Implications of the Revised Criteria for Diagnosis and Classification of Diabetes Mellitus

Diabetes mellitus is a heterogeneous disease. It comprises several distinct pathophysiologic disorders of carbohydrate metabolism, each of which ultimately manifests with hyperglycemia. Although the prevalence of the disease is unknown, >13 million people are estimated to have diabetes in the US [1]. The severe complications (renal, retinal, and cardiovascular) associated with the disease contribute to the $92 000 000 000 in annual healthcare costs in the US (1992 estimate) [2]. Therefore, the recent Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus that recommends new classification and diagnostic criteria for diabetes [3] merits contemplation.

Since the advent of blood glucose assays, the exclusive criterion for the diagnosis of diabetes has been hyperglycemia, either fasting or postprandial. For many years diabetes was diagnosed by the oral glucose tolerance test (OGTT), the cutoff having been established as 2SD above the mean of the glucose concentrations in healthy volunteers. In 1975 Siperstein estimated that more than half the population older than 60 years was abnormal by these criteria [4]. However, those values had more statistical than clinical significance, as follow-up for 10 years revealed that a substantial proportion of these individuals did not develop diabetes and many returned to normal glucose tolerance. Moreover, there was considerable variability among diabetologists in the diagnostic criteria used in practice [5]. To resolve these issues, in 1979 the National Diabetes Data Group [6] proposed criteria that were based on the bimodal distribution of blood glucose concentrations in populations with a high prevalence of diabetes, such as Pima Indians and Nauruans. Optimal separation between nondiabetic and diabetic subjects in these groups is at 11.1 mmol/L (200 mg/dL, 2000 mg/L) 2 h after an oral glucose load and at 7.8 mmol/L (140 mg/dL) for fasting plasma glucose (FPG). Thus, the diagnostic criteria were (a) classic symptoms of diabetes with unequivocal increase of plasma glucose, (b) FPG ≥11.1 mmol/L, or (c) a 2-h (and one other) postload value ≥11.1 mmol/L during an OGTT [6].

Although widely adopted, these criteria are imperfect. The most obvious disparity is that the fasting and 2-h values are not equivalent. Almost all subjects with FPG ≥7.8 mmol/L have a 2-h glucose ≥11.1 mmol/L in an OGTT. In contrast, in individuals without previously identified diabetes, FPG ≥7.8 mmol/L is seen in only 25% whose 2-h glucose is ≥11.1 mmol/L [7]. The OGTT is more sensitive than FPG, as impaired release of insulin in response to glucose develops early in the course of type 2 diabetes; increased fasting blood glucose concentration is a later manifestation. The Diabetes Control and Complications Trial (DCCT) demonstrated that hyperglycemia contributes to the microvascular complications of diabetes and that intensive therapy reduces long-term complications [8]. Therefore, a rational approach to define a cutoff value for diagnosis could be established on the basis of a correlation between blood glucose concentrations and the risk of subsequent complications. Analysis of several clinical studies reveals that the prevalence of retinopathy increases substantially at FPG ≥6.7 mmol/L (120 mg/dL). Moreover, FPG of 6.7–7 mmol/L (120–126 mg/dL), not 7.8 mmol/L, is equivalent to a 2-h postload glucose of 11.1 mmol/L [3]. These factors, coupled with the marked increase in the incidence of fatal coronary artery disease in individuals with FPG >6.7–6.9 mmol/L (120–125 mg/dL), provided the impetus for the new recommendations.

Three ways to diagnose diabetes are provided in the revised criteria. These are (a) symptoms of diabetes plus casual (i.e., regardless of the time of the preceding meal) plasma glucose ≥11.1 mmol/L, (b) FPG ≥7 mmol/L, or (c) 2-h postload glucose ≥11.1 mmol/L during an OGTT [3]. If one of these criteria is met, confirmation is required by repeat testing on a subsequent day.

In addition, the report recommended modification to the classification. The 1979 classification scheme recognized two major forms of diabetes, namely, type 1 (insulin-dependent) diabetes mellitus (IDDM) and type 2 (non-insulin-dependent) diabetes mellitus (NIDDM) [6]. Insulin-dependent diabetes mellitus is primarily due to autoimmune destruction of the pancreatic islet β-cells; non-insulin-dependent diabetes mellitus, the more prevalent form, results from a combination of insulin resistance and relative insulin deficiency. To base the classification on etiology rather than treatment, the revised classification eliminates the terms IDDM and NIDDM, which are now called type 1 and type 2 diabetes, respectively.

Diagnostic criteria for gestational diabetes mellitus are essentially unchanged. Screening by measuring plasma glucose concentration 1 h after a 50-g oral glucose load is recommended between 24 and 28 weeks of gestation. If the glucose concentration is ≥7.8 mmol/L, a full 3-h OGTT should be performed [9]. The only modification suggested is that screening for gestational diabetes mellitus is unnecessary in women <25 years of age who are at low risk. The Committee acknowledged that the diagnostic scheme has been challenged, the Somogyi–Nelson assay used in the O’Sullivan study having been accused of producing glucose cutoffs that are too high [10]. However, no change was recommended at present.

Two other revisions are likely to impact the clinical laboratory. The OGTT is no longer recommended for routine use, except in pregnancy. In addition, screening for diabetes in asymptomatic individuals by measuring FPG is suggested at age 45 years (or younger in subjects at increased risk), with follow-up testing every 3 years. Prior recommendations had discouraged screening in apparently healthy subjects.

