Procedures in Family Practice

The Oral Glucose Tolerance Test

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Present perception of diabetes mellitus is bathed in controversy in many areas. The glucose tolerance test, in this context, is no exception. There is debate about the efficacy of control of blood glucose, the potential benefits and dangers of oral hypoglycemic agents, the etiology of diabetes mellitus, and even its diagnosis. The latter controversy, when and how to diagnose diabetes mellitus, is germane to this approach to the use and interpretation of the procedure known as the glucose tolerance test. The following three areas will be discussed: (1) the definition of diabetes mellitus, (2) use of the oral glucose tolerance test, and (3) the interpretation of the glucose tolerance test.

Knowledge and perceptions of diabetes mellitus are constantly changing. This discussion relies to a significant degree on the Report of the National Commission on Diabetes[1] and the preliminary report of the National Diabetes Data Group of the National Institutes of Health.* The latter report is most current and seems to reflect a consensus of many experts in the field. The considerations of the National Commission and others have also included epidemiological and other research aims and screening for diabetes mellitus. The former areas are not of direct interest here and the value of the latter approach is currently in question. However, uniform terminology, diagnostic criteria, and a widely accepted working classification are greatly needed. The report of the National Diabetes Data Group seems to offer real hope for this uniformity.

Definition of Diabetes Mellitus

As the criteria for diagnosis continue to be difficult to agree upon, even by the "experts,"[2] so the definition of diabetes is approached with increasing timidity. A recent definition, which alludes to the confusion over the relationship of the complications of diabetes mellitus to the insulin deficiency or to the abnormality in blood glucose, is as follows: "a complex metabolic derangement, characterized by relative or absolute insulin deficiency. More information is still needed about the surmise that this deficiency is usually or frequently accompanied by microvascular and macrovascular pathology, unique in part, and in part merely an accelerated process of aging."[1]

The heterogeneity of the disease(s) called diabetes mellitus is probably at the root of some of the confusion. It is now becoming evident that diabetes mellitus is a group of different syndromes with glucose intolerance as the common denominator. A knowledge of the "types" of diabetes mellitus is important for present thinking and may be critical to diagnosis and management in the future. Heterogeneity, according to age of onset and insulin requirements, has been recognized for years. However, the dominant assumption has been that these differences among diabetics are the result of varying degrees of insulin insufficiency within the same fundamental disease process. Maturity onset type or non-insulin dependent diabetes (NIDDM) has long been distinguished from juvenile onset type or insulin dependent diabetes mellitus (IDDM) (it is preferable to use the insulin dependent and non-insulin dependent designations since both occur to some degree in both young and older age groups). The two diabetic syndromes, IDDM and NIDDM, have now been distinguished from each other on the basis of studies of the circulating histocompatibility complex antigens (HLA) and on the basis of twin studies.[3] IDDM is clearly associated with the presence of certain HLA antigens (B8 and BW15)

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*Harris M, Cahill G, and other members of the National Diabetes Data Group: Classification of diabetes mellitus and other categories of glucose intolerance. Reprints are available upon request from Maureen Harris, PhD, MPH, Program Director, National Diabetes Data Group, NIAMDD, National Institutes of Health, Westwood Building, Room 605-B, Bethesda, MD 20016.

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and NIDDM is not. A stronger pattern of concordance for diabetes in monozygotic twins is found in NIDDM than in IDDM, further supporting the existence of these two different types of diabetes. At least one subtype of NIDDM can be identified, a distinct autosomal dominant form in children and adolescents, which has been called maturity onset diabetes of the young.[4] This subtype seems to be associated with a low incidence of complications and rarely develops into the insulin dependent type. IDDM has been further subdivided into two types which are associated with increased incidence of B8 and BW15 HLA antigens, respectively.[3] The HLA-B8 form has characteristics of and association with autoimmune disease while the HLA-BW15 form does not. Microangiopathy seems increased and antibody response to exogenous insulin decreased in the B8 form as compared to the BW15 form. In addition to these syndromes, a large group of less common and very diverse genetic disorders, eg, Down syndrome and Turner syndrome, are associated with carbohydrate intolerance.[5]

