Counterpoint: The Oral Glucose Tolerance Test Is Superfluous

The oral glucose tolerance test (OGTT) has been used in clinical medicine for nearly 90 years (1). As heretical as this may sound, it is time for it to be retired. It no longer provides unique and important clinical information that cannot be obtained by other means. The main reason for performing it is to diagnose impaired glucose tolerance (IGT) or diabetes by virtue of the 2-h value (2,3). Both of these are risk factors for cardiovascular disease (CVD) (4,5), and IGT predicts the development of diabetes (6). However, abnormal carbohydrate metabolism is only one of a number of risk factors for CVD, the combination of which is termed the insulin resistance syndrome. Clinically, the insulin resistance syndrome is diagnosed if three of the following five risk factors for CVD are present: central obesity (waist circumference >88 cm in women and >102 cm in men), elevated triglyceride concentrations (>1.7 mmol/l or 150 mg/dl), decreased HDL cholesterol levels (<1.0 mmol/l or 40 mg/dl in men, <1.3 mmol/l or 50 mg/dl in women), hypertension, and hyperglycemia (impaired fasting glucose, IGT, or diabetes) (7).

Two articles in this issue of *Diabetes Care* demonstrate that the 2-h value on the OGTT adds nothing (8) or very little (9) for identifying CVD risk if the other risk factors are taken into account. Stern et al. (8) followed 2,662 Mexican Americans and 1,595 non-Hispanic whites who were between 25 and 64 years of age and did not have diabetes or CVD at baseline for 7–8 years. Addition of 2-h glucose values from the OGTT to models incorporating readily available CVD risk factors did not improve their power to predict CVD. More specifically, further unpublished analysis of these data revealed that if 1,000 people were screened for CVD risk factors and those who fell into the top 20% of the distribution were considered to be at increased risk, 24 of 37 cases of future CVD events would be identified with the multivariate model that excluded the 2-h value on the OGTT. Using the multivariate model that included the 2-h value identifies 25 of 37 cases of future CVD events. In other words, one would have to perform 1,000 OGTTs to identify one additional case of future CVD events (personal communication, M.P. Stern).

Meigs et al. (9) evaluated 3,370 subjects from the Framingham Offspring Study who had no clinical evidence of CVD, i.e., coronary artery disease, stroke, or intermittent claudication, during 1991–1995 and followed them for 4 years for incident CVD. They showed that if standard CVD risk factors were taken into account, "the marginal predictive capacity of postchallenge hyperglycemia was small" and concluded that "eliminating the OGTT for the screening and diagnosis of diabetes would have minimal impact in terms of identifying CVD risk." Further unpublished analysis of this Framingham data set revealed that the addition of the 2-h value on the OGTT to the multivariate proportional hazards regression model lead to no more than two additional future CVD cases being detected per 1,000 individuals screened (personal communication, J.B. Meigs).

The results of the DECODE study (10) are the major argument offered for the importance of performing an OGTT to diagnose IGT that places these individuals at an increased risk for CVD. OGTTs were performed in 18,048 men and 7,316 women over the age of 30 years from 13 prospective European cohort studies; the subjects were then followed for a median of 7.3 years with mortality as the outcome. Men and women with IGT at baseline had hazard ratios of 1.51 and 1.60, respectively, for death. Men and women with newly diagnosed diabetes by virtue of a 2-h value on the OGTT ≥11.1 mmol/l at baseline had hazard ratios of 2.02 and 2.77, respectively. Although causes of death were not specified, it seems reasonable to assume that the majority was from CVD in these groups of subjects. However, it cannot be known whether the individuals with IGT had progressed to diabetes in the interim before death.

This may be an important question given the follow-up data of the Mexican American subjects enrolled in the San Antonio Heart Study who underwent a repeat OGTT 7.7 years after the baseline OGTT and who were followed for an additional 7.7 years after the second OGTT (11). Compared with individuals who had normal glucose tolerance (NGT) at baseline and did not progress to diabetes during the follow-up period, increased all-cause and CVD mortality occurred only in those who did progress to diabetes from either IGT or NGT at baseline. Those with IGT at baseline who remained free of diabetes at follow-up did not have an increase in either all-cause or CVD mortality. Thus, in this cohort, IGT that did not progress to diabetes was not a risk factor for CVD over a 15-year period.

