Point: Impaired Fasting Glucose: The Case for the New American Diabetes Association Criterion

In 1979 and 1980, both the National Diabetes Data Group (1) and the World Health Organization (WHO) (2) formally defined a postchallenge state of glucose tolerance that lay between what was considered normal and diabetic. This state was defined as an elevated 2-h plasma glucose with a nondiabetic fasting glucose level and was termed "impaired glucose tolerance" (IGT). Those individuals falling within the new IGT range were known to have an increased risk of future diabetes and of cardiovascular disease (CVD). It took almost another 20 years to officially recognize that a similar category existed for elevated, but nondiabetic, fasting glucose levels.

In 1997 and 1999, the American Diabetes Association (ADA) and the WHO, respectively, added the term "impaired fasting glucose" (IFG) (with the WHO using "impaired fasting glycemia") to the available diagnostic categories (3,4). It was defined as a fasting plasma glucose (FPG) of 110–125 mg/dl (6.1–6.9 mmol/l). While it was clear that FPG values below the diabetes threshold were predictive of future diabetes and CVD, it was less obvious where the appropriate cut point between normal and IFG status should lie.

The report of the ADA's 1997 Expert Committee on the Diagnosis and Classification of Diabetes (3) cites several earlier studies on which the cut point of 110 mg/dl (6.1 mmol/l) was based. The first is, in fact, the origin of both the name, IFG, and the cut point (5). In an analysis of the Paris Prospective Study, Charles et al. (5) selected a group of people just below the then fasting diabetes threshold of 140 mg/dl (7.8 mmol/l) from the cohort to determine whether elevated, nondiabetic fasting glucose levels were comparable to IGT in predicting incident diabetes. To make the comparison with IGT even handed, they chose a fasting glucose cut point that would include an equal number of individuals in the new fasting category as was included in the IGT category. A nondiabetic fasting category of 110–140 mg/dl (6.1–7.8 mmol/l) thus provided similarity with IGT, at least in terms of prevalence. Indeed, the analysis that they undertook also showed similarity in terms of risk of progressing to diabetes. Unfortunately, at the moment of the official birth of IFG as an entity in 1997, these justifications, based on similarities with IGT, were spirited away by the change of the fasting diabetes cut point from 140 to 126 mg/dl (7.8 to 7.0 mmol/l). The decapitation of IFG on its day of delivery removed those at highest risk of progression, hence reducing its prevalence and altering its predictive characteristics.

The second strand of evidence that was provided to support the lower limit of 110 mg/dl (6.1 mmol/l) was a small, and rather more aged, report (6) that examined insulin secretion in response to intravenous glucose administration. The study indicated that above an FPG of 115 mg/dl (6.4 mmol/l), the acute insulin response was lost. However, with only three participants in the category above 115 mg/dl (115–150 mg/dl [6.4–8.3 mmol/l]), this analysis included far too few participants in the correct glucose range to provide any reasonable accuracy in setting cut points.

The ADA referred to further support for 110 mg/dl (6.1 mmol/l) from another analysis of the Paris Prospective Study that showed a significant risk for CHD mortality associated with elevated, but nondiabetic, fasting glucose values (7). However, on this occasion, the glucose category analyzed that was associated with elevated risk was 104–126 mg/dl (5.8–7.0 mmol/l).

In 1997, the ADA stated that the choice of 110 mg/dl (6.1 mmol/l) as the lower limit of IFG was "somewhat arbitrary" (3). In reviewing the supporting data, it is clear that this comment was entirely justified.

Once IFG had been defined, data from many studies were used to examine the characteristics of the new category, especially in relation to IGT, and a series of reports demonstrated important differences between the two categories. IFG had a lower prevalence than IGT in virtually every population examined (8). It also had a lower sensitivity for predicting future diabetes (i.e., identifying fewer of the individuals in a population who actually go on to develop diabetes), though maintained a similar positive predictive value (the proportion of those with IFG who progress to diabetes is similar to the proportion of people with IGT who progress). The data further showed that there was a very limited overlap between IGT and the new IFG, with only ~25–50% of people who were identified as having one of the conditions also having the other.

