Classification and Diagnostic Criteria for Diabetes Mellitus

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For a clinician, a decision as to whether a patient has a particular condition is tripartite: It is based on the probability that the patient, with a set of demographic characteristics (age/sex/race/family history/etc.), has a defined probability of having the disease; on the particular set of signs, symptoms and laboratory findings that the patient presents with; and on the currently accepted consensus of whether those signs, symptoms and lab results indicate a disease is present, i.e., the diagnostic criteria for the disease. For diabetes, this constellation of decisions has been especially difficult, as each has been changing over time.

Our U.S. national health surveys indicate an upward trend in the prevalence of diabetes in many demographic groups. The recognition that certain of these are at high risk for diabetes (i.e., Hispanics, Black women) has placed clinicians on the alert to look for diabetes in these groups. Recent surveys of the general population indicate that their search is not illfounded, as there appears to be a high prevalence of undiagnosed diabetes in the U.S. The medical literature indicates that diabetics are presenting earlier in the course of their disease, with less severe symptoms, possibly because of vigorous screening efforts to detect asymptomatic diabetics; concomitantly, consensus on the level of blood glucose that is diagnostic for diabetes has changed several times and a variety of terms have been invented to describe these different levels.

Being able to accurately diagnose a disease is important to the clinician to properly guide the treatment of a patient with that disease. However, this accuracy is essential to the researcher who is trying to ascertain the disease's etiology and pathogenesis. It is likely that, in the past, types of diabetes with very different etiologies and pathologic courses have been grouped together in clinician's and researcher's minds, so that our current understanding of the syndrome of hyperglycemia is imperfect, confused, and perhaps even inaccurate. Further, the fact that numerous different sets of criteria for diagnosing diabetes have existed has led to the development of data that lack comparability internationally or even within a single nation. It is highly likely that, because of this lack of comparability, we have lost many opportunities in the past for developing
accurate data on the etiology and pathogenesis of diabetes.

It is for these reasons that an international workgroup, organized by the National Diabetes Data Group of the National Institutes of Health, set out to reach a consensus on diagnostic criteria for diabetes and classification of the various types of diabetes.

**The Classification System**

In developing the classification, our aims were three:

1. to serve as a uniform basis on which to plan and conduct clinical research on diabetes, including its causes, treatment, development of complications, and prevention;
2. to serve as a framework for the collection of epidemiologic data on the etiology, natural history, and impact of diabetes and its complications in diverse populations throughout the world;
3. to aid the clinician in categorizing patients who have various degrees of glucose intolerance or who possess characteristics that place them at increased risk of developing diabetes.

In addition, we determined that any terminology and classification system we developed 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 subsequently;
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 and well defined as current knowledge of the etiopathology of diabetes allows, so that each class contains a population as homogeneous as possible;
4. the terminology should be precise and well defined and should describe the phenotypic expression of the abnormality as much as possible;
5. the classification should be adaptable and able to incorporate new research findings on the etiopathology of diabetes.

Have these aims been achieved, and have these requirements been fulfilled?

It appears that the classification system is permeating the international research community and is being used in clinical and epidemiologic research. The terms IDDM and NIDDM, and their counterparts Type I and Type II, are appearing in the diabetes medical journals, and researchers are making an effort to discriminate between these two subtypes of diabetes. Several factors appear to have made this 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 somewhat imperfect but, for
the first time, a classification system and diagnostic criteria for diabetes are based on sound scientific research performed over the past decade. Second, the endorsement by the Expert Committee on Diabetes of the World Health Organization accelerated the international recognition of the classification. And, third, the U.S. National Institutes of Health began requiring that researchers receiving grant funds either adhere to the classification and diagnostic criteria or at least clearly define the glucose tolerance and other characteristics of their research subjects. It is to be hoped that new research will produce findings that can be used to test the classification system and the validity of the diagnostic criteria, so that these can be altered and refined to further hone our knowledge of diabetes.

For the third aim, it is likely that we have not been as successful and that we may have generated as much confusion as we cleared up. First, we took away from the clinician many terms that were in frequent use. Everyone knew, or thought they knew, what juvenile diabetes was, and yet the workgroup recommended that that term be abolished, as evidence indicates that many cases of "juvenile" diabetes have their onset in adults. (Just how many, and whether their characteristics are the same as those of the childhood onset cases, we don't know and perhaps the new classification will stimulate such research.) We also recommended that the term "borderline" diabetes be abolished, as several prospective studies on persons in this category indicated that they have as much tendency to revert to normal glucose tolerance as to proceed to overt, well-recognized diabetes, and that microvascular complications do not develop until they do proceed to the diabetic state. In addition we recommended that "prediabetes" and "potential diabetes" be abolished because they had been misused in the clinical situation by being applied to people who do not have diabetes, giving them the label "diabetes" with its concomitant social, psychologic and economic sanctions. Persons who had been told by physicians that they had these three conditions 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 (Table 1).

