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 diabetes, 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, HbA_{1c} 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 HbA_{1c}. The first is by definition the lowest glucose level during the day, during a few early morning hours. HbA_{1c} 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 glycemia usually lasts from 6 to 9 h a day (11). Even though there are moderate correlations between these parameters of glycemia, 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 HbA_{1c}, 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 HbA_{1c}.

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.

Type 2 diabetes and asymptomatic hyperglycemia affect mostly the older segment of the population (6), even though it may be increasingly seen in younger subjects. The increase in hyperglycemia in the population with age is almost entirely due to the increase in 2-h glucose levels. In the developed countries, the prevalence of impaired glucose tolerance (IGT) in 70-year-olds is >20%, as compared with ~5% prevalence of impaired fasting glucose (IFG). The percentages are almost similar for asymptomatic diabetes identified by isolated 2-h hyperglycemia and isolated fasting hyperglycemia, respectively.

How well does HbA_{1c} predict mortality?

A British study recently showed that CVD mortality increased with increasing HbA_{1c} >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 HbA_{1c} 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

all, both studies were relatively small and had a short follow-up. Thus, the number of events was small and the studies were clearly underpowered for multivariate analyses. Second, the study populations were relatively young, contributing to the low power and, more importantly, comprising an incorrect target group to study the effects of high postchallenge glucose on CVD. The high postchallenge glucose is particularly a problem among older people, and it predicts the risk in this segment of the population, as also shown by Meigs et al. Authors of both articles note this problem, but only in passing. In properly powered studies in which older people have also been included, such as the DECODE study, 2-h postchallenge glucose remained an independent predictor of CVD mortality after adjusting for other risk factors (7,21). Third, the definition of a CVD event was very wide in these two studies and included heterogeneous nonacute diseases. For instance, Stern et al. had only 22 CVD deaths out of 159 events (14%), of which the majority consisted of self-reported events (13). Thus, it is not possible to generalize these results to the prediction of acute CVD, CVD mortality, or total mortality. Fourth, the issue of colinearity, i.e., the well-known fact that glucose is part of the metabolic syndrome, is not discussed, and the low power of the studies does not permit any stratified analyses to clarify this important matter. Finally, the issue of prevalent diabetes is handled in a way that would significantly reduce the importance of glucose in multivariate models. Stern et al. excluded subjects with prevalent diabetes at baseline, truncating their sample for glycemic parameters only, and Meigs et al. included prevalent diabetes in their Framingham Risk Score that was adjusted for in multivariate analyses. Thus, the highest glucose values that are known to carry the highest CVD risk were not included in the prediction of the outcome.

It is commonly agreed that screening for blood glucose in the general population is not justified for several reasons. It is possible to identify the target groups at a high risk of type 2 diabetes, to whom the search for asymptomatic diabetes can be restricted, even without any clinical or laboratory measurements (22,23). We also know that without performing an oral glucose tolerance test we would miss a large proportion of subjects who have isolated postchallenge hyperglycemia defined by a diabetic postglucose challenge level of plasma glucose (≥11.1 mmol/l) but a normal FPG level (<7.0 mmol/l) (24). Prospective studies carried out in such subjects have revealed that this abnormality is not only common but that it doubles the mortality risk (7,25). The Rancho Bernardo Study confirmed that, in older women, isolated postchallenge hyperglycemia more than doubles the risk of fatal CVD (6). It is important to note that the importance of asymptomatic postchallenge hyperglycemia is always underestimated in prospective studies in which usually a single glucose testing is done at baseline, since many people initially having normal glucose tolerance will develop abnormal glucose tolerance during the follow-up. Thus, by the time of the CVD event, many more of these subjects have been exposed to hyperglycemia than originally found at baseline. This was elegantly illustrated by a very interesting recent study from Sweden. It revealed that, of patients with acute myocardial infarction, 31% had asymptomatic diabetes and another 35% had IGT when tested for glucose tolerance (26). In comparison, 31% had hypertension, 34% were smokers, and 33% had history of angina pectoris. Even though this study cannot show the causal relation between undiagnosed glucose intolerance and myocardial infarction, the prevalence of glucose intolerance was far too high to be just a coincidence. Thus, another important target group for testing for glucose intolerance seems to be the patients with a new CVD event.

Early-phase insulin release and postprandial hyperglycemia

Type 2 diabetes is characterized by two fundamental defects: insufficient production of insulin by pancreatic β-cells and reduced target-tissue sensitivity to the effects of insulin (insulin resistance). An important defect in insulin secretion is the impairment of early-phase insulin release, which is always present in type 2 diabetic patients and occurs early in the development of this disease (27). In normal individuals, the early phase is a burst of insulin release that begins within minutes of a glycemic stimulus. Early-phase insulin primes tissues that are sensitive to it, in particular liver tissue, which results in the reduction of hepatic glucose output.

In patients with IGT, the early-phase insulin response to glucose is reduced, and in type 2 diabetic patients, the early-phase of insulin release is both delayed and blunted (28). The loss of early-phase insulin release during and after the prandial phase has several deleterious effects on normal glucose homeostasis: hepatic glycogenolysis and gluconeogenesis are not inhibited sufficiently, and glucose uptake by muscle is insufficient. This leads to the postprandial hyperglycemia observed 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 different from elevated fasting glucose. In addition, it seems to mark the earliest abnormalities 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 development 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 deterioration of elevated postchallenge glucose can be delayed. In the current era of evidence-based medicine, this unequivocal knowledge should be the strongest argument 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).

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