How Do We Diagnose Diabetes and Measure Blood Glucose Control?

View 1 (Diagnosing)
A Clinical Basis for the Diagnosis of Diabetes

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In Brief

In 1979, criteria for the diagnosis of diabetes were selected based on levels of glycemia on the oral glucose tolerance test (OGTT) that were associated with the subsequent development of retinopapthy. Since then, five long-term studies have demonstrated that when HbA_{1c} levels are maintained below 7% (normal 6%), development of retinopathy and microalbuminuria is practically nil. Approximately 60% of people with fasting plasma glucose (FPG) concentrations of 126–139 mg/dl and 70% of those with 2-h values on the OGTT of 200–239 mg/dl have normal HbA_{1c} levels, with another third having values between 6 and 7%. This article offers an alternative approach to diagnosis using both FPG and HbA_{1c} values.

Except for a few populations in which the prevalence of diabetes is very high and therefore the distribution of blood glucose concentrations is bimodal,[1,2] a unimodal distribution is the norm.[3,4] Thus, there is no clear-cut demarcation between normal and abnormal blood glucose concentrations.

Before 1979, there were at least six sets of criteria upon which to base the diagnosis of diabetes. This led to an untenable situation in which the prevalence of diabetes in populations differed and diabetes could be either absent or present in an individual depending on which set of criteria was used.[5]

In 1979, the National Diabetes Data Group (NDDG) adopted a set of criteria for the diagnosis of diabetes and impaired glucose tolerance (IGT),[6] which were slightly modified a year later by the World Health Organization[7] (Table 1). An oral glucose tolerance test (OGTT) was administered to 1,277 individuals who were followed for 3–8 years for the subsequent development of diabetic retinopathy. The rationale was that this specific complication of diabetes would identify those subjects whose blood glucose values were high enough to reliably make the diagnosis of diabetes. The criteria in Table 1 were based on the glucose concentrations of only 77 individuals who did subsequently develop this complication.[8]

Several years ago, the American Diabetes Association (ADA) convened an Expert Committee to re-examine the diagnosis and classification of diabetes in light of new information acquired since the NDDG report.[9] One of the goals of the committee was to make the fasting plasma glucose (FPG) and the 2-h blood glucose concentrations on the OGTT criteria equivalent for the diagnosis of diabetes, i.e., if one of these criteria were met, the other would likely be as well. This is not the situation with the

Table 1. Previous World Health Organization Criteria for the Diagnosis of (IGT) and Diabetes

	IGT	Diabetes
FPG	<140 mg/dl	≥140 mg/dl
	and	**or**
OGTT (2-h)*	140–199 mg/dl	≥200 mg/dl

*2-h plasma glucose concentration following 75 g of oral glucose

Table 2. Expert Committee criteria for the diagnosis of diabetes

1. Symptoms of diabetes plus casual plasma glucose concentration ≥200 mg/dl. Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

or

2. FPG ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 h.

or

3. 2-h plasma glucose ≥200 mg/dl during an OGTT. The test should be performed as described by the World Health Organization[7] using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia with acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

two criteria in Table 1. Although ~95% of individuals with an FPG concentration ≥140 mg/dl had a 2-h value on the OGTT ≥200 mg/dl,[10] only one-fourth to one-half of people with 2-h values ≥200 mg/dl had FPG levels ≥140 mg/dl.[10–12]

The committee decided to retain the 2-h criterion of ≥200 mg/dl because of the many epidemiological studies that used it to define diabetes. Changing it, the committee noted, "would be very disruptive."[9] The FPG concentration that yields an equivalent prevalence of diabetes diagnosed by a 2-h value on the OGTT of ≥200 mg/dl is 126 mg/dl.[9]

The committee also made several other recommendations.[9] Because of its poor reproducibility[13–16] and limited use in clinical practice,[17,18] the OGTT was not recommended to be used routinely to diagnose diabetes. (Personally, I agree with that position.)

The criteria the committee did recommend for the diagnosis of diabetes are shown in Table 2. They also defined a normal FPG concentration as <110 mg/dl and individuals with FPG concentrations of 110–125 mg/dl as having impaired fasting glucose (IFG).