The implications of the occurrence of these various syndromes to the controversies in diabetes mellitus are numerous. For instance, the viral etiology theory may be correct but only in certain subgroups of diabetes because of an inherited propensity to pancreatic viral damage. The controversy on efficacy of control may be explained by the fact that higher complication rates occur in only certain syndromes and/or are sensitive to improved control in only certain syndromes. Thus, the efficacy of control or lack of it may be masked by the heterogeneity of types within a given study group.

Use of the Oral Glucose Tolerance Test

The indications for a glucose tolerance test are controversial.[1,6] However, pregnancy is one area in which diabetologists seem to agree. Contemporary methodology of intensive care of the pregnant diabetic patient and her newborn has decreased perinatal mortality.[7] For this reason, identification of and appropriate management of all gestational diabetic subjects (not diabetic prior to pregnancy) is indicated. Of course, any subject with glycosuria should have an oral glucose tolerance test to decide whether renal glycosuria or diabetes mellitus is present. Upon first being seen for a given pregnancy, the following indications for study exist: (1) age 25 or over, (2) past history of multiple spontaneous abortions, stillbirths, and/or birth defects, (3) prior polyhydramnios and large babies, (4) family history in a first degree relative, (5) obesity in the mother, and (6) parity of five or greater.

If the initial glucose tolerance test is normal and glycosuria does not later occur to signal need for a subsequent test, a repeat assessment should be performed between the 28th and 32nd weeks of pregnancy when the diabetogenic effect on the mother is much greater. Most diabetologists would treat most or all subjects with abnormal glucose tolerance with insulin and recommend fetal and maternal monitoring, as done in an established diabetic.

The decision to perform glucose tolerance tests in nonpregnant subjects is clouded because there is no convincing proof that therapeutic interventions (weight loss, diabetic or "atherogenic" dietary manipulation, oral hypoglycemic agents or insulin) reduce mortality and morbidity in NIDDM. In other words, why raise the specter of diabetes if therapy is not of proven benefit? Many subjects with an increased statistical risk of diabetes mellitus, eg, obesity, strong family history, and certain racial or ethnic groups, are included in this question. While making no concrete recommendations at present, this author's personal view is that early diagnosis allows improved prognostication and may well facilitate future management.

Other indications for the oral glucose tolerance test include evaluation of hypoglycemia and suspected hypoglycemic states, certain rare metabolic disorders, and certain endocrine disturbances. Both the intravenous glucose tolerance test and the cortisone glucose tolerance test seem of value primarily in research.

Interpretation of the Glucose Tolerance Test

Whatever the best formal definition of diabetes mellitus or the nature of the syndromes which comprise it, the clinical definition is still stated in terms of elevated blood glucose.* Not only has the definition been approached with increasing caution in recent years, but the diagnostic criteria continue to change with increasingly higher

*Actually, in the clinical setting glucose is now almost always determined on plasma or serum which yields a value that is 15 percent higher than blood glucose. Plasma values are used in this discussion.

plasma glucose levels being considered as the upper limits of normal. Part of the impetus for raising diagnostic limits has been the realization that only a modest percentage of subjects meeting lower or "borderline" criteria ultimately become clearly diabetic. This caution in terms of overdiagnosis is particularly important because of insurance and employment considerations.

There is general agreement that a confirmed fasting plasma glucose found to be above 200 mg/100 ml indicates diabetes, particularly with weight loss and symptoms of polyuria and polydypsia. Most would accept the diagnosis of diabetes mellitus if the fasting values were consistently above 140 mg/100 ml and would consider the glucose tolerance test to be unnecessary.

