

Impaired Fasting Glucose: How Low Should It Go?

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OBJECTIVE — Impaired fasting glucose (IFG) has been recently introduced as a stage of abnormal carbohydrate metabolism, but the evidence on which its glucose limits (fasting plasma glucose [FPG] 6.1–6.9 mmol/l) are based is not strong. The aim of this study was to determine if 6.1 mmol/l represents a clear cutoff in terms of the risk of future diabetes and in terms of elevated cardiovascular risk factor levels, and to examine the use of other lower limits of IFG.

RESEARCH DESIGN AND METHODS — A population-based survey of the island of Mauritius was undertaken in 1987, with a follow-up survey 5 years later. On both occasions, an oral glucose tolerance test was performed and cardiovascular risk factors were measured.

RESULTS — Data were available from 4,721 nondiabetic people at baseline, and from 3,542 at follow-up. At baseline, blood pressure, lipids, and obesity increased in a linear fashion with increasing FPG, with no evidence of a threshold effect. The risk of developing hypertension at follow-up was greater for those people with baseline FPG ≥ 6.1 mmol/l ($P < 0.001$). The risk of developing diabetes at follow-up increased with increasing baseline FPG, but there was little evidence of a threshold near 6.1 mmol/l.

CONCLUSIONS — Cardiovascular risk and risk of future diabetes increase continually with increasing FPG, and there is no threshold value on which to base a definition of IFG. If a lower limit of ~ 5.8 mmol/l is used, the category defines a group more similar to the group with impaired glucose tolerance, with regard to total prevalence and the risk of subsequent diabetes.

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A number of studies over the last few years have shown that levels of fasting glucose below the diagnostic threshold for diabetes (7.0 mmol/l) may not be normal, in that they are associated with an increased risk of both macrovascular disease and future diabetes. The Paris Prospective Study reported that the risk of developing diabetes over 3 years was greater among middle-aged men with a fasting plasma glu-

cose (FPG) > 6.1 mmol/l than it was for those with a lower FPG (1). Within the same cohort, it has also been reported that coronary heart disease mortality is elevated among people with FPG 5.8–6.9 mmol/l (2). Evidence from such studies has led to the introduction of impaired fasting glucose (IFG) by the American Diabetes Association (ADA) (3), as a stage in the natural history of disordered glucose metabolism,

analogous to (although clearly different from) impaired glucose tolerance (IGT). This category has been supported by the World Health Organization (WHO) in a recent consultation document (4). Both the ADA and WHO have adopted the same criteria for IFG, an FPG ≥ 6.1 mmol/l and < 7.0 mmol/l, although studies now show that the individuals identified by these limits are mostly different from those identified as having IGT (5,6).

In the few studies that have investigated nondiabetic FPG levels, only broad categories of FPG have been assessed, so that it is not possible from the published data to determine whether 6.1 mmol/l is the ideal lower limit for IFG. In an ideal scenario, there would be an FPG threshold for risk of disease that would clearly identify two different groups with low and high risk. The risks might be associations with cardiovascular disease, lipid abnormalities, obesity, or the subsequent development of diabetes.

The aim of this study was to determine whether such a natural lower threshold for IFG exists. Furthermore, since IFG and IGT both represent states intermediate between normality and diabetes, we sought to describe how IFG, when defined by a range of thresholds, compares with IGT with respect to the risk of developing future diabetes and hypertension.

In a population-based survey in Mauritius in 1987, we determined glucose tolerance status by oral glucose tolerance test (OGTT), and investigated cardiovascular risk factors. Diabetes, almost universally type 2, was found in 11.9% of adults aged 25–74 years (7). A follow-up survey was performed in 1992, measuring the same parameters. This allowed us to assess the associations between a range of FPG values and parameters related to diabetes, both cross-sectionally and prospectively.