<table>
<thead>
<tr>
<th>Type of glucose intolerance</th>
<th>Thousands of persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>4,986</td>
</tr>
<tr>
<td>Borderline diabetes</td>
<td>2,794</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>113</td>
</tr>
<tr>
<td>Potential diabetes</td>
<td>1,221</td>
</tr>
<tr>
<td>Total</td>
<td>9,114</td>
</tr>
</tbody>
</table>
In place of borderline diabetes, we created a class entitled Impaired Glucose Tolerance which specifically does not contain the term “diabetes” for the reasons given above. In some studies, persons with IGT were at an increased risk for development of diabetes and also coronary heart disease. However, this risk may be associated with increased levels of cardiovascular risk factors such as obesity, hypertension, hypercholesterolemia, and cigarette smoking, and it is presently unclear what contribution impaired glucose tolerance makes to morbidity and mortality. The association of hyperglycemia with cardiovascular disease is thus far indirect and varies widely among populations. The category of IGT certainly deserves more research to determine its clinical significance.

Further confusion in the clinician’s mind has arisen from our division of diabetes into the two subtypes, Insulin dependent and Noninsulin dependent. Dependent on what? Dependent on insulin for maintenance of life in the former, but only for correction of symptoms or persistent fasting hyperglycemia in a percentage (about 20% in the U.S.) in the latter. Thus, these terms really define a phenotypic, clinical conditions, whereas a good classification system should be based on etiology, including both genetic and environmental components. Here is where past research was inadequate, as we felt we had insufficient evidence to call one type “HLA-virus-autoimmune diabetes” and to call the other “obesity-atherosclerotic-hyperinsulinemic diabetes.” Hopefully, the classification system has pointed up our lack of knowledge and will stimulate new research to determine the etiologies of the different types of diabetes.

To turn to the five requirements we established: We believe that, as defined, the classes are mutually exclusive. However, sufficient information is required to classify an individual, and sometimes this information is difficult to obtain. For example, a person can be classified as having diabetes secondary to the use of thiazide diuretics only if plasma glucose was measured before diuretic therapy began, or if the patient was taken off the drug to determine whether plasma glucose returns to normal. If these cannot be done, the patient will be likely classed as a Type II diabetic. If many of these misclassifications occur, Type II diabetes becomes almost a meaningless grabbag of hyperglycemic persons and the results of research on this group will be comparably meaningless. As mentioned earlier, a classification based on etiology is the most desirable, and only the subclass “Diabetes Associated with other Diseases and Conditions” approaches this. Ideally, we would like eventually to move all Type I and Type II diabetics into this class as the etiologies of their hyperglycemia are revealed. At present, however, the vast majority of diabetics are in the Type I and Type II subclasses and it is likely that both are highly heterogeneous in their etiology and their natural history.

Thus, although the classification requires only a few clinical measurements or descriptive observations (Table 2), often these may not be made by the clinician or may not be able to be made by the researcher. It is virtually impossible for
the epidemiologic researcher to know for sure if hyperglycemia is drug-induced, and obtaining evidence of ketosis in epidemiologic surveys, to classify a subject as Type I, is also difficult. Even making the plasma glucose determinations that are required for diagnosis have imposed an additional task on the clinician and the researcher, a task which, however, the workgroup felt is now essential.

The third requirement, precision in the definition of the classes, was limited by our relative lack of knowledge of the etiology and pathogenesis of the different types of diabetes. Much of this limitation was due to the fact that, in the past, the different types had studied and reported on together rather than as distinctly different diseases. In selecting the studies that did discriminate, however, much of our definition of Type II diabetes was of a negative nature, i.e., not HLA-associated, not autoimmune, not ketosis-prone. The precision of the terminology (requirement 4) reflects this, as we called Type II diabetes "noninsulin-dependent," a totally inadequate name which does not describe the disease at all well.

Finally, we believe the classification is adaptable to new research findings primarily because it is only a bare-bones outline which separates the heterogeneous syndrome of hyperglycemia into a few classes. It is certain that, as etiology and pathogenesis become better understood, pieces of each subclass will be placed in their own distinct class of diabetes and we will be able to quantify with certainty the statistical risk of PrevAGT and PotAGT.

In sum, improvement and refinement of the classification system depends on new research, such as that which is contained in the other chapters of this volume. The deficiencies discussed above point the way to the directions new research should take. Some major research questions remaining are:

1. Can we find specific genetic markers for Type I and Type II diabetes so that we do not have to rely on the phenotypic marker of blood glucose?
2. Can Type I diabetics be differentiated into those with greater and those with lesser risk for development of complications?
3. Do Type I diabetics with onset in adulthood differ from those with onset in childhood?
(4) Should obesity be used to differentiate Type II diabetes into two subtypes, obese and nonobese?
(5) Is obesity the main etiologic factor in onset of Type II diabetes, or does some other (unknown) factor create both obesity and hyperglycemia?
(6) Does the classification scheme apply worldwide, or only to Caucasian populations?
(7) Are there other well-defined types of diabetes that occur in specific populations that should be included in the classification?

