Fasting Versus Postload Glucose Levels

Why the controversy?

In 1997, the American Diabetes Association (ADA) published updated criteria for the diagnosis of diabetes and states of glucose tolerance (1). Its recommendation that the oral glucose tolerance test (OGTT) not be routinely used to identify people with either diabetes or impaired glucose tolerance (IGT) has fueled considerable controversy regarding the importance of such testing in either a clinical or epidemiological context (2–9). Generally, these reports have pointed out that a fasting plasma glucose (FPG) level alone will underestimate the prevalence of diabetes and/or underestimate the prevalence of IGT. Moreover, they have also pointed out that postload hyperglycemia is an early risk factor for cardiovascular (CV) events and that it may be a stronger predictor of CV events than fasting hyperglycemia (4). These observations have been cited to support a re-evaluation of the ADA recommendation and retention of the OGTT for routine use. However, a careful examination of the ADA recommendation suggests that this may in part be based on a misinterpretation of its underlying rationale. A brief review of some relevant data and of the significance of a diagnosis of diabetes and IGT may help to inform ongoing discussions regarding this issue.

WHITHER THE DIAGNOSTIC THRESHOLDS FOR DIABETES AND IGT?

In the ADA report of the expert committee, epidemiological data regarding the clinical significance of an OGTT were reviewed. In at least three different populations, a 2-h plasma glucose level ≥11.1 mmol/l (200 mg/dl) (measured after a 75-g oral glucose load) was a strong predictor of subsequent eye and kidney disease. Therefore, these data *1*) confirmed that this 2-h glucose level was an appropriate cutoff in which to base a diagnosis of diabetes, *2*) highlighted the fact that the glucose criteria for a diagnosis of diabetes are derived from data relating glucose concentrations to the risk of eye and kidney disease, and *3*) reinforced the relevance of the postload value as the "gold standard" or diagnostic standard for diabetes. The data also supported the suggestion that the FPG could be used as a simple test for detecting the presence or absence of this diagnostic standard. In this context, it is important to emphasize that although diabetes is clearly a strong independent risk factor for CV disease (CVD), the diagnostic thresholds for diabetes were not based on any analysis of the glucose-CVD risk relationship.

The ADA also reviewed and supported previous glycemic criteria for the diagnosis of IGT, i.e., a 2-h post–75-g glucose load plasma glucose value ≥7.8 mmol/l (140 mg/dl) and <11.1 mmol/l (200 mg/dl) in someone without diabetes. IGT was simply defined as a state intermediate between normal glucose homeostasis and diabetes. Many epidemiological studies have reported that IGT is a strong risk factor for subsequent diabetes (10). It is also a risk factor for CVD (7,11,12). Nevertheless, the glycemic cutoffs for IGT were not based on either the IGT-diabetes or the IGT-CV event relationship; indeed, several reports suggest that lower degrees of dysglycemia than those defined by IGT are also associated with a higher-than-normal risk for CVD (11–14).

SIMPLE TESTS TO DETECT DIABETES AND IGT

The clinical importance of easily detecting people with diabetes is related to strong evidence that the consequences of diabetes can be delayed or prevented with glucose lowering and other therapies (15–17). Similarly, the importance of being able to easily detect people with IGT is related to emerging evidence that diabetes can be delayed or prevented in people with IGT (18).