RESEARCH DESIGN AND METHODS — Mauritius is an Indian Ocean island nation ~ 800 km east of Madagascar. The population consists of $\sim 70\%$ Asian Indians, 2% Chinese, and 28% “general population” who are predominantly people of African ancestry (Creoles) with varying amounts of European, Malagasy, and Indian admixture. A population-based sur-

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Abbreviations: 2-h PG, 2-h plasma glucose; ADA, American Diabetes Association; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PPV, positive predictive value; ROC, receiver operator characteristic; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

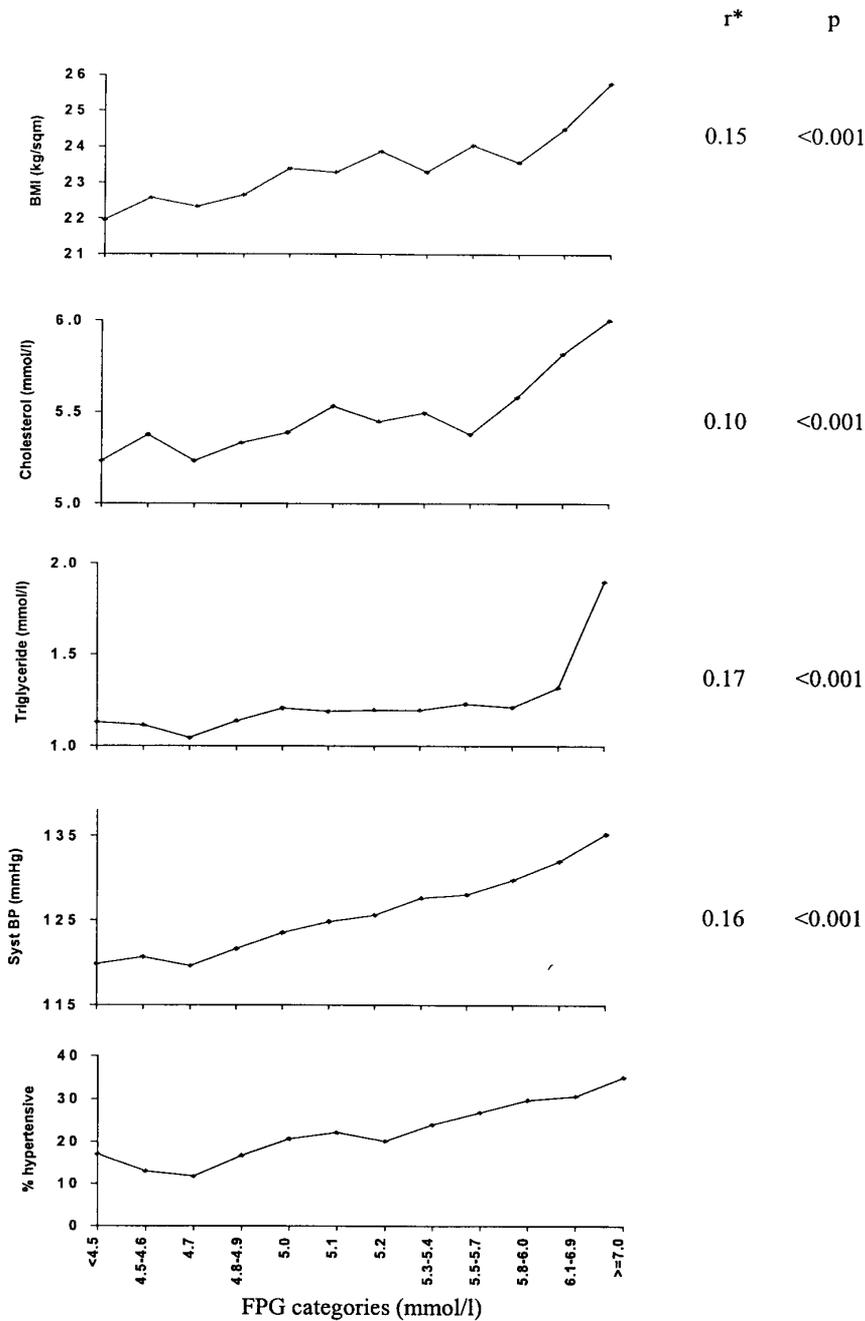


Figure 1—Age-adjusted means of baseline cardiovascular risk factors according to FPG categories. Data are age-adjusted means (geometric means for triglycerides) and age-adjusted percentages. *Age-adjusted partial correlation with FPG.