The glucose load has been most frequently used to diagnose diabetes mellitus when the fasting plasma glucose is below 140 mg/100 ml and herein lies the controversy. What values are normal and what values indicate diabetes mellitus? Ordinarily, in the case of a new laboratory test, the measurement is performed in a group of presumed normal individuals and those values greater than two standard deviations from the mean are considered abnormal. In other words, with a "normal" frequency distribution, 2.5 percent of a population will have abnormally elevated values by definition. The earliest standards for the oral glucose tolerance test were based on tests performed upon young healthy individuals. It has now become clear that glucose tolerance decreases with age. Although fasting plasma glucose varies little with age, values at one and two hours after oral glucose administration increase approximately 5-15 mg/100 ml per decade of life. One analysis performed by age was done by Andres.[8] He developed a nomogram from studies of the blood glucose level (after oral glucose) which gives percentile rankings based on age. As implied above, the cutoff point for abnormality is arbitrary. Andres recommended that the upper two percentile at age 20 years be considered abnormal and that one additional percent be considered abnormal per decade of age. Thus, at age 20, two percent of the population in the United States would be labeled diabetic. At age 70, seven percent would be considered to be diabetic. For the arbitrary definition of diabetes mellitus and borderline diabetes mellitus the National Commission on Diabetes has proffered what they consider to be the highest limits (Andres criteria) and the lowest limits (Fajans criteria) currently in use. The plasma glucose values before and after oral glucose administration, for these two sets of criteria, are shown in Tables 1A and 1B for the various ages. The National Commission asserts that almost everyone would agree that diabetes exists at plasma glucose values above the Andres criteria and that almost everyone would agree that values below the Fajans criteria were normal. The glucose determinations in the area of disagreement between these two sets of criteria are to be considered "borderline."

Table 1. Glucose Tolerance with Age[1]

A. Adapted from Fajans (Lowest)

Age	Fasting Value	1-Hour Value	2-Hour Value
-50	110	185	140
50-60	110	195	150
60-70	110	205	160
70-80	110	215	170

B. Adapted from Andres (Highest)

Age	Fasting Value	1-Hour Value	2-Hour Value
-30	110	185	165
30-40	112	191	175
40-50	114	197	186
50-60	116	203	195
60-70	120	215	215

In this author's view, the simplest and best recommendations to date are the proposed diagnostic criteria of the National Diabetes Data Group. Appendix 1 which follows is adapted from their proposals and includes recommendations for a standardized glucose tolerance test (A) as well as abnormal (B) and normal diagnostic criteria (C). The former is essentially a modified version of the recommendations of the American Diabetes Association in 1968 and I strongly endorse its use. Without a standardized glucose tolerance test the criteria themselves are less meaningful. The criteria for diabetes mellitus, impaired glucose tolerance, and normal glucose tolerance, respectively, were mutually exclusive as originally proposed by the National Diabetes Data Group, which was a very appealing aspect of the recommendation. The revised criteria, as shown in Appendix 1, has an upper limit of normal for fasting plasma glucose of 115 mg/100 ml as compared to the original recom-

mendation of 140 mg/100 ml. Thus, there is now an intermediate group which is not considered normal and not considered to have impaired glucose tolerance. The National Diabetes Data Group believes that fasting plasma glucose values between 115 and 140 mg/100 ml are probably "abnormal and should not be ignored."

The committee has widely solicited comments and suggestions, and the revised document has recently been endorsed by the American Diabetes Association.* It is noteworthy that they do not mention age adjusted criteria. However, their reliance upon a two-hour plasma glucose of 200 mg/100 ml or greater for all age groups, if fasting plasma glucose is not consistently above 140 mg/100 ml, will avoid overdiagnosis in the younger age group. The older age group will still have a relatively large percentage of diabetic subjects by these criteria as is evident from the above discussion of age and glucose tolerance.