HbA_{1c} Versus OGTT

If one accepts the logic that the level of glycemia chosen to diagnose diabetes should be one that is associated with the specific complication of diabetic retinopathy (and I do), HbA_{1c} levels are a better measure of glycemia than values on the OGTT for two reasons. First, they reflect months of prevailing glucose concentrations rather than one instance of time. Second, there have been five studies in several thousand diabetic patients carried out over 6–9 years relating the average HbA_{1c} level to the development and progression of the microvascular complications of diabetes.[19–24] All five demonstrated that if the average HbA_{1c} level were <1% above the upper limit of normal (ULN) for the assay used (e.g., <7% for the assay used in the Diabetes Control and Complications Trial, in which the ULN was 6.0%), there was virtually no development or progression of diabetic retinopathy or nephropathy. If the average HbA_{1c} levels were between 1 and 2 percentage points above the ULN, there was a slight increase in the development and progression of these complications. Average values >2% above the ULN were associated with much higher risks for the microvascular complications.

My colleagues and I have had the opportunity to examine the relationship between HbA_{1c} levels and FPG concentrations[25] and 2-h glucose values on an OGTT[26] in two large populations. One cohort of 8,917 individuals was identified from published reports of the Meta-Analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels (MRG)[10] and therefore was not randomly selected. The second cohort was the 2,836 randomly selected individuals evaluated in the Third National Health and Nutrition Examination Study (NHANES III).

The distribution of HbA_{1c} levels and selected intervals of FPG and 2-h glucose concentrations are shown in Table 3. Note that 60% of the patients with FPG concentrations of 126–139 mg/dl—the group of diabetic patients diagnosed by the new (but not by the old) FPG criterion—had normal HbA_{1c} levels in both popula-

Table 3. Distribution (%) of HbA_{1c} Levels

Glucose (mg/dl)	NHANES III				MRG Data Set			
	No. of Subjects (%)[a]	HbA_{1c} (%)[b]			No. of Subjects (%)[c]	HbA_{1c} (%)[d]		
		≤6.1	6.2–7.0	≥7.1		≤6.3	6.4–7.2	≥7.3
Fasting								
<110	2,284 (84)	97.3	2.7	0.1	7,908 (89)	96.2	3.63	0.2
110–125	373 (11)	86.7	13.1	0.2	602 (7)	81.4	16.4	2.2
126–139	77 (2)	60.9	35.8	3.4	131 (1)	59.6	16.4	7.6
≥140	102 (3)	18.6	32.5	48.9	276 (3)	16.7	21.0	62.3
2-h OGTT								
<140	2,021 (76.2)	97.2	2.7	0.1	7,248 (81.3)	97.1	2.8	0.1
140–199	554 (17.1)	91.4	8.5	0.1	1,109 (12.4)	88.4	11.1	0.8
200–239	111 (2.80)	69.4	29.5	1.1	209 (2.4)	62.2	32.1	5.7
≥240	150 (3.9)	40.9	24.7	34.4	349 (3.9)	21.8	25.8	52.4

[a]Based on U.S. population after weighting the surveyed population, which oversampled minorities.
[b]Upper limit of normal = 6.1%.
[c]Percent of MRG population.
[d]Upper limit of normal = 6.3%.

tions. Furthermore, another one-third had HbA_{1c} levels <1% above the ULN for the assays used, values that were associated with virtually no development or progression of the microvascular complications of diabetes.[19–24] Regarding the 2-h glucose criterion on the OGTT of ≥200 mg/dl, unchanged by the ADA Expert Committee,[9] approximately two-thirds of individuals with values of 200–239 mg/dl had normal HbA_{1c} levels, and most of the remainder had values <1% above the ULN, suggesting that ≥240 mg/dl may be a more appropriate cutoff point.

The Case for HbA_{1c}

In view of the close relationship between HbA_{1c} levels and the microvascular and neuropathic complications of diabetes, and the dictum that only blood glucose concentrations that are associated with the subsequent development of retinopathy are suitable for the diagnosis of diabetes, what is the justification of making this diagnosis in individuals with normal HbA_{1c} values? Not only will ~60% of people with FPG concentrations of 126–139 mg/dl have normal HbA_{1c} levels, an additional one-third will have values that meet the ADA goal (i.e., <7% for assays with a ULN of 6%) before any treatment is initiated.