vey in 1987 included 86.2% of all enumerated adults (both diabetic and nondiabetic) aged 25–74 years living in 10 randomly selected population centers, plus a purposely selected area of Chinatown in the capital, Port Louis. Full details have been published previously (7). For the 1992 survey, all participants from the 1987 survey were invited. The survey methodology was

the same on both occasions. All eligible people were asked to attend a survey site between 0730 and 1000, after an overnight fast. Following registration, all participants had fasting blood samples taken, and all people except those on treatment for diabetes, had an OGTT (250 ml of a solution containing 75 g dextrose monohydrate). Fasting and 2-h plasma glucose (2-h PG)

were determined with a YSI glucose analyzer (Yellow Springs, OH). For this analysis, classifications of diabetes, IGT, and IFG were based on the recent ADA recommendations (3). Diabetes was diagnosed on the basis of a 2-h PG ≥ 11.1 or FPG ≥ 7.0 mmol/l or current treatment with insulin or oral hypoglycemic drugs. IGT was defined as an FPG < 7.0 mmol/l, together with a 2-h PG ≥ 7.8 and < 11.1 mmol/l. IFG was defined as FPG ≥ 6.1 and < 7.0 mmol/l. Participants with FPG in the IFG range and 2-h PG ≥ 11.1 mmol/l were included or excluded according to the analysis being done (see “Statistical methods” and RESULTS).

Total and HDL cholesterol and triglycerides were determined from fasting blood specimens by manual enzymatic methods. Blood pressure was measured in the right arm of seated participants with a standard mercury sphygmomanometer after a 5-min rest, using the first and fifth Korotkoff sounds, and was recorded to the nearest 2 mmHg. Blood pressure was recorded twice, and the mean value was used. Hypertension was diagnosed on the basis of WHO criteria (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) (8) or of self-reported antihypertensive medication taken in the past week.

Height and weight were measured in light clothing without shoes, and the BMI was calculated as weight (in kilograms) divided by height (in meters) squared. Waist circumference was measured at the level of the minimum girth between the umbilicus and xiphoid process. Hip circumference was measured at the level of the maximum girth around the buttocks. Waist and hip circumferences were measured twice, and the means were used to calculate the waist-to-hip ratio (WHR).

Statistical methods

Participants were grouped according to baseline FPG. Those with FPG < 4.5 mmol/l formed the lowest group, those with FPG > 7.0 mmol/l formed the highest group, and the remainder were divided into deciles. This approach was used because it provided the best precision for examining possible threshold effects, while maintaining adequate numbers within each group. Age-adjusted mean baseline values of the cardiovascular risk factors (BMI, WHR, lipids, and systolic and diastolic blood pressures) were calculated for each of the 12 FPG groups, using analysis of covariance. Age-adjusted partial correlation coefficients between each of these

parameters and FPG were also calculated using multiple linear regression. The proportion of participants from each FPG group with hypertension at baseline and the proportion who progressed to diabetes and hypertension were both calculated and then age-standardized by the direct method to the age structure of the total survey population. Participants with hypertension at baseline were excluded from the calculations of incident hypertension.

The predictive parameters of future diabetes were calculated in two different scenarios, according to whether FPG alone or the OGTT was used to classify participants at baseline and at follow-up. Where FPG was used alone, people with baseline 2-h PG ≥ 11.1 mmol/l but FPG < 7.0 mmol/l are included in the analysis of prediction of diabetes.

A receiver operator characteristic (ROC) curve for predicting future diabetes was derived from plotting sensitivity against 100-specificity for all lower limits of the fasting category between 4.8 and 6.9 mmol/l. Separate ROC curves were derived using either FPG alone or the OGTT for classification of diabetes.