There are a number of drawbacks to performing an OGTT. From a clinical perspective, the most serious is its lack of reproducibility (12–15). This is why both the American Diabetes Association (ADA) (2) and the World Health Organization (3) require a second OGTT to confirm the diagnosis of diabetes. Two studies (14,15) have compared the diagnosis in the same individual on the first and second OGTTs performed within 2–6 weeks of each other. In those with IGT on the first OGTT, this diagnosis of IGT was sustained less than one-half of the time on the second OGTT. In one study of 198 people having IGT on the first OGTT, the second diagnosis was IGT in 48%, NGT in 39%, and diabetes in 13% of the subjects (14). The results of the other study (15), in which 93 individuals had IGT on the first OGTT, agreed remarkably well, with the second diagnosis being IGT in 44%, NGT in 46%, and diabetes in 10%. These data would suggest that we should repeat the OGTT to confirm the diagnosis of IGT as is recommended for the diagnosis of diabetes. Other drawbacks are that it is inconvenient, sometimes causes symptoms, and, at least in the U.S., few physicians are using it (16,17).

How about the utility of the OGTT for diagnosing diabetes? In 1979 the National Diabetes Data Group (NDDG) promulgated OGTT criteria for the diagnosis of diabetes using the principle that the level of glycemia chosen should be associated with the specific microvascular complication of diabetic retinopathy (18). The 2-h criterion of ≥11.1 mmol/l (200

mg/dl) was chosen based on the development of this diabetic complication in 77 of 1,213 subjects followed for 3–8 years after a baseline OGTT (19). Thus, this sacrosanct value is based on <100 individuals who had one 2-h value on an OGTT at one point in time. Since then, several long-term intervention studies have conclusively shown that microvascular complications are causally related to HbA_{1c} levels (20–22). However, these values are normal in two-thirds of people with 2-h glucose concentrations on an OGTT of 11.1–13.3 mmol/l (200–239 mg/dl) and in 20–40% of those with 2-h levels >13.3 mmol/l (240 mg/dl) (23). If the principle of setting a glycemic level for the diagnosis of diabetes that is associated with the microvascular complications of the disease is valid (and I believe that it is), how can we diagnose diabetes in people with normal HbA_{1c} levels? This is not a benign misdiagnosis. In this country, there are certain negative insurance, and possibly employment, consequences of carrying the diagnosis of diabetes. For instance, people with the diagnosis of diabetes are eight times more likely to be unable to obtain medical insurance because of poor health or illness than people without diabetes (24).

How about the utility of the OGTT for helping to guide therapy? It is of no help in this arena as well. Subjects with IGT have normal glucose levels in their daily lives (25). The results of an OGTT are also not helpful for deciding therapy in patients diagnosed with diabetes. Although CVD is associated with glucose levels (4), the risk is a continuous one occurring throughout the normal range of glucose (5). For example, men between the ages of 45 and 74 years whose HbA_{1c} levels were between 5.0 and 5.4% had a 2.7-fold increase in myocardial infarctions over 4 years compared with those with HbA_{1c} values <5.0% (26). Even if a goal HbA_{1c} level of <5.0% was realistic (which it's not), there is no evidence to date that lowering glycemia in diabetic patients benefits patients with macrovascular disease (22,27).

Regarding microvascular disease, lowering glycemia (as judged by HbA_{1c} levels) is helpful (20–22). However, >90% of people who would be diagnosed with diabetes by an OGTT already meet the ADA's goal HbA_{1c} level of <7.0% (assuming an upper limit of normal of 6.0%) (28). For example, in the subjects in the data set from the Meta-Analysis Research Group (MRG) on the Diagnosis of Diabetes Using Glycated Hemoglobin (29) who were diagnosed with diabetes with 2-h glucose values ≥11.1 mmol/l (200 mg/dl), but had fasting plasma glucose concentrations (FPG) of <7.0 mmol/l (126 mg/dl), 94% of those with a normal FPG concentration of <6.1 mmol/l (110 mg/dl) and 90% of those with impaired fasting glucose (IFG), i.e., FPG concentrations of 6.1–7.0 mmol/l (110–125 mg/dl), had HbA_{1c} levels <7% (personal communication, David Schriger). The MRG data were obtained from 10 published studies in which subjects were nonrandomly self-referred from the general population or referred from high-risk populations and thus more likely to have hyperglycemia. People from a randomly selected population who were diagnosed with diabetes by 2-h values on the OGTT, but did not meet the FPG concentration criterion, are even less likely to have HbA_{1c} levels above the ADA goal of 7%. In the weighted data from the Third National Health and Nutrition Examination Survey (NHANES III), no one with a normal FPG concentration had an HbA_{1c} >7%, and 95% of those with IFG had values <7% (personal communication, Brett Lorber).

The therapeutic approach to all those diagnosed with IGT and >90% of those diagnosed with diabetes by the OGTT is lifestyle modification of diet and exercise patterns. Indeed, even those with HbA_{1c} values >7% at diagnosis should initially receive lifestyle modification unless they have symptoms of uncontrolled diabetes (30). Treatment of hypertension and hyperlipidemia is also important, but the OGTT is not involved in identifying these risk factors.