We must balance the advantages of diagnosing diabetes against its potential disadvantages in terms of insurance (both life and medical), employment, and psychosocial implications.[27–29] For instance, people carrying the diagnosis of diabetes are eight times more likely to be unable to obtain medical insurance because of poor health or illness than are those without diabetes.[29]

It is not clear that it would be helpful to label people with FPG concentrations of 126–139 mg/dl (or 2-h values on an OGTT of 200–239 mg/dl) but with normal or only slightly elevated HbA_{1c} levels as having diabetes. Their treatment would be the same lifestyle therapies of diet and exercise as would be prescribed for individuals with similar HbA_{1c} levels but FPG concentrations of 110–125 mg/dl, which qualifies them for the diagnosis of IFG.[9]

Some argue that the new, lower FPG concentrations for diagnosis are justified because there are so many individuals with undiagnosed type 2 diabetes, and at diagnosis, ~10% of patients already have nephropathy,[30] and 20% already have retinopathy.[31] In my view, this argument does not hold. These people remain undiagnosed because they are not evaluated, not because the FPG concentration for diagnosis is too high.

Similarly, the ADA committee included macrovascular disease in its contention that earlier diagnosis and appropriate treatment would decrease the subsequent complications of diabetes.[9] This reasoning is also suspect because the increased risk for coronary artery disease extends all the way down to the highest quartile of normal FPG concentrations.[32–34] (After this article was submitted, a new study was published of the 4-year incidence of the age-adjusted rate of ischemic heart disease in 4,662 men aged 45–79 years. It revealed a marked increase in the relative risk of those with HbA_{1c} levels ≥5.0% compared with individuals with lesser values,[41] confirming the earlier studies that utilized glucose concentrations.)

Furthermore, improved glycemic control (unfortunately) has little effect on the morbidity and mortality from cardiovascular disease in people with diabetes.[35] A number of other risk factors need addressing, but their prevalences are similar in those with IFG (FPG concentrations of 110–125 mg/dl) and those in the new cohort of diabetes (FPG concentrations of 126–139 mg/dl).[36] Thus, from a macrovascular perspective, there is no advantage in distinguishing between the two groups and labeling people in the latter group as having diabetes.

Not only are HbA_{1c} levels so tightly linked to diabetic retinopathy, nephropathy, and neuropathy,[19–24] but recent reports have also demonstrated that blocking the production of advanced glycosylation end products beyond the formation of HbA_{1c} (and therefore independent of hyperglycemia) markedly retards the development of these complications.[37–40]

Given the importance of excessive glycation of proteins in the pathogenesis of the diabetic microvascular and neuropathic complications and the principle that the level of glycemia associated with these complications is appropriate for the diagnosis of diabetes, an alternative approach to diagnosis, which takes into account these clinical outcomes, is suggested in Figure 1. This diagnostic algorithm uses measurements of FPG concentrations followed by HbA_{1c} levels in people whose FPG values are neither normal (<110 mg/dl) nor meet the older criterion for the diagnosis of diabetes (≥140 mg/dl). The HbA_{1c} level determines whether an individual with an FPG concentration of 110–139 mg/dl has diabetes or a milder degree of hyperglycemia. An HbA_{1c} level 1 percentage point or more above the ULN for the assay used, if confirmed, makes the diagnosis of diabetes. A lower value makes the diagnosis of IFG, which is a high-risk category for the future development of both diabetes and cardiovascular disease and warrants close follow-up and aggressive treatment of the risk factors for each.

It has been argued that HbA_{1c} assays are not yet standardized enough to be used in the diagnosis of diabetes.[9] However, using an assay

