Point: A Glucose Tolerance Test Is Important for Clinical Practice

There is no doubt that clinical, symptomatic diabetes is a risk factor for cardiovascular disease (CVD) and all-cause mortality. It has also been shown that the risk is graded across the entire range of hyperglycemia (1,2). However, it has been debated during the last decades whether asymptomatic, unrecognized diabetics, or even a lesser degree of hyperglycemia, increases the risk of CVD and death. Traditionally, investigators who studied the association between hyperglycemia and the development of diabetic complications focused on fasting glucose levels (3). Until the 1980s, the standards for measuring blood glucose concentration varied, HbA1c was not available, and consequently, the results between the studies were conflicting. Now that we have data from the multitude of studies in which recommended standards have been applied (4,5), it has been possible to get a clearer picture of the matter. A plethora of recent studies from diverse populations have demonstrated that asymptomatic hyperglycemia is an independent risk factor (6–10).

Determination of hyperglycemia

Hyperglycemia, however, is not a simple issue. Blood glucose has a strong diurnal variation; it also varies seasonally and changes with age. Hyperglycemia can be determined at least in three ways by measuring fasting glucose, postchallenge (or postprandial) glucose, and HbA1c. The first is by definition the lowest glucose level during the day, during a few early morning hours. HbA1c indicates the mean glycemic level during a lengthy period of time—several weeks or months—summarizing both fasting and postprandial glucose levels. Postchallenge glucose level shows the magnitude of glucose elevation (peak) after the glucose load, lasting 1–3 h. If one eats the usual three meals a day, the postprandial glycaemia usually lasts from 6 to 9 h a day (11). Even though there are moderate correlations between these parameters of glycaemia, in the general population they are independent to a great extent. This means that none of them can be used alone to identify people who have asymptomatic diabetes, since one would always miss those who have isolated elevation of either fasting or 2-h postchallenge glucose. This applies even to HbA1c, since in the case of isolated high fasting but low 2-h glucose or isolated high 2-h but low fasting glucose, the long-term average would not show a clear elevation in HbA1c.

Many investigators have attempted to find the “corresponding” values of the other two by measuring only one of the three glycemic parameters. It is probably time to stop such efforts, because it will not lead us anywhere. The colinearity among these three may be high, as seen in the Pima Indians (12), but only in some extreme situations in which people are very obese and sedentary or in a large proportion that carries the diabetes susceptibility genes. This may also apply to Mexican Americans, including those studied in San Antonio, Texas (13). The results from the DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) Study, on the other hand, showed that in lean Asian people, who show the same prevalence of diabetes as Europeans, much more people have elevated postchallenge than fasting hyperglycemia (14).

Type 2 diabetes is characterized not only by fasting but also by postprandial hyperglycemia, and by nature, high postprandial glucose levels are also present in patients who have high fasting blood glucose. Recent evidence suggests that high postprandial glucose may be of a greater importance than had been thought previously (15). The current guidelines do not recommend the measurement of postprandial glucose; rather, they recommend obtaining information by use of a glucose tolerance test, as the latter can be better standardized. Even though the postchallenge glucose is not the same as postprandial glucose after a mixed meal, it can be used as a proxy for it. It is common to use nonphysiologic challenge tests in detecting endocrinological abnormalities. The 2-h postchallenge glucose has been criticized for its higher variability compared with the fasting glucose. The fasting glucose level in a population does not increase with age, like 2-h glucose does. This is understandable, because it measures the lowest glucose level during the day. This low variability makes it a poor, insensitive screening test and increasingly poorer with age, whereas the 2-h postchallenge glucose has sufficient variation to distinguish between normal and elevated values.

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How well does HbA1c predict mortality?

A British study recently showed that CVD mortality increased with increasing HbA1c >5.8% (16). Unfortunately, no other glycemic parameters were available in this study. The data from the Hoorn study indicated that 2-h postchallenge glucose was a better predictor than HbA1c for all-cause and CVD mortality (17). The results from the Framingham Offspring Study now confirm this finding (18). The data from the Finnish East-West study (follow-up of the Seven Countries Study) also support this (19). All three of these studies show that fasting glucose is clearly the least predictive glycemic parameter for mortality. Also, the earlier data from the Islington study in the U.K. are in keeping with this notion (20).

Implications from findings from prospective studies for the measurement of glycemic parameters and prevention of CVD

The studies of Stern et al. (13) and Meigs et al. (18) both had major problems when attempting to evaluate the role of asymptomatic hyperglycemia and postchallenge glucose as a risk factor for CVD. First of
tion is not justi-
for blood glucose in the general popula-
to carry the highest CVD risk were not
justed for in multivariate analyses. Thus,
lent diabetes at baseline, truncating their
Stern et al. excluded subjects with preva-
tance of glucose in multivariate models.
ment of the population, as also shown by
measures should be targeted to entire
nostrance of nonacute diseases. For instance,
ranal phase has several deleterious effects
served in glucose-intolerant and type 2
diabetic patients (29). It is important to
acknowledge these pathophysiologic changes since they point out that elevated
postchallenge/postprandial glucose is dif-
dent from elevated fasting glucose. In addi-
tion, it seems to mark the earliest ab-
normalities that we can detect in clinical
practice. Our goal should be to provide
advice and help to our clients as early as
possible in order to stop or inhibit the
process leading to β-cell failure.

Oral glucose tolerance test: implications for the prevention of
type 2 diabetes
The encouraging results from the recent
trials to prevent type 2 diabetes (30,31)
call for immediate action. The potential to
prevent or significantly postpone the de-
velopment of type 2 diabetes in high-risk
subjects should not be overlooked. It is
important to note that these, like other
type 2 diabetes prevention trials, have
been carried out in people with IGT.
Thus, we have firm evidence that deteri-
oration of elevated postchallenge glucose
can be delayed. In the current era of evi-
dence-based medicine, this unequivocal
knowledge should be the strongest argu-
ment to test for glucose intolerance in
people known to be otherwise at high risk
for type 2 diabetes. Obviously, preventive
measures should be targeted to entire
populations, but, in addition, individual
management of high-risk subjects is also
necessary.

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