National Diabetes Data Group's decision on diagnostic criteria seemed heavily based on two types of studies.* The first type consisted of long-term follow-ups of patients previously considered "borderline" (generally these subjects had fasting glucose levels less than 140 mg/100 ml and levels two hours after glucose of 140 to 200 mg/100 ml. The second was a group of studies dealing primarily with glucose tolerance tests in certain racial populations. The following is a summary of the Data Group's survey of the reports of long-term follow-up of borderline subjects: "(1) The overwhelming majority of individuals whose blood glucose levels fall between normal values and "borderline" diabetic levels constitute a category separate from individuals with gross glucose intolerance; (2) Development of overt diabetic symptoms, or decompensation to well-recognized abnormal glucose tolerance in the absence of symptoms, occurs at a rate of only 1-5 percent per year; a large proportion of individuals show spontaneous reversion to normal glucose tolerance and the remainder stay in the "borderline" category; (3) Restriction of carbohydrate or treatment with oral hypoglycemic agents has little influence on development of diabetes in this group; and (4) The visual and renal microvascular complications of diabetes generally do not develop; however, there is significantly increased frequency of morbidity and mortality from atherosclerotic disease for subjects in the 'borderline' group."

The other major argument for the proposed diagnostic criteria of the National Diabetes Data Group has to do with the frequency distribution of blood glucose levels in certain defined populations. Generally, blood glucose values show a unimodal distribution which is skewed to the high side. Thus, there is a continuous spectrum of values between normal and clearly diabetic subjects. However, in several discrete populations the distribution of plasma glucose is bimodal with a clear cutoff point between nondiabetic and diabetic subjects of 140 mg/100 ml fasting and 200 mg/100 ml at the two-hour value of the glucose tolerance test.*

In addition to the three categories operationally defined by the criteria in Appendix 1 (B), the National Diabetes Data Group proposes three others which are as follows: (1) Previous abnormality of glucose tolerance test; (2) Potential abnormality of glucose tolerance test ("high-risk" subjects); and (3) Glucose intolerance associated with certain conditions and syndromes.

Conclusion

Diagnostic criteria for diabetes mellitus, albeit empirical, may soon be generally accepted and refreshingly noncontroversial, at least for the moment! The recommendations of the National Diabetes Data Group are rational, clear, and helpful in everyday clinical practice.

References

1. National Institutes of Health (Bethesda, Md): Report of the National Commission on Diabetes to the Congress of the United States, vol 3, pt 1: Scope and Impact of Diabetes. DHEW publication No. (NIH) 76-1021. Government Printing Office, 1976, pp 45-64

2. West KM: Substantial differences in diagnostic criteria used by diabetic experts. Diabetes 24:641, 1975

3. Rooter JI, Rimoin DL: Heterogeneity in diabetes mellitus: Update, 1978. Diabetes 27:599, 1978

4. Tattersall RB, Fajans SS: A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 24:44, 1975

5. Rimoin DL: Inheritance in diabetes mellitus. Med Clin North Am 55:807, 1971

6. Carey RM, Tompkins WF, Russell JK, et al: Diabetes mellitus updated: Standards of quality care in office and hospital practice. Virginia Med Monthly 105:195, 1978

7. Stowers JM, Sutherland HW: Carbohydrate Metabolism in Pregnancy and the Newborn. Edinburgh, Churchill-Livingstone, 1975, p 205

8. Andres R: Effect of age in interpretation of glucose and tolbutamide tests. In Fajans SS, Sussman KE (eds): Diabetes Mellitus: Diagnosis and Treatment, vol 3. New York, American Diabetes Association, 1971, pp 115-119

*Harris M, Cahill G, and other members of the National Diabetes Data Group: Classification of diabetes mellitus and other categories of glucose intolerance. Reprints are available upon request from Maureen Harris, PhD, MPH, Program Director, National Diabetes Data Group, NIAMDD, National Institutes of Health, Westwood Building, Room 605-B, Bethesda, MD 20016.