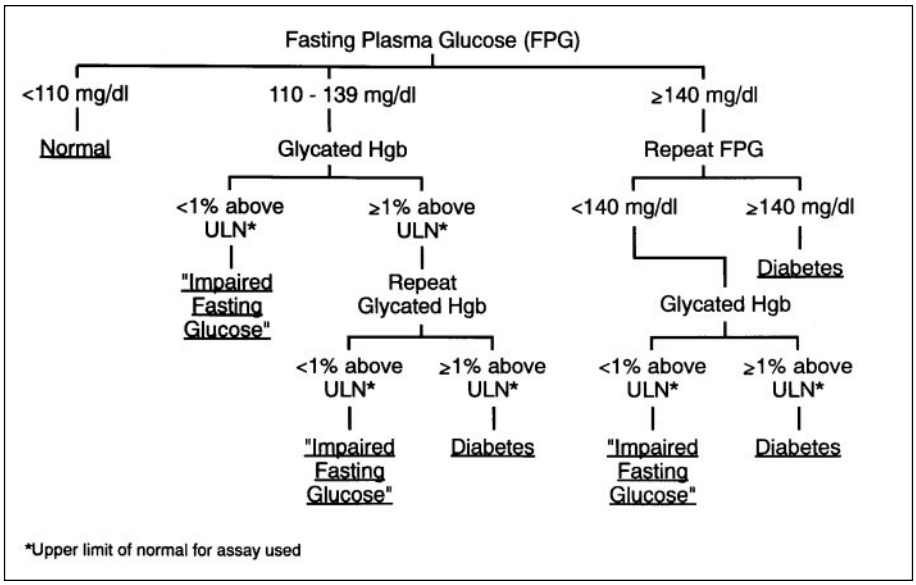

Figure 1. An approach to the diagnosis of diabetes based on clinical outcomes.

meeting the recent standards of the National Glycohemoglobin Program to analyze the NHANES III data, Rohlfing and colleagues[41] concluded that HbA_{1c} levels are both sensitive and specific for detecting diabetes.

If the approach outlined in Figure 1 is followed, diabetes will be diagnosed in those at clear risk for developing the microvascular and neuropathic complications. Individuals with milder degrees of hyperglycemia (who are currently not at risk for these complications) will also be identified so that appropriate measures can be instituted to reduce their chances of developing diabetes or cardiovascular disease.

References

[1]Zimmet P, Whitehouse S: The effect of age on glucose tolerance: studies in a Micronesian population with a high prevalence of diabetes. *Diabetes* 28:617–623, 1979

[2]McCance D, Hanson RL, Charles M-A, Jacobsson LTH, Pettit DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 308:1323–1328, 1994

[3]Gordon T: Glucose tolerance of adults, United States, 1960-1962: diabetes prevalence and results of glucose tolerance test, by age and sex. *Vital and Health Statistics*. Washington D.C., U.S. Government Printing Office, 1964, Series 11, No. 2

[4]Hayner NS, Kjelsberg MD, Epstein FH, Francis T: Carbohydrate tolerance and diabetes in a total community, Tecumseh, Michigan. I. Effects of age, sex, and test conditions on one-hour glucose tolerance in adults. *Diabetes* 14:413–423, 1965

[5]Valleron AJ, Eschwege E, Papoz L, Rosselin GE: Agreement and discrepancy in the evaluation of normal and diabetic oral glucose tolerance test. *Diabetes* 24:585–593, 1975

[6]National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979

[7]World Health Organization: World Health Organization Expert Committee on Diabetes Mellitus: Second Report. Technical report 646. Geneva, Switzerland, World Health Organization, 1980

[8]Davidson MB, Peters AL, Schriger DL: An alternative approach to the diagnosis of diabetes with a review of the literature. *Diabetes Care* 18:1065–1071, 1996

[9]Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997

[10]Peters AL, Davidson MB, Schriger DL, Hasselblad V, for the Meta-Analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. *JAMA* 276:1246–1252, 1996

[11]Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and glucose levels in U.S. population aged 20–74 yr. *Diabetes* 36:523–534, 1987

[12]Modan M, Harris MI: Fasting plasma glucose in screening for NIDDM in the U.S. and Israel. *Diabetes Care* 17:436–439, 1994

[13]Olefsky JM, Reaven GM: Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes* 23:449–453, 1974

[14]Kosaka K, Mizuno Y, Kuzuga T: Reproducibility of the oral glucose tolerance test and the rice-meal test in mild diabetes. *Diabetes* 15:901–904, 1966

[15]Mooy JM, Grootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996

[16]Ko GTC, Chan JCN, Woo J, Lau E, Yeung VTF, Chow C-C, Cockram CS: The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. *Ann Clin Biochem* 35:62–67, 1998

[17]Melton LJ, Palumbo PJ, Chu C-P: Incidence of diabetes mellitus by clinical type. *Diabetes Care* 6:75–86, 1983

