

Impaired Glucose Tolerance

Why is it not a disease?

The devastating consequences of diabetes on atherosclerotic vascular disease are well recognized. Most deaths in diabetic populations result from complications from accelerated cardiovascular and cerebrovascular atherosclerosis (1). In the presence of diabetes, the death rate attributable to cardiovascular disease (CVD) is increased 1.5- to 4.5-fold (2), and all-cause mortality is increased 1.5- to 2.7-fold (1). Although other risk factors for atherosclerosis, such as hypertension and dyslipidemia, frequently coexist with diabetes (3), the Multiple Risk Factor Intervention Trial (MRFIT) identified diabetes as an independent risk factor for cardiovascular mortality (4).

Despite this, diabetes is currently diagnosed at glucose levels that are associated with an increased risk of developing microvascular complications, i.e., retinopathy, rather than macrovascular disease (5). A postchallenge venous plasma glucose level of 11.1 mmol/l appears to best represent the threshold for this increased microvascular risk, and, thus, is recommended in the most recent diagnostic criteria proposed by the American Diabetes Association (ADA) (5) and the World Health Organization (WHO) (6). Although the fasting plasma glucose (FPG) level required for the development of microvascular disease is not as well established (7), population data indicate that an FPG level of 7.0 mmol/l appears to most closely correspond to a postchallenge level of 11.1 mmol/l (8,9). Therefore, an FPG level of 7.0 mmol/l is currently recommended by the ADA as the threshold for diagnosing diabetes (5) and is being considered by the WHO (10).

The degree of abnormal glucose homeostasis required to produce deleterious effects on the macrovasculature is not yet known. A body of evidence is accumulating that suggests that diabetes-associated macrovascular disease develops earlier than microvascular disease, when plasma glucose levels are in the prediabetic range (11). Because these abnormalities occur well before the onset of diabetes (as currently defined), we will refer to this

form of macrovascular disease as dysglycemic macroangiopathy.

In this issue of *Diabetes Care*, Tominaga et al. (12) provide additional insight into our understanding of dysglycemic macroangiopathy. A cohort of 2,651 Japanese subjects was identified through a diabetes prevalence study conducted in Funagata, Japan during 1990–1992. Except for 117 subjects with previously diagnosed diabetes, each subject underwent oral glucose tolerance testing using 75 g of oral glucose and was classified by WHO criteria (6) as having normal glucose tolerance (NGT) ($n = 2,016$), impaired glucose tolerance (IGT) ($n = 382$), or diabetes ($n = 136$) (both previously and newly diagnosed, $n = 253$). At the end of 1996, death certificates were examined for the entire cohort. In short, the authors report that, compared with NGT, risk of death from CVD was significantly increased in those with IGT (hazard ratio 2.219, $P = 0.0309$), which, interestingly, was not different from that in those with diabetes.

Using FPG data obtained at enrollment, the authors reclassified the subjects according to the current ADA criteria (5), which resulted in the following distribution of the cohort: normal fasting glucose ($n = 2,307$), impaired fasting glucose (IFG) ($n = 155$), and diabetes ($n = 189$). While the authors found diabetes (based on FPG) to be a substantial risk factor for CVD mortality (hazard ratio 2.484, $P = 0.0116$), they found that IFG was not (hazard ratio 1.136, $P = 0.8342$).

This 6.5-year study by Tominaga et al. complements previous studies that implicate postchallenge hyperglycemia as an important predictor of atherosclerotic complications. The Chicago Heart Study group reported that CVD mortality was significantly increased in men with asymptomatic postchallenge hyperglycemia (≥ 11.1 mmol/l 1-h after 50-g oral glucose tolerance test [OGTT]) (13). Data from the Rancho Bernardo cohort suggest that older women with isolated postchallenge hyperglycemia, i.e., 2-h postchallenge glucose ≥ 11.1 mmol/l, but FPG < 7.0 mmol/l, have a CVD mortality rate 2.6 times that of

age-matched euglycemic control subjects (14). Results of the 11-year Diabetes Intervention Study further suggest that postprandial hyperglycemia may be a better predictor of CVD mortality than fasting hyperglycemia (15).