People on treatment for diabetes (insulin or oral hypoglycemic agents) at baseline were excluded from all analyses. Triglycerides were log transformed for all analyses, and the geometric means are presented. All analyses were performed using the Statistical Package for the Social Sciences for Windows 6.0 (SPSS, Chicago).

RESULTS — In the cross-sectional analysis, data were available from 4,721 participants, and from 3,542 participants for the longitudinal study. The mean (range) number of participants per FPG group was 393 (268–624) for the cross-sectional analysis and 295 (195–417) for the longitudinal analysis.

Cardiovascular risk factors

Figure 1 shows the relationship at baseline between FPG categories and a number of parameters related to diabetes and cardiovascular disease (adjusted for age). For each parameter, there was a significant, though relatively weak, positive correlation with FPG. Mean values of cardiovascular risk factors increased gradually with increasing FPG, with no evidence of a threshold, except for lipids. For cholesterol, there was a suggestion of a threshold at an FPG value of 5.5–5.7 mmol/l. For triglycerides, the group with FPG ≥ 7.0

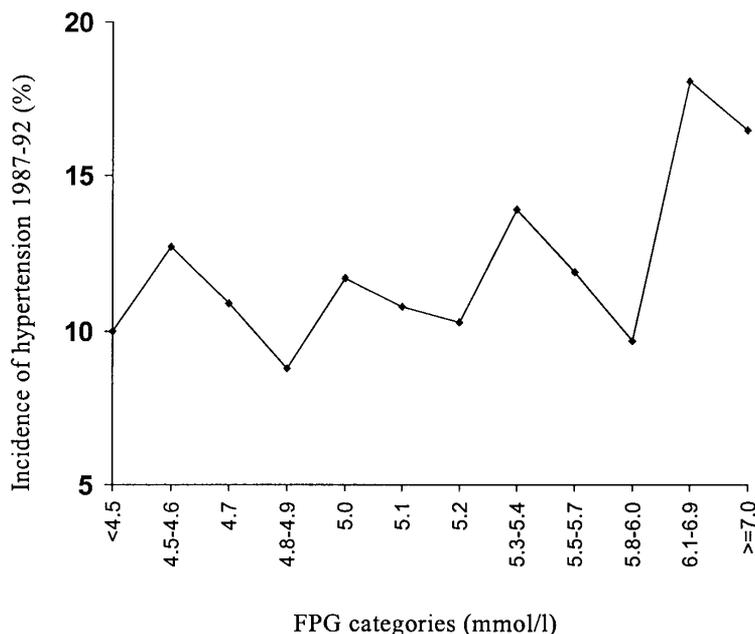


Figure 2—Five-year age-adjusted incidence of hypertension according to baseline FPG categories.

