Importance of Classification and Diagnostic Criteria for Diabetes*

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INTRODUCTION

Diabetes mellitus is heterogeneous in its etiology, clinical presentation, and natural history. Indeed, we believe that diabetes is a syndrome, consisting of a collection of diseases that may have only glucose intolerance in common. Consequently, to understand the multiple etiologies and manifestations of this syndrome, it is important that there be standard definitions and classification system for the different types of diabetes. Further, because varying degrees of glucose intolerance convey different risks for morbidity and mortality, diagnostic criteria based on these risks are essential. In particular, all of these are required to assure comparability of data between studies, not only within one nation, but, more importantly, on an international basis.

It was for these reasons that efforts in England, Europe, the United States through the National Diabetes Data Group (NDDG), organizations in other countries, and internationally through the World Health Organization (WHO) led to a consensus in 1979-1980 on terminology for diabetes and classification of the various types of the disease (1,2). The classification system includes two highly prevalent forms of diabetes, IDDM or Type 1, and NIDDM or Type II, as well as malnutrition-related diabetes, diabetes secondary to other conditions, and gestational diabetes in which pregnant women have mildly abnormal glucose tolerance tests. Finally, it includes impaired glucose tolerance (IGT) which is not diabetes but which we believe conveys increased risk for diabete-onset and for macrovascular complications.

Agreement was reached on the procedure for an oral glucose tolerance test (OGTT), and on diagnostic criteria, including three methods: elevated fasting glucose levels, elevated OGTT levels, and obvious clinical signs of diabetes together with abnormal glucose values. Although OGTT criteria for diabetes appear different between the NDDG and WHO systems, in that NDDG requires a midtest glucose value, in practice there is concordance between the two systems in that more than 90% of persons classified by WHO as having diabetes are also classified as diabetic by NDDG. Criteria for IGT remain discordant between the two systems and about twice as many persons are classified as having IGT in the WHO system as in the NDDG system. However, the NDDG has recommended that, for epidemiologic studies, the criteria of WHO be used which omit the midtest glucose value. With this revision, there is identicality between the two systems.

Several factors appear to have made this consensus occur. First, the diabetes community had been calling for a consensus for at least a decade, and it was recognized that some agreement needed to be reached, no matter how imperfect. Indeed, the classification is still somewhat imperfect, in that it combines both clinical manifestations (e.g. insulin-dependent) and etiologic characteristics (e.g. secondary diabetes). However, for the first time, classification and diagnostic criteria for diabetes are based on sound scientific research, namely long-term prospective studies conducted on English people, on Pima Indians, and on gestational diabetics. These studies investigated the development of diabetes and its diabetes complications, primarily microvascular in nature, in persons with varying degrees of glucose intolerance after an OGTT. The major findings were that microvascular complications rarely occurred in persons with IGT but were confined to persons with 2-hr glucose values that exceed 200 mg/dl. Persons with IGT showed only a slow rate of progression to overt diabetes, indeed many retested with normal glucose tolerance or remained as IGT for a number of years.

AIMS FOR THE CLASSIFICATION AND DIAGNOSTIC CRITERIA

In developing the classification system, our aims in the United States were three-fold: 1) to serve as a uniform basis on which to plan and conduct clinical research into the causes, treatment, pathogenesis, and prevention of diabetes, 2) to serve as a framework for the collection of epidemiologic data on the etiology, natural history, risk factors, and

impact of diabetes and its complications in diverse populations, 3) to aid the clinician in categorizing patients who have various degrees of glucose intolerance or who posses characteristics that place them at increased risk of developing diabetes. In addition, we believed that any terminology and classification system had to fulfill the following requirements: 1) the classes should be defined so as to be mutually exclusive, that is, an individual at any given time in his life can be placed in only one class, although with prospective follow-up he may change characteristics and need to be reclassified, 2) the classification should require only simple clinical measurements or descriptive observations that are readily obtainable and have biologic significance, 3) the classes should be as precise, well-defined and as homogeneous as current knowledge of the etiopathology of diabetes allows, 4) terminology should also be precise and well-defined and should describe the phenotypic expression of the abnormality to the degree possible, 5) the classification should be adaptable and able to incorporate new research findings on the etiopathology of diabetes.

BENEFICIARIES OF THE CLASSIFICATION, TERMINOLOGY, AND DIAGNOSTIC CRITERIA

Have these aims been achieved, and have these requirements been fulfilled? Four groups in particular benefit from standard definitions, classification, and diagnostic criteria for the diseases that are collectively termed "diabetes mellitus": clinicians who treat patients that have diabetes or might develop the disease, researchers who study the etiology and pathogenesis of diabetes; diabetic patients, and persons who are at risk for diabetes. For a clinician, the decision as to whether a patient has a particular condition or is at risk for that condition is tripartite. It is based on the probability that a patient who has a set of demographic characteristics and risk factors (age, sex, race, obesity, family history) has a defined probability of having the disease, on the particular set of signs, symptoms, and laboratory findings that a patient presents with, and on the currently accepted consensus regarding whether those signs, symptoms, and laboratory results indicate a disease is present, ie., the diagnostic criteria for the disease.