Population studies indicate that cardiovascular mortality may not be dependent on the duration of diabetes, since it is equally prevalent in both established and newly diagnosed diabetes (16,17). This suggests that macrovascular disease initially occurs during a period that precedes the onset of frank diabetes. This premise was strengthened by a report from Yamasaki et al. (18), who used ultrasonographic techniques to demonstrate that subjects with IGT had a significant increase in carotid intimal wall thickness compared with normoglycemic control subjects. In a 20-year follow-up of the Whitehall, Paris Prospective, and Helsinki Policemen Studies, Balkau et al. (19) reported that nondiabetic men in the upper 2.5 percentiles of fasting glucose and 2-h postchallenge glucose levels had age-adjusted hazard ratios for CVD death of 1.8 and 2.7, respectively. By using metaregression analysis, Coutinho et al. (20) recently calculated the relative risks of CVD events associated with an FPG of 6.1 mmol/l (110 mg/dl) and a 2-h postchallenge glucose of 7.8 mmol/l (140 mg/dl) to be 1.33 and 1.58, respectively. The Honolulu Heart Study suggested that CVD risk is distributed across a continuum of postchallenge glucose levels (21). The data presented by Tominaga et al. add to this compelling body of data suggesting that any degree of postchallenge glucose intolerance (dysglycemia) is associated with the development of premature atherosclerotic vascular disease and mortality.

It is unlikely that hyperglycemia per se is responsible for the increased prevalence of macrovascular disease in dysglycemia. Indeed, patients with type 1 diabetes appear to have less risk for macroangiopathy than patients with type 2 diabetes (2). Moreover, patients with dysglycemia and type 2 diabetes often present with a plethora of metabolic perturbations (22)

and CVD risk factors (3,23), of which hyperglycemia is only one. This greater than chance clustering of CVD risk factors is variably called the metabolic, dysmetabolic, or insulin resistance syndrome, or syndrome X (24). It is more likely that a dysglycemic OGTT response is merely a marker for this syndrome.

The disparity in CVD risk between IFG and IGT suggests that these classifications reflect different metabolic states. Since the CVD mortality risk appears to be smaller in IFG versus IGT, it follows logically that the IFG group includes a substantial number of people with normal postchallenge glucose tolerance. Data from the Third National Health and Nutrition Examination Survey, in fact, demonstrate that IFG comprises a very inhomogeneous group, with 43% having NGT, 39% having IGT, and 18% having diabetes (25,26). Although similar findings have been reported from other countries, some ethnic differences do occur in this pattern of distribution (27,28). Population data from Mexico, for example, have estimated that in those with IFG, 38% have IGT and an astounding 39% have diabetes (26). Thus, while the Funagata IFG cohort may have had a lower prevalence of IGT and diabetes than a comparable western cohort, it is clear that IFG and IGT do not define the same group of people with respect to CVD mortality. These observations further suggest that IFG is not a marker of increased CVD risk, but postchallenge (and presumably postprandial) dysglycemia clearly is. If postchallenge dysglycemia is such a potent marker for CVD risk, one could strongly argue that we need to screen for it in at-risk individuals.

By performing an OGTT in patients with IFG (FPG 6.1–7.0 mmol/l), the detection of IGT and diabetes would be increased greatly (27,29). A similar approach to the diagnosis of diabetes is under consideration by the WHO (10). Unfortunately, surveys have indicated that clinicians seldom use the OGTT for the diagnosis of diabetes (30,31). Unless the OGTT is recommended and promoted, its use is not likely to increase.

Currently, practicing clinicians have very little guidance toward the management of IGT. In fact, IGT is officially recognized only as a risk for future development of diabetes (5), despite the overwhelming evidence that it is a potent marker of CVD risk. If IGT is nearly as potent as diabetes in increasing CVD, as

the current body of data indicates, should we not be treating IGT as aggressively as diabetes in regard to risk factor modification? Indeed, in a post hoc analysis of the Scandinavian Simvastatin Survival Study trial, subjects with IFG randomized to simvastatin were found to have a 56% reduction in CVD mortality ($P = 0.005$) (32). One can reasonably speculate that individuals with IGT may have even greater potential for reduced mortality with this therapy. Clinical trials designed to examine the impact of risk factor modification on CVD outcomes in individuals with IGT are urgently needed. Only after such trials will we learn whether interventions are clinically and cost effective.

In summary, compelling evidence has accumulated suggesting that dysglycemic macroangiopathy is a disease of the non-fasting state (11,33), and, therefore, assessment of metabolic derangements during the fasting period may be inadequate. Current diagnostic criteria for diabetes are designed to detect those at risk for microvascular disease. Yet, most individuals at risk for type 2 diabetes are plagued with complications related to macrovascular disease long before the onset of diabetes. Given that IFG fails to identify many patients at risk for dysglycemic macroangiopathy, it is critical that we revisit the use of the OGTT in individuals with IFG with the intention to prevent, or to slow the progression of, macrovascular disease. Is it not time to call IGT a disease?

R. CLARK PERRY, DO
ALAIN D. BARON, MD

From the Division of Endocrinology and Metabolism, Department of Medicine, Indiana University, Indianapolis, Indiana.

Address correspondence to Alain D. Baron, MD, Division of Endocrinology and Metabolism, 541 North Clinical Dr., CL459, Indianapolis, IN 45202-5111.

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