Science: Moving Us in the Right Direction

The new classification and diagnostic criteria for diabetes presented in the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus published in this issue of *Diabetes Care* (1) reflect approximately two decades of accumulated new knowledge and information about diabetes. The recommendations are a significant advance for people with diabetes as well as those who care for them. While the new criteria represent the best thoughts of experts and leaders in the international diabetes community, questions may arise over the need for new criteria, their validity, and their health and societal implications.

Classification systems should reflect new understanding of the etiology and pathophysiology of disease and should allow both practitioner and investigator a clearer framework of the particular health condition during their daily work. Thus, there is no question that a new etiology-based classification is timely and appropriate. Many significant advances in understanding the molecular pathophysiology of diabetes have occurred in the approximately two decades since the National Diabetes Data Group (1a) and World Health Organization (2) recommended the previous classification systems. The new classification is a big step away from the older "treatment-based" system toward a completely etiologic classification, such as exists for many other diseases. The task is not complete, however, because the precise etiology process in the majority of patients with type 2 diabetes under the new system remains unknown. Nevertheless, this "limitation" is likely to become less significant in the future as advances in understanding the molecular basis of different types of type 2 diabetes unfold.

The scientific rationale behind the new diagnostic criteria is clearly stated in the report. The new criteria bring into much closer alignment the fasting and postprandial levels of glycemia at which diabetes should be routinely diagnosed and the risk of microvascular and macrovascular complications of diabetes (3). Diagnosis based primarily on fasting plasma glucose (FPG) should be applauded, since FPG is much easier to obtain and is less subject to day-to-day variation than is the oral glucose tolerance test (OGTT) (4). As a result of the new recommendations, the diagnosis of diabetes is rendered no more difficult than establishing the presence of other conditions that require a fasting sample, e.g., dyslipidemias. In any case, abandoning routine use of the OGTT hardly seems a loss, since it was never widely used in clinical practice.

In addition to the practical value of using an FPG to diagnose diabetes, the level of FPG required to establish this condition, ≥126 mg/dl (7 mmol/l), is also an important clinical step forward. People with diabetes who would have been identified at a later stage in the natural history of diabetes can now easily be diagnosed before complications occur. Under the old criteria, 10–20% of patients developed retinopathy and nephropathy by the time they reached an FPG >140 mg/dl (7.8 mmol/l) (5,6). Thus, the FPG previously recommended for diagnosis, ≥140 mg/dl (7.8 mmol/l), was not concordant with the recommended 2-h postprandial value of 200 mg/dl (11.1 mmol/l). These problems will be remedied by the new criteria, in which an FPG of ≥126 mg/dl (7 mmol/l) both is consistent with a 2-h postprandial value of ≥200 mg/dl (11.1 mmol/l) and is likely to identify people with "early" diabetes before microvascular complications. The benefit of treating hyperglycemia has now been established by clinical trials and observational studies in both type 1 and type 2 diabetes (7–9), and the American Diabetes Association recommends treatment of all patients with the goal of normoglycemia (10). The new criteria thus provide the opportunity to diagnose diabetes in all patients before complications have gained a foothold. We predict that implementation of these new diagnostic criteria will significantly reduce microvascular complications of type 2 diabetes in future years if proper treatment goals are pursued earlier in the course of diabetes. In addition, data from the U.K. Prospective Diabetes Study suggest that early treatment may preserve β-cell function, delaying the need for more complicated and expensive treatment regimens (11).

These new recommendations are important not only to diabetes specialists and investigators but particularly to the primary care community, who now and likely in the future will continue to provide diagnostic and treatment strategies for the majority of individuals with known or as yet unrecognized diabetes. Given that primary care physicians practice in settings where an OGTT is time-consuming, expensive, and unacceptable to most patients, the new blood glucose criteria offer the primary care provider the opportunity to diagnose diabetes early in its natural history without doing this cumbersome test. As discussed carefully in the report, several concerns currently remain about the utility of glycosylated hemoglobin measurements for diagnosis (12). We therefore anticipate that the diagnosis of early type 2 diabetes will largely be made by primary care physicians obtaining fasting blood work for evaluation or routine follow-up of dyslipidemia, hypertension, obesity, or other conditions. It should also be somewhat easier to compare the diabetes burden across regions and countries where OGTTs are not feasible.