What are the implications of these modifications for laboratory professionals? We can anticipate an increase in...
the number of requests for glucose assays. Because these assays are commonly performed, highly automated, and inexpensive, the financial and workload impact is unlikely to be significant. However, it will be important to ensure that clinicians follow appropriate sample-handling procedures to minimize glycolysis before analysis. The continued use of blood glucose as the sole diagnostic criterion reflects to a large extent the accuracy, precision, and reliability of this assay. For example, College of American Pathologists (CAP) surveys reveal a CV $\leq$ 3.0% for virtually all automated assays [11], and both Reference Methods and a Definitive Method are available.

The situation for glycohemoglobin offers a stark contrast to that for glucose. Numerous published studies, including the DCCT, have validated the clinical utility of glycohemoglobin. However, CAP surveys reveal CVs as great as 16.5% for assays of this analyte [12]. Therefore, although an integral component of monitoring patients with diabetes and proposed by some as a diagnostic test [13], measurement of Hb A1c was specifically excluded from the diagnostic criteria. This decision was based on the lack of correlation among assays, a problem that has been extensively addressed in Clinical Chemistry [14–17]. Considerable progress has recently been made towards standardization of Hb A1c assays (see 17, 18, and references therein). Specifically, the new Reference Method with electrospray ionization mass spectrometry [18] is a significant advance towards the achievement of this goal. Resolution of this issue by laboratorians could lead to acceptance of Hb A1c as a diagnostic criterion in the future.

The new diagnostic criteria are a substantial improvement over previous recommendations, given that the cutoff value for FPG is linked to the risk of developing microvascular and macrovascular complications. Elimination of the OGTT is an important practical change because the test has poor reproducibility [19], is time-consuming and expensive, requires extensive patient preparation, lacks standardization of the glucose load, requires multiple venipuncture or an indwelling catheter, and is unpalatable to many patients. Replacement of the OGTT with the simpler FPG will facilitate screening, enhance patient compliance, and encourage diagnosis by primary-care physicians. The Committee anticipates a small, but significant, decrease in the prevalence of the disease through elimination of the more-sensitive OGTT. Outside of epidemiologic studies, however, this prediction is unlikely to have practical significance because the OGTT is rarely used to diagnose diabetes in clinical practice [20]. In fact, use of the lower cutoff for FPG should substantially increase the number of diagnosed patients. This earlier diagnosis should result in an overall decline in the incidence of complications, lessening the burden to society.

Despite these advances, deficiencies remain. The major shortcoming is that the diagnosis remains indirect and is not based on an assay that measures the underlying molecular pathophysiology of the disease. In fact, there has been relatively little progress in the diagnosis of diabetes over the last 2000 years. The only improvement is that we have moved from a qualitative (and subjective) analysis in Roman times of tasting the glucose in the urine to a more accurate (and aesthetically more acceptable) automated analysis of glucose in the blood. The sole diagnostic criterion, namely, increased glucose, has not been modified. Obviously, elucidation of the pathogenic mechanisms is necessary for the development of more-accurate diagnostic tests. Type 1 diabetes is predominantly an autoimmune disease, and the vast majority of patients have measurable concentrations of autoantibodies in their blood [21]. Notwithstanding this progress in understanding the disease, reference ranges have not been clearly defined, and a negative screen does not exclude disease because the autoantibodies are present only transiently. Moreover, not all individuals with autoantibodies ultimately develop diabetes. Less is known about the pathogenesis of type 2 diabetes, which includes resistance to the actions of insulin combined with a secretory defect of the pancreas. However, neither the molecular mechanism(s) responsible for the insulin resistance nor those that lead to progressive loss of pancreatic $\beta$-cell function have been identified [22, 23]. The fundamental defects in insulin resistance and secretion are likely to be multifactorial and include environmental and genetic elements. Identification of the primary genetic factors that predispose individuals to develop type 1 diabetes or type 2 appears to offer the most promise for direct and early diagnosis [22–24]. Unfortunately, the heterogeneity of complex polygene disorders (particularly for type 2) has impeded progress, and screening for diabetogenes is unlikely to be feasible for some time.

The onset of type 2 diabetes is estimated to occur $\sim$10 years before clinical diagnosis [1]. As a result, retinopathy and proteinuria are present in as many as 29% and 37% of these patients, respectively, at the time of diagnosis [25]. Similarly, immunologic abnormalities have been documented 10 years before the clinical presentation of type 1 diabetes, suggesting that progressive destruction of $\beta$-cells develops over several years [26]. Early diagnosis, before the development of hyperglycemia, is an essential prerequisite to establish therapeutic approaches targeted to the molecular lesion at times when treatment would potentially delay or even prevent the onset of the disease and its debilitating complications. With criteria for glucose testing now refined, molecular and immunological assays appear to be the next phase in the evolution of the diagnosis of diabetes.

References


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Call for Nominations

The Nominating Committee of the American Association for Clinical Chemistry, Inc., is accepting nominations for the 1998 association election. The president-elect, secretary, two positions on the board of directors, and four positions on the nominating committee are to be elected to serve beginning January 1, 1999. Nominations should be sent in writing to: Catherine Smith, Ph.D., Gen-Probe Incorporated, 10210 Genetic Center Drive, San Diego, CA 92121. The letter should indicate the office for which the nominee is proposed and one or two sentences justifying the nomination. All letters must be received by January 30, 1998. The nominating committee will obtain the candidates consent to run for office.

Members of the 1998 Nominating Committee are: Catherine Smith, Ph.D. (Chair), Edward Ashwood, Ph.D., Mary Burritt, Ph.D. (chair-elect), Lawrence Broussard, Ph.D., Daniel Chan, Ph.D., John Chapman, Ph.D., Mark Jandreski, Ph.D., and Robert Williams, Ph.D.