Appendix 1.
The Oral Glucose Tolerance Test and Criteria for the Diagnosis of Diabetes Mellitus, Impaired Glucose Tolerance, Gestational Diabetes, and Normal Tolerance in Adults

A. The Oral Glucose Tolerance Test

The standard oral glucose tolerance test is often unnecessary for the diagnosis of diabetes, as for example when the fasting blood glucose concentration is elevated on more than one occasion. When it is used, however, it should be performed in the morning following at least three days of unrestricted diet and physical activity. The subject should have fasted for at least 10 hours but no more than 16 hours; water is permitted during this period. The subject should remain seated and not smoke throughout the test.

The dose of glucose administered should be 1.75 gm per kg body weight, up to a maximum of 75 gm of glucose. A carbohydrate load equivalent to the glucose dose is also acceptable. Commercially prepared solutions of glucose, maltose, and low molecular weight dextrins with flavoring provide a very palatable carbohydrate load, which is rapidly hydrolyzed to glucose in the stomach. In order to use the criteria for Gestational Diabetes below, a dose of 100 gm is required.

A fasting blood sample should be collected, after which the glucose dose in a concentration no greater than 25 mg/100 ml of flavored water should be drunk in approximately five minutes. Zero time is the beginning of the drink, and blood samples should be collected at 30 minute intervals for two hours. For pregnant subjects, the criteria below for Gestational Diabetes require sampling at fasting, one, two, and three hours. If possible, venous blood samples should be collected, and unless glucose concentrations can be determined immediately using a rapid glucose analyzer, blood should be collected in a tube containing sodium fluoride (5 ml whole blood to 30 mg NaF). The sample should be centrifuged and separated within four hours of collection, and the plasma frozen unless glucose levels are to be determined immediately.

Plasma glucose is the preferred measurement by any of the following methods, which have been shown to be comparable when performed with adequate quality control procedures: glucose oxidase, hexokinase, o-toluidine, Somogi-Nelson, AutoAnalyzer ferricyanide, or AutoAnalyzer neocuproine. See Cooper GR: Methods for determining the amount of glucose in blood. *CRC Crit Rev Clin Lab Sci* 4:101-145, 1973.

See Klimt CR, Prout TE, and other members of the Committee on Statistics of the American Diabetes Association: Standardization of the oral glucose tolerance test. *Diabetes* 18:299-307, 1969, for discussion of factors other than diabetes which influence glucose tolerance.

B. Criteria for Diagnosis

The values below refer to venous plasma samples. Values for venous whole blood glucose concentration should be 15 percent lower. Values for capillary samples (plasma or whole blood) should be ten percent higher than the respective venous values.

Criteria for Diagnosis of Diabetes Based on Fasting Plasma Glucose Concentration:

Fasting plasma glucose concentration $\geq$ 140 mg/100 ml on more than one occasion

Criteria for Diagnosis Based on the Oral Glucose Tolerance Test

Not required if the fasting plasma glucose concentration is $\geq$ 140 mg/100 ml on more than one occasion):

Diabetes Mellitus: Two-hour plasma glucose concentration $\geq$ 200 mg/100 ml
and
At least one value between zero time and two hours $\geq$ 200 mg/100 ml

Impaired Glucose Tolerance: Two-hour plasma glucose concentration $\geq$ 140 mg/100 ml
and $<$ 200 mg/100 ml
and
At least one value between zero time and two hours $\geq$ 200 mg/100 ml

Gestational Diabetes: Gestational diabetes is diagnosed when two or more of the
following plasma glucose values are met or exceeded (after 100 gm glucose dose):
fasting-105 mg/100 ml
one-hour-190 mg/100 ml
two-hour-165 mg/100 ml*
three-hour-145 mg/100 ml

C. Normal Glucose Values

Fasting plasma glucose concentration $<$ 115 mg/100 ml
and
Two-hour plasma glucose concentration $<$ 140 mg/100 ml

*Several members of the workgroup recommended that a category "Impaired Gestational Glucose Tolerance" be defined by a two-hour plasma glucose level between 120 mg/100 ml and 164 mg/100 ml.