A further offshoot of the new criteria is additional attention to the relationship between diabetes and macrovascular disease risk, which is detailed in the report. Diabetes diagnosed by the new criteria (and also by the old) confers a two- to fourfold increased risk of macrovascular disease and should alert patients and health care providers to the need for more aggressive treatment of smoking, hypertension, dyslipidemia, overweight, and sedentary lifestyle. Previously, multiple–risk factor interventions included only these traditional risk factors; now, treatment of the "diabetes component" can be included in the therapeutic regimen. While vascular disease may begin quite early in diabetes, the new recommended diagnostic criteria indicate a threshold above which the morbidity and mortality associated with the vascular disease increase substantially (3).

While we feel strongly that the new recommendations represent a significant step forward in our understanding of diabetes, as well as in consideration of earlier use of "preventative treatment" strategies, additional concerns need to be discussed. As pointed out by the authors in Table 4 of the report (1), the new criteria reduce the total prevalence of diabetes (diagnosed plus undiagnosed) from 14.3 to 12.3% of the popu-

lation ≥20 years of age. The net total prevalence decreases by 2 percentage points because 1% of the population are reclassified as having diabetes by virtue of an FPG ≥126 mg/dl, while 3% classified as having diabetes by OGTT (currently referred to as undiagnosed diabetes) will now be classified as having impaired or normal fasting glucose. The risk to those now reclassified as having normal (FPG <110 mg/dl [6.1 mmol/l]) or impaired fasting glucose (FPG 110–125 mg/dl [6.1–6.9 mmol/l]) appears acceptable, since these patients lack significant risk for microangiopathy; all have an FPG below 126 mg/dl, the threshold for microvascular complications. Further, those who develop diabetes are likely to be detected during follow-up—every 3 years—as fasting glucose deteriorates.

The greatest impact of the new criteria is that the number of patients diagnosed with diabetes will likely increase because of the utility and ease of obtaining FPG. The potential total increase is ~2 million individuals (1), increasing the total of those diagnosed with diabetes from 8 million to ~10 million. The vast majority of these potential 2 million individuals with newly diagnosed diabetes will likely emerge from the large number of individuals with extant but undiagnosed diabetes.

Understandably, given the present challenges in improving the care of people with established diabetes in the U.S. (13,14), there will be concerns voiced about provider workload, patient anxiety, economic impact, and issues such as insurability and employability in those newly diagnosed. We believe these concerns are overshadowed by the long-term health and potential cost benefits of appropriate early diagnosis. Keep in mind that individuals diagnosed under the new criteria would have been identified in any case had an OGTT been performed. Rather than living with undiagnosed diabetes with hyperglycemia of sufficient magnitude to lead to complications and untreated macrovascular risk factors, these patients and their health care providers can take steps to reduce hyperglycemia and the likelihood of vascular disease. Past experience with dyslipidemia and hypertension suggests that patients, practitioners, and policy makers will take advantage of the opportunity to identify and treat a significant risk factor early in the course of a disease to attain reduced morbidity and mortality later in life. Lifestyle changes and effective patient education programs can have a significant impact on early type 2 diabetes and should be the initial treatment. In addition, five classes of drugs (sulfonylureas, insulin, biguanides, thiazolidinediones, and disaccharidase inhibitors) are now available if lifestyle changes fail.

In summary, we believe the new criteria for diabetes are firmly grounded in science, will greatly benefit patients whose diabetes is currently undiagnosed by virtue of the impracticality of performing the OGTT in routine practice, and will provide an opportunity to diagnose diabetes and institute treatment before complications develop. Additional information will accumulate, and clarification of the new recommendations will inevitably occur. At present, however, the National Institute of Diabetes and Digestive and Kidney Diseases and the Centers for Disease Control and Prevention strongly recommend that the new classification and diagnostic criteria be adopted, promulgated, and implemented by all individuals and organizations involved in the identification and care of those with diabetes.

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