In diabetes, this constellation of decisions had been especially difficult, since each had been changing over time. Risks associated with particular population groups, such as American Indians, Hispanics, and Blacks who we now know are at high risk for diabetes, were poorly quantified. Because of intensive screening efforts, larger numbers of patients were presenting without the classical symptoms of diabetes, but there was no consensus on procedure for administration of the OGTT: varying glucose loads were administered, and plasma or blood glucose levels were measured for varying periods of time. Numerous different sets of diagnostic criteria were employed for interpreting fasting values and values during the OGTT. A number of these resulted in inclusion into the group termed "diabetes" of persons who we now know are not at risk of developing diabetes complications. These "borderline" diabetics thus incurred social, psychologic, and economic sanctions that were not justified in light of the lack of severity of their glucose intolerance. Persons who have been told by physicians that they have borderline diabetes are not an insignificant number. In 1976, we surveyed a representative sample of the U.S. population and almost as many people reported they had one of these conditions as reported they had diabetes.

Finally, a variety of terms were used in the past to describe what were thought to be different manifestations of diabetes. In addition to "borderline" diabetes, these included such ill-defined terms as juvenile-onset and adult-onset, ketosis-prone and ketosis-resistant diabetes, brittle and mild diabetes, asymptomatic, chemical, subclinical, latent, potential and prediabetes. All these components must have brought confusion into determining how to diagnose diabetes, who should be considered to have diabetes, and the degree of their risk for developing complications. It also must have brought confusion into treatment of diabetes, if it was believed that a patient had "mild" diabetes, it seems logical that an aggressive treatment strategy would not have been pursued. Hopefully, our consensus on classification and criteria has made it easier to determine who does and does not have diabetes and to counsel those at risk for the disease.

Being able to accurately diagnose a disease is important to the clinician to properly guide treatment of a patient with that disease and to counsel those at risk. However, this accuracy is essential to the researcher who is trying to ascertain the disease's etiology and pathogenesis. We believe that different types of diabetes have very different etiologies. Further, risk factors in common may have varying impact on development of different types of diabetes and their complications. It is likely that, in the past, types of diabetes with very different etiologies and pathologic courses were grouped together so that our understanding of the syndrome

of hyperglycemia and its extreme manitestation, diabetes, is imperfect and perhaps even inaccurate. Further, the fact that numerous different sets of criteria for diagnosing diabetes existed has surely led to development of data that lack comparability internationally or even within a single nation.

RESULTS OF THE NEW CONSENSUS ON CLASSIFICATION AND DIAGNOSTIC CRITERIA

What are some examples of research results that can be ascribed to the new consensus? The very fact of classification appears to have stimulated new studies. The terms IDDM and NIDDM, and their counterparts Type I and Type II, now appear in research reports and scientists are discriminating between these two major subtypes of diabetes. As a result of increased interest in malnutrition-related diabetes mellitus (MRDM), including that of the 1985 WHO Study Group on Diabetes (3), more data on these entities are being generated to define their clinical and epidemiologic characteristics.

A number of new studies are in progress which use the recommended 75 gm, 2-hr OGTT. In the United State these include: 1) two new sample surveys of the U.S. population, the Hispanic HANES and the NHANES III surveys; 2) new studies in U.S. population subgroups including Hispanic Americans in Texas and Colorado, Japanese Americans in Seattle, Washington, and Caucasians in southern California, Utah, and Minnesota, as well as ongoing studies on American Indians in Arizona and Oklahoma. Internationally there are continued analysis of the Whitehall and Bedford populations in England, in addition to new studies on NIDDM among populations in Australia, France, India, Israel, Italy, Japan, Lithuania, the South Pacific, and a number of other countries. Since these research efforts are employing the standard OGTT, they are also collecting data on the clinical and epidemiologic significance of IGT.

Studies on IDDM have also expanded. Since this disease is so much rarer than NIDDM, it is imperative that these two forms of diabetes be differentiated. A major international effort is being coordinated by the University of Pittsburg, called Diabetes Epidemiology Research International (DERI). Using a standard set of definitions, criteria, and protocols, research on the etiology, pathogenesis, and mortality of IDDM is being conducted through registries in Pittsburgh, Wisconsin, Colorado, Finland, Japan, Israel, and other countries.

Finally, there is a new WHO effort to assess worldwide prevalence of diabetes. It would not have been possible 10 years ago to develop consistent data based on the same criteria, because so many criteria and classifications systems were in effect. This effort is directed by Dr. Hilary King, and for the first time will produce international prevalence data on diabetes and IGT that are standardized for age, diagnostic criteria, and classification of the type of diabetes.

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