**Diagnostic Criteria**

The international workgroup of the National Diabetes Data Group also proposed a set of diagnostic criteria for diabetes and for impaired glucose tolerance. These, rather than being based on the expert opinion of a group of diabetologists or on statistics (e.g., two standard deviations above the mean) as in the past, have a sound scientific basis in research. The findings of Keen and Jarrett in their Bedford, Birmingham, and Whitehall studies, Bennett in the Pimas, and O'Sullivan in Boston provide this scientific basis for the new criteria. These studies showed that the symptoms and microvascular complications of diabetes are largely confined to persons with fasting plasma glucose values greater than 140 mg/100 ml and to persons who, even though their fasting level is less than 140 mg/100 ml, exhibit sustained elevation of plasma glucose after an oral challenge (greater than 200 mg/100 ml at 2 hr after administration of an oral glucose dose).

We concluded that only persons who meet these criteria should be termed diabetic. In the British studies, persons whose 1 hr value was greater than 200 mg/100 ml but whose 2 hr value was between 140 and 200 mg/100 ml (comparable to the old criteria for chemical or borderline diabetes) showed only a low rate of progression to overt diabetes (approximately 1% to 2% per year). The majority returned to normal tolerance or remained in this state of impaired tolerance for years and did not have development of the symptoms and microvascular complications of diabetes. In view of these new data, we considered it inaccurate to diagnose such individuals as diabetics, and we selected the designation of IGT as more accurate clinically.

How valid are these criteria? Their validity should be judged by their ability to predict the complications of diabetes, for the presence of hyperglycemia *per se* is meaningless unless it has untoward effects on a patient. Bennett's studies on the Pima Indians, and Jarrett and Keen's prospective studies in England, indicated that the cut-off points we chose do tend to group people into those who are more likely to develop complications (FPG ≥ 140 or 2 hr ≥ 200) and those that are less likely to do so (FPG < 140, 2 hr < 200). Further prospective studies specifically designed to test these cut off points will be valuable. In particular, we do not know if these criteria are universally applicable. It is
possible that in countries with low rates of diabetes, such as Japan, persons are more resistant to high blood glucose concentrations and only develop diabetes and its complications at levels higher than our proposed criteria.

We will only know whether the criteria should be used more widely if careful studies are done under the standardized conditions recommended by the National Diabetes Data Group. We recently applied these criteria to the OGTT values obtained on a statistical sample of the U.S. population. A large percentage met the criteria for diabetes and IGT and it appears that the prevalence of undiagnosed diabetes in the U.S. is virtually equal to the prevalence of diagnosed diabetes (Table 3). These percentages increased with age and, adding the diagnosed and undiagnosed together, it appears that approximately 17% of persons age 60-74 years are diabetic by the NDDG criteria. Earlier criteria had called for an adjustment for age, generally by increasing the cut-off glucose value 10 mg/100 ml for every decade of age over 40 years. Such an adjustment would reduce the prevalence of diabetes in the older age group of our sample. We do not know if we should apply this adjustment to the new criteria however, as sufficient research on older persons with varying glucose levels has not been performed.

We have recommended that, for epidemiologic purposes, only the 2-hr plasma glucose value is required to place a subject in the diabetic class and that an intervening value between the fasting and 2-hr sample is not necessary. The results of our survey indicate that the 2-hr value appears sufficient, as 92% of persons whose 2-hr plasma glucose level was equal to or greater than 200 mg/100
ml also had their 1 hr value at this level. It is possible that, for the remaining 8%, we missed the peak intervening value and that it occurred after we took the 1 hr blood sample. For IGT, however, use of an intervening value markedly changes prevalence estimates. The number of persons with IGT is more than doubled if the requirement for an intervening value equal to or greater than 200 mg/100 ml is not imposed (Table 4).

The final point to be discussed is the problematical differences between the NDDG criteria and the WHO criteria. The first difference is in conversion from mg/100 ml to mmol/l. The WHO Expert Committee on Diabetes used the same mg/100 ml values as the NDDG, but in converting to mmol/l they rounded off to the nearest whole mmol/l. Their intention was presumably to create convenient numbers, not to create values different from those proposed by the NDDG. The second difference is that NDDG requires a fasting, a 2-hr, and an intervening plasma glucose value from the OGTT, while the WHO requires only a fasting and a 2-hr sample. As mentioned earlier, the intervening value seems to add little to ascertainment of diabetes, but it radically changes the prevalence of persons with IGT. Consequently, this is a major difference between the two sets of diagnostic criteria, and researchers should carefully report their results on IGT, clearly stating which criteria they used to classify their research subjects. At present, because of our lack of knowledge of the clinical significance of IGT, we have no sound basis to select one set of criteria in preference to the other.

Finally, it is important to remember that neither the NDDG nor the WHO recommendations are written in stone, never to be effaced. The spirit that created this consensus on classification and criteria for diabetes will cause their revision when new research findings show that this is necessary.

References