[18]Orchard TJ: From diagnosis and classification to complications and therapy. *Diabetes Care* 17:326–338, 1994

[19]The DCCT Research Group: The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

[20]The DCCT Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995

[21]Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motooyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995

[22]Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995

[23]Tanaka Y, Atsumi Y, Matsuoka K, Onuma T, Tohjima T, Kawamori R: Role of glycemic control and blood pressure in the development and progression of nephropathy in elderly Japanese NIDDM patients. *Diabetes Care* 21:116–120, 1998

[24]Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski A: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relatioinship with hyperglycemia. *Diabetes* 49:94–100, 2000

[25]Davidson MB, Schriger DL, Peters AL, Lorber B: Relationship between fasting plasma glucose and glycosylated hemoglobin: potential for false-positive diagnoses of type 2 diabetes using new diagnostic criteria. *JAMA* 281:1203–1210, 1999

[26]Davidson MB, Schriger DL, Peters AL, Lorber B: Revisiting the oral glucose tolerance test criterion for the diagnosis of diabetes. *J Gen Intern Med* 15:551–555, 2000

[27]Tattersall RB, Jackson JGL: Social and emotional complications of diabetes. In *Complications of Diabetes*. Keen H, Jarrett J, Eds. Chicago, Year Book Medical Publishers, 1982, p. 271

[28]Knowler WC: Screening for NIDDM: opportunities for detection, treatment and prevention. *Diabetes Care* 17:445–450, 1994

[29]Harris MI, Cowie CC, Eastman R: Health-insurance coverage for adults with diabetes in the U.S. population. *Diabetes Care* 17:585–591, 1994

[30]Ballard DJ, Humphrey LL, Melton J III, Frohnert PP, Chu C-P, O'Fallon WM, Palumbo PS: Epidemiology of persistent proteinuria in type II diabetes. *Diabetes* 37:405–412, 1988

[31]Harris MI: Undiagnosed NIDDM: public health issues. *Diabetes Care* 16:642–652, 1993

[32]Bjornholt JV, Erikssen G, Aaser E, Sandvik L, Nitter-Hauge S, Jervell J, Erikssen J, Thaulow E: Fasting blood glucose: an underestimated risk factor for cardiovascular death: results from a 22-year follow-up of healthy nondiabetic men. *Diabetes Care* 22:45–49, 1999

[33]Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events; a metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999

[34]Balkau B, Bertrais S, Ducimetiere P, Eschwege E: Is there a glycemic threshold for mortality risk? *Diabetes Care* 22:696–699, 1999

[35]Wild SH, Dunn CJ, McKeigue PM, Comte S: Glycemic control and cardiovascular disease in type 2 diabetes: a review. *Diabetes Metab Res Rev* 15:197–204, 1999

[36]Lerman-Garber I, Zamora-Gonzalez J, Ono AH, Yamamoto-Kimura L, Cardosa-Saldana G, Posadas-Romero C: Effect of the new diagnostic criteria for diabetes in the Mexico City study. *Endocr Pract* 5:179–183, 1999

[37]Bucala R, Cerami A, Vlassara H: Advanced glycosylation end products in diabetic complications. *Diabetes Rev* 3:258–268, 1995

[38]Cohen MP, Sharma K, Jin Y, Hud E, Wu V-Y, Tomaszewski J, Ziyadeh FN: Prevention of diabetic nephropathy in db/db mice with glycated albumin antagonists. *J Clin Invest* 95:2338–2345, 1995

[39]Nakamura S, Makita Z, Ishikawa S, Yasamura K, Fujii W, Yanagisawa K, Kawata T, Koike T: Progression of nephropathy in spontaneous diabetic rats is prevented by OPB-9195, a novel inhibitor of advanced glycation. *Diabetes* 46:895–899, 1997

[40]Clements RS Jr, Robsion WG Jr, Cohen MP: Anti-glycated albumin therapy ameliorates early

retinal microvascular pathology in db/db mice. *J Diabetes Complications* 12:28–33, 1998

[41]Rohlfing CL, Little RP, Wiedmeyer H-M, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE: Use of GHb (HbA_{1c}) in screening for undiagnosed diabetes in the U.S. population. *Diabetes Care* 23:187–191, 2000

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