Several authors, recognizing the deficiency in available data, sought to determine an ideal cut point for IFG. Two studies, using receiver operator characteristic analyses in predominantly Asian populations, showed that the FPG value that maximized the sensitivity and specificity for predicting either current undiagnosed diabetes or future diabetes was ~100 mg/dl (5.6 mmol/l) (9,10). However, it was also demonstrated that there is no natural or obvious cut point, if it is to be based on risk of future disease. There is no level of FPG that has been identified below which risk is unrelated to FPG and which would then provide a natural cut point between normality and a risk category. In longitudinal data from Mauritius (9), we demonstrated that the risk of future diabetes rises continuously with increasing FPG, and the risk extends well into the normal range. This has recently been confirmed in a very large prospective study from Israel (11). The same pattern has also been demonstrated for the association of FPG with mortality (12). Thus, it is apparent that whatever cut point is selected, it is, to a certain extent, arbitrary.

Other limitations of IFG using the 110 mg/dl (6.1 mmol/l) cut point include the potential instability on retesting, its sensitivity for undiagnosed diabetes, and the ability to identify people with IGT

who may benefit from interventions to prevent diabetes.

The original definition of IFG, 110–125 mg/dl (6.1–6.9 mmol/l), is a very narrow band, particularly given the day-to-day variability of glucose measurements. Most individuals within the original IFG category will have an FPG value that is only within a few milligrams per deciliter/millimoles per liter of either normal or diabetes status, and repeat testing is likely to show that many people "jump ship" to another category. This is likely to be confusing for patients and health care professionals. An illustration of the effect of random variation on the classification of individuals is given using data from the AusDiab (Australian Diabetes, Obesity and Lifestyle Study) (13). The FPG and 2-h plasma glucose results of each individual were changed at random, up to a maximum of ±5% of the recorded value. When this was done, 22% of the individuals who were classified as IFG (110–125 mg/dl [6.1–6.9 mmol/l]) on the recorded value, and 10% of those with IGT, were reclassified to another category (J.E.S., personal communication).

IFG is a useful category for identifying those people who may then be demonstrated to have undiagnosed diabetes on an oral glucose tolerance test (OGTT). Nonetheless, analyses have shown that ~20% of all those with diabetes based on an OGTT have an FPG <110 mg/dl (6.1 mmol/l), with the figure being higher among women, the elderly, and Asian populations. In most screening settings, this is an unacceptably large group of individuals to overlook and can be reduced to ~10% by lowering the action point at which to order an OGTT to 100 mg/dl (5.6 mmol/l). Before the recent ADA lowering of the fasting cut point for IFG, at least one national guideline (Australia) had, for this reason, already adopted 98 mg/dl (5.5 mmol/l) as the level above which an OGTT should be recommended (14). A fasting glucose might also be considered a useful starting point for screening for IGT, particularly now that there is clear evidence that diabetes can be prevented, or at least delayed, by treating people with IGT with lifestyle changes and by a number of different drugs (8). Since the median FPG among people with IGT is 97 mg/dl (5.4 mmol/l) (9), using IFG (as originally defined) as a means of identifying people with IGT will have very limited success.

In recognition of all of these limitations of 110 mg/dl (6.1 mmol/l) as a cut point, the ADA, in 2002, reconvened its Expert Committee on the Diagnosis and Classification of Diabetes (15). The ADA requested that the committee critically review all the available data on IFG to determine whether 110 mg/dl (6.1 mmol/l) was the best cut point. In addition to the data reviewed above, the ADA obtained data from four well-described longitudinal studies to ascertain the FPG value that optimized the prediction of future diabetes. Using receiver operator characteristic curves to identify the FPG value that came closest to providing 100% sensitivity and 100% specificity for future diabetes, the figure was 103 mg/dl (5.7 mmol/l) in a Dutch population, 97 mg/dl (5.4 mmol/l) in a Pima-Indian population, 94 mg/dl (5.2 mmol/l) in a Mauritius population, and 94 mg/dl (5.2 mmol/l) in a San Antonio population (15). Thus, 100 mg/dl (5.6 mmol/l) reasonably approximated to the ideal value for prediction of future diabetes. Further support for lowering the cut point from 110 mg/dl (6.1 mmol/l) came from studies showing that the upper limit of normality (based on the 95th percentile in healthy people) was 106 mg/dl (5.9 mmol/l) (16). Since the ADA's publication, additional evidence has been published supporting a lowering of the cut point. Data from >450 intravenous glucose tolerance tests show that first-phase insulin secretion begins to fall once the FPG rises above 90–97 mg/dl (5.0–5.4 mmol/l) (17). Although first-phase insulin secretion is not a physiological phenomenon, this nevertheless shows that pancreatic β-cell function starts to alter well before the putative, magical level of 110 mg/dl (6.1 mmol/l) is reached.

