. The latter's predisposition to type 2 diabetes makes it a potential risk factor for CVD as well. Pre-diabetes moreover aggregates commonly with other CVD risk factors that make up the metabolic syndrome.

An ongoing debate is whether pre-diabetes deserves targeted identification and clinical intervention (1). Pre-diabetes generally is defined by either an elevation of fasting or post-prandial plasma glucose levels. Elevated hemoglobin A_{1c}, or glycosylated hemoglobin (HbA_{1c}), which integrates plasma glucose over time, is promoted by some as another indicator of pre-diabetes. This paper will review the pathogenesis and diagnostic criteria for pre-diabetes, its relation to macrovascular and microvascular diseases, and potential intervention strategies.

What Is Pre-Diabetes?

The term *pre-diabetes* has had a checkered history. Alberti (2) states that it was first used to denote abnormalities of pregnancy (e.g., high–birth weight babies, hydramnios) or a strong family history of type 2 diabetes. However, in 1980, the World Health Organization (WHO) (3) discarded the term largely because many subjects with borderline glucose levels do not convert to diabetes and because many would be alarmed unnecessarily. These problems still pertain. Yet in 2005, the American Diabetes Association (ADA) reintroduced pre-diabetes to cover impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) but not other risk factors for diabetes (4). In 2008, WHO's diabetes task force again repudiated the term and discouraged its use (5). Instead, they suggested "intermediate hyperglycemia" to signify IGT and IFG. The ADA nonetheless continues to use *pre-diabetes* and defines it as IFT, IGT, and now, HbA_{1c} of 5.7% to 6.4% (6).

Any definition of pre-diabetes that is restricted to IGT and/or IFG fails to include other risk factors for diabetes, such as, a family history of type 2 diabetes or the metabolic syndrome. Another telling criticism of the term *pre-diabetes* is that the many subjects with either IFG or IGT will not

From the Center for Human Nutrition and Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas. Dr. Grundy has reported that he has no relationships relevant to the contents of this paper to disclose.

Manuscript received June 14, 2011; revised manuscript received August 17, 2011, accepted August 23, 2011.

JACC Vol. 59, No. 7, 2012
February 14, 2012:635–43

Abbreviations and Acronyms

ADA = American Diabetes Association

CI = confidence interval

CKD = chronic kidney disease

CVD = cardiovascular disease(s)

HbA_{1c} = glycosylated hemoglobin

HDL = high-density lipoprotein

IFG = impaired fasting glucose

IGT = impaired glucose tolerance

LDL = low-density lipoprotein

OGTT = oral glucose tolerance test

RR = relative risk

WHO = World Health Organization

progress to type 2 diabetes. For this reason, another name might be preferable. The WHO task force's "intermediate hyperglycemia" so far has not been widely adopted (5). Another possible name is "borderline diabetes," but this term is not currently recommended and has no formal definition. In this review, the term *pre-diabetes* will be used throughout, but with the recognition that it is not universally accepted nor does it always foretell conversion to diabetes.

Pre-Diabetes as Intermediate Hyperglycemia

The ADA previously equated pre-diabetes with the WHO's intermediate hyperglycemia, but recently added borderline levels of hemoglobin A_{1c} as another indicator. The WHO so far has not done so. The ADA's 3 indicators can be considered along with their pathogenesis and clinical significance.

Pathogenesis of intermediate hyperglycemia. Two metabolic defects occur in most patients with type 2 diabetes: insulin resistance and deficient insulin secretion. Elevated glucose levels in the intermediate range are caused primarily by a deficiency in insulin secreted by pancreatic beta cells. Deficient insulin secretion can result either from a loss of beta cells or impairment of beta cell function. Both occur in type 2 diabetes (7,8). Similar but less severe defects, especially in insulin secretion, characterize pre-diabetes (9). Most persons with pre-diabetes also are insulin-resistant (9).

Impaired glucose tolerance. Normal fasting plasma glucose is a level of <100 mg/dl (<5.6 mmol/l) or a 2-h plasma glucose in response to a 75-g oral glucose tolerance test (OGTT) of <140 mg/dl (<7.8 mmol/l). IGT is recognized as an intermediate level of post-prandial glucose that carries essentially no risk for microvascular complications (10). It is diagnosed exclusively by OGTT; the 2-h plasma glucose is 140 to 199 mg/dl (7.8 to 11.0 mmol/l). According to recent NHANES (National Health and Nutrition Examination Survey) data (11), overall IGT prevalence in U.S. adults >20 years of age is 13.8%. The prevalence rises progressively with age. In the European DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study, IGT rose from 2.9% in 30- to 39-year-old men to 15.1% in 70- to 79-year-old men (12). One disadvantage of testing for IGT is the necessity for OGTT; another is that the results are not highly reproducible. Nonetheless, it is a relatively strong, albeit variable, predictor of type 2 diabetes (13). A predominant metabolic characteristic is insulin resistance in muscle, which exists along with defective insulin secretion (9). In most Western countries, conversion rates for isolated IGT range from 4.35% to 6.35% per year (14). In the DPP (Diabetes Prevention Program) study, in which IFG also was common, conversion to diabetes was approximately 10% yearly (13,15).

Impaired fasting glucose. IFG was introduced by the ADA in 1997 to classify fasting plasma glucose levels of 110 to 125 mg/dl (6.1 to 7.0 mmol/l) (16). By these criteria, the estimated U.S. prevalence of IFG in adults >20 years of age was approximately 6.9% (17). In 2003, the ADA changed its definition of IFG from a fasting level of 110 to 125 mg/dl to 100 to 125 mg/dl (18). The rationale for the ADA's change was several-fold. First, glucose levels of 100 to 110 mg/dl carry higher risk for diabetes compared with normoglycemia. Second, receiver-operator characteristic analysis of several studies found that 100 mg/dl is a threshold level of fasting glucose that maximizes sensitivity and specificity for predicting diabetes. Third, the expert committee postulated that reducing the threshold for IFG would make the prevalence of IFG and IGT concordant. However, the latter did not work out. Prevalence of IFG in the United States after lowering the threshold jumped from 6.9% to 25.7%, which was double the 12.9% for IGT (11). Applying this percentage to the U.S. population >20 years of age gave IFG to an estimated 57 million adults (19). Ethnic breakdown for IFG prevalence showed 21.1% in non-Hispanic blacks, 25.1% in non-Hispanic whites, and 26.1% in Mexican Americans. Other populations had similar increases after this change in IFG definition, for example, from 11.8% to 37.6% in Denmark and from 10.6% to 37.6% in India (5).

There have been 2 major criticisms of the ADA's change in definition of pre-diabetes based on fasting glucose levels. First, a high proportion of the population becomes "medicalized," and second, persons with fasting glucose levels of 100 to 110 mg/dl convert to diabetes with a lower frequency than do those with levels of 110 to 125 mg/dl. Regarding the latter, compared with individuals with fasting levels of 100 to 110 mg/dl, those in the range of 110 to 125 mg/dl have a 2- to 6-fold higher risk for developing diabetes (5).

Combined Impaired Glucose Tolerance and Impaired Fasting Glucose

One reason the ADA lowered the threshold for IFG was to avoid the need for OGTT to diagnose IGT. This aim did not entirely succeed. From 1988 to 1994, among U.S. adults aged 40 to 74 years, 33.8% had IFG by the revised definition, whereas only 15.4% had IGT (19). Only about 6% of the population had IGT but not IFG because of normal fasting glucose. This latter percentage raises the question whether there is any utility in doing OGTT at all. Two proposed reasons for OGTT are to identify persons