In summary, the OGTT is not helpful clinically. It is not necessary for identifying individuals at risk for CVD. Far too many people whose diagnosis of diabetes depends solely on the 2-h value have normal HbA_{1c} levels and therefore (in my view) should not be given the diagnosis of diabetes. Furthermore, the OGTT is useless in guiding therapy, either in those with IGT or with diabetes, regardless of the criteria used to diagnose the latter. An argument perhaps can be made to use it for epidemiological studies. Indeed, the ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus decided to retain the 2-h value of ≥11.1 mmol/l (200 mg/dl) because a large number of epidemiological studies in the literature used this value to define diabetes and changing it "would be very disruptive" (2). However, based on the above data, the OGTT has clearly outlived its clinical usefulness and should be retired.

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See Meigs et al. (p. 1845) and Stern et al. (p. 1851)

References

1. Jacobsen A: Untersuchungen uber den einfluss des chloralhydrats auf experimentelle hyperglykamieformen. *Biochem Z* 51:443, 1913
2. The 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
3. Alberti KGMM, Zimmet PZ, for the WHO Consultation: Definition, diagnosis and classification of diabetes mellitus and complications. I. Diagnosis and classification of diabetes: provisional report of a WHO consultation. *Diabet Med* 15:539–533, 1998
4. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL: Postchallenge hyperglycemia and mortality in a national sample of U.S. adults. *Diabetes Care* 24: 1397–1402, 2001
5. Barrett-Connor E, Wingard DL: "Normal" blood glucose and coronary risk: dose response effect seems consistent throughout the glycaemic continuum. *BMJ* 322: 5–6, 2001
6. Rewers M, Hamman RF: Risk factors for non-insulin-dependent diabetes. In *Diabetes in America*. 2nd ed. Bethesda, MD, National Diabetes Data Group, 1995, p. 179–220 (publication no. 95-1468)
7. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285:2486–2509, 2001
8. Stern MP, Fatehi P, Williams K, Haffner SM: Predicting future cardiovascular disease: do we need the oral glucose tolerance test? *Diabetes Care* 25:1851–1856, 2002
9. Meigs JB, Nathan DM, D'Agostino RB, Wilson PWF: Fasting and postchallenge

glycemia and cardiovascular risk: the Framingham Offspring Study. *Diabetes Care* 25:1845–1850, 2002
10. The DECODE Study Group, on Behalf of the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
11. Hunt KJ, Resendez RG, Williams K, Haffner SM, Stern MP: Excess mortality among individuals with impaired glucose tolerance (IGT) is limited to those who develop diabetes: the San Antonio Heart Study (Abstract). *Diabetes* 51 (Suppl. 2): A229, 2002
12. Olefsky JM, Reaven GM: Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes* 23:449–453, 1974
13. 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
14. Mooy JM, Grootenhuis PA, de Vries H, Kostene 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
15. 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 factor. *Ann Clin* Biochem 35:62–67, 1998
16. Melton LJ, Palumbo PJ, Chu C-P: Incidence of diabetes mellitus by clinical type. *Diabetes Care* 6:75–86, 1983
17. Orchard TJ: From diagnosis and classification to complications and therapy. *Diabetes Care* 17:326–338, 1994
18. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 28:1039–1057, 1979
19. 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
20. 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
21. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi 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. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
23. 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
24. Harris MI, Cowie CC, Eastman R: Health-insurance coverage for adults with diabetes in the U.S. population. *Diabetes Care* 17:585–591, 1994
25. Golay A, Chen Y-DI, Reaven GM: Effect of differences in glucose tolerance on insulin's ability to regulate carbohydrate and free fatty acid metabolism in obese individuals. *Diabetes Care* 62:1081–1088, 1986
26. Khaw K-T, Wareham N, Luben R, Bingham S, Oakes S, Welch A, Day N: Glycosylated haemoglobin, diabetes and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ* 322:15–18, 2001
27. Huang ES, Meigs JB, Singer D: The effect of intreventions to prevent cardiovascular disease in patients with type 2 diabetes mellitus. *Am J Med* 111:633–642, 2001
28. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes* Care 25 (Suppl. 1):S33–S49, 2002
29. Peters AL, Davidson MB, Schriger DL, Hasselblad V, for the Meta-Analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels: A clincial approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. *JAMA* 276:1246–1252, 1996
30. American Diabetes Association: The pharmacological treatment of hyperglycemia in NIDDM (Consensus Statement). *Diabetes Care* 18:1510–1518, 1995