Because it is often difficult or clumsy to perform the diagnostic standard test for a disease, clinical scientists have identified simpler, albeit less accurate, tests that serve as substitutes for the difficult diagnostic test. In addition, epidemiologists have developed a methodology to evaluate and quantify the usefulness of these substitute tests. It is clear that the OGTT is an example of one such difficult diagnostic standard. It is difficult to perform, may cause discomfort and nausea, requires careful preparation, has high variability, and is simply not performed on a regular basis (1). It was because of these reasons and the fact that a large proportion of all people with diabetes are undiagnosed that the expert committee discouraged the use of the OGTT to diagnose diabetes and recommended using an FPG ≥7.0 mmol/l (126 mg/dl). Data supporting this recommendation consistently demonstrate that this FPG cutoff has >95% specificity for a 2-h glucose level ≥11.1 mmol/l (200 mg/dl). That is, most studies report that <5% of people with a 2-h glucose level <11.1 mmol/l (200 mg/dl) have an FPG ≥7.0 mmol/l (126 mg/dl) (5,19). Unfortunately, these data also demonstrate that this cutoff is insensitive: approximately as few as 50% of people who would have been classified with diabetes based on the 2-h glucose had a fasting level <7.0 mmol/l. Thus, the FPG identifies people with diabetes with high certainty and misclassifies some individuals who actually have diabetes as being free of diabetes.

Similar considerations apply to the detection of IGT. As both the ADA and the World Health Organization (20) define impaired fasting glucose (IFG) and IGT as being intermediate between normal glucose homeostasis and diabetes, it is reasonable to assess whether IFG can be used to identify people with IGT. The available data show again that the FPG cutoff has high specificity but low sensitivity for the presence of IGT. For example, a 6-year prospective study of 1,342 nondiabetic white Dutch individuals aged 50–75 years who had an OGTT at baseline (21) was recently published. In this population, IFG had 92% specificity and 28% sensitivity for the presence of IGT. Thus, only 8% of individuals with normal glu-

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cose tolerance had IFG, but >70% of people with IGT had FPG levels <6.1 mmol/l (110 mg/dl). Once again, using the FPG alone errs on the conservative side—the presence of IFG indicates that the person may have IGT. The absence of IFG, however, does not rule out the possibility that IGT is present. Indeed, as shown in other studies that did not exclude people with diabetes, an FPG level <6.1 mmol/l (110 mg/dl) does not even rule out diabetes diagnosed by a 2-h postload glucose value (5,19).

More importantly, this same study also assessed the relative value of IFG and IGT as predictors of future diabetes (21). It showed that both IGT and IFG were strong predictors of subsequent diabetes and that few people with normal fasting glucose levels or normal glucose tolerance developed future diabetes during the follow-up period. Similar findings were reported from other communities (5,8).

THE VALUE OF FASTING DATA ALONE

The above discussion clearly illustrates that an abnormal FPG clearly provides important information. If a patient's FPG is ≥7.0 mmol/l (126 mg/dl), he/she is very likely to have diabetes (defined based on a 2-h plasma glucose ≥11.1 mmol/l or 200 mg/dl), and if it is ≥6.1 mmol/l he/she may have either IGT or diabetes based on the postload glucose values. This is another way of saying that individuals with a fasting glucose level ≥6.1 mmol/l (110 mg/dl) are at high risk for CVD; individuals with a level between 6.1 mmol (110 mg/dl) and 7.0 mmol are also at high risk of future diabetes; and individuals with a level of ≥7.0 mmol/l (126 mg/dl) have diabetes and are therefore also at high risk for microvascular disease.

The above discussion also clearly shows that FPG levels <6.1 or 7.0 mmol/l provide no reliable information on whether an individual has either IGT or diabetes. Therefore, if the goal is to be certain that a diagnosis of diabetes is accurate and to avoid over-diagnosing diabetes, the FPG performs very well. However, if the goal is to identify everyone with IGT or diabetes and/or everyone at risk for future diabetes or CV eye, kidney, nerve, and other disease, an OGTT must be performed. Alternatively, a lower fasting glucose value, perhaps in combination with another test, such as a HbA_{1c}, needs to be established and validated (5,22). Large ongoing studies in diabetes and CV prevention should allow exploration of different diagnostic approaches. Until then, it is more important to advocate the widespread use of a test that is easy to access and that minimizes the possibility of an individual being falsely labeled as having a disease than to insist on the routine use of a difficult and inaccessible one. Clearly, however, there are clinical and research situations in which a full OGTT is warranted.

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