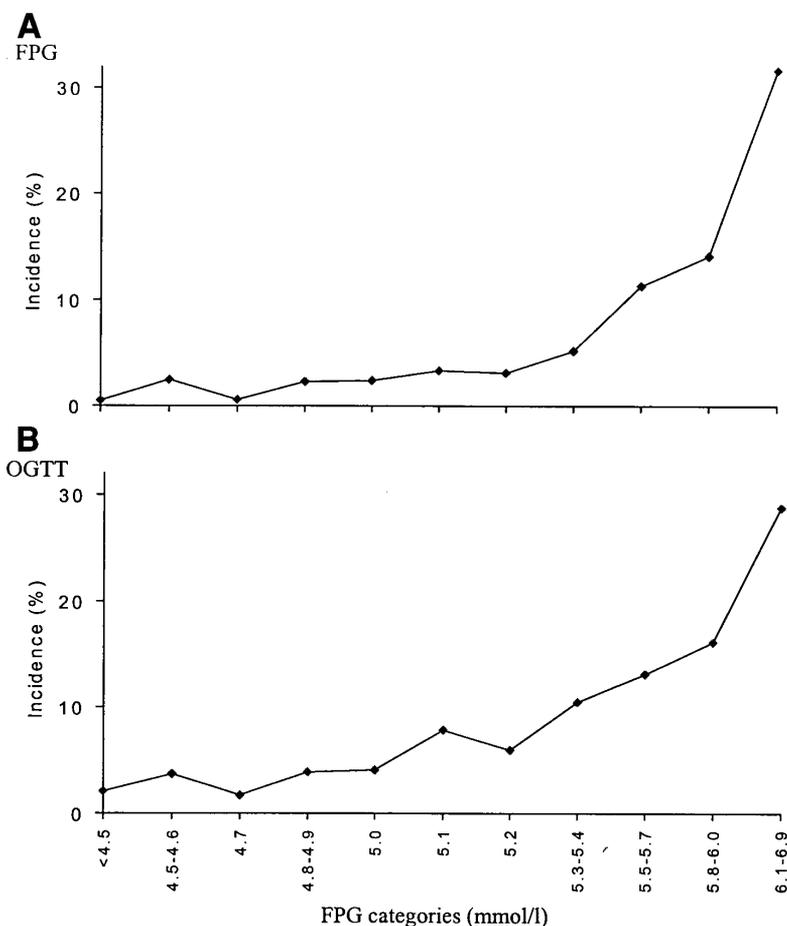


Figure 3—Five-year diabetes incidence according to baseline FPG categories. A: The incidence of diabetes as defined by FPG alone in subjects with baseline FPG < 7.0 mmol/l. B: The incidence of diabetes as defined by OGTT in subjects with baseline FPG < 7.0 mmol/l and 2-h PG < 11.1 mmol/l.

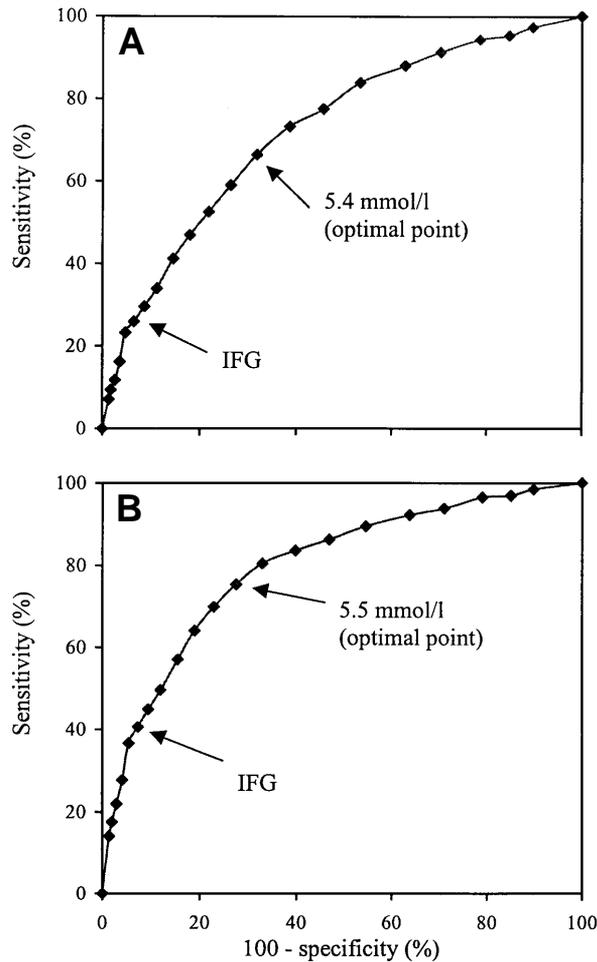


Figure 4—ROC curves for FPG predicting future diabetes. Prediction of diabetes is shown when a range of glucose values (4.6–6.6 mmol/l) is used as the lower limit of the fasting category. This is illustrated in (A) when diabetes is defined by the OGTT and in (B) when diabetes is defined by FPG alone. The points corresponding to IFG (lower limit 6.1 mmol/l), and the optimal value (defined as the closest point to the top lefthand corner of each graph) are shown on each graph.

mmol/l had a considerably greater geometric mean triglyceride than all other groups. Further subdivision of this group into tertiles of FPG showed that the geometric mean triglyceride for these tertiles was 1.8, 1