The relationship between IFG and mortality was not reviewed when the ADA revised the diagnostic criteria for IFG. However, many now see mortality as a much more important outcome than diabetes against which to judge the validity of potential cut points. Several studies have indicated that the original definition of IFG was associated with increased mortality. The DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study of >25,000 adults from 13 European cohort studies (18) showed a statistically significant increase in total mortality of 20% (after adjustment for age and sex) in those with an FPG of 110–125 mg/dl (6.1–6.9 mmol/l). However, after adjustments for other risk factors, including lipids and blood pressure, the risk fell and was no longer statistically significant for either total or CVD mortality (19). The DECODA (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia) analysis of five Asian cohorts reported similar findings, with IFG showing an association with mortality that disappeared after adjustment for other risk factors (20). In both DECODE and DECODA, IGT and fasting diabetes (FPG ≥126 mg/dl [7.0 mmol/l]) remained strong predictors of mortality, even after accounting for other risk factors. A recent study of >36,000 Taiwanese men (21) showed no excess mortality among those whom the ADA's new definition adds to IFG (FPG 100–109 mg/dl [5.6–6.0 mmol/l]). However, while the original IFG definition was associated with increased mortality, once again this disappeared after adjusting for other risk factors. Only the BLSA (Baltimore Longitudinal Study of Aging) has concluded that mortality risks increase at an FPG of 110 mg/dl (6.1 mmol/l), but not at 100 mg/dl (5.6 mmol/l) (22). However, these data were adjusted only for age, obesity, and smoking, so no light can be shed on the true independence of IFG as a risk factor for mortality.

Thus, it appears that unlike IGT, IFG, however it is defined, is not an independent risk factor for total or CVD mortality. In the absence of such an association with mortality, it would be unwise to use any mortality analyses to set IFG cut points. The ability to predict future cases of type 2 diabetes is, therefore, currently the best way of defining IFG.

It should not come as a surprise that the lowering of the lower limit of IFG to 100 mg/dl (5.6 mmol/l) has a significant impact on the prevalence of the condition. Data from Denmark showed that the change in definition increased the prevalence of IFG from 12 to 38%, with similar increases in other populations (23). Such increases in prevalence (though only to levels that are very similar to the prevalences of the other major CVD risk categories: hypertension and dyslipidemia) indicate the importance of ensuring that the diagnostic criteria are as accurate as possible and that errors in either direction (setting the cut point too high or too low) could have a significant impact on both personal and public health.

In 1997, the ADA made a valuable contribution by recognizing the importance of IFG. Unfortunately, the available data at the time did not allow the setting of the most appropriate cut point for the lower limit. As further data have been

published, it is clear that 100 mg/dl (5.6 mmol/l) represents a better validated cut point; it is closer to an ideal cut point for predicting future diabetes and to a level at which insulin secretion becomes abnormal. Future reviews by international and national expert committees should examine this critically as more information becomes available. There are some that believe that the current classification method for glucose intolerance is, in any case, flawed. It could be more productive, and scientific, to abolish somewhat artificial cut points and assess risks according to the continuous distribution of glucose levels, although, in practical terms, this will be hard to implement.

In summary, IFG is a useful concept, but the original definition of its lower limit was not based on good evidence. Predicting future diabetes is the most reliable way to define IFG's lower limit, and careful analyses undertaken in recent years indicate that 100 mg/dl (5.6 mmol/l) provides the best cut point for such predictions. Finally, one should bear in mind that the FPG cannot replace the OGTT as a diagnostic test for diabetes or as a means of identifying those at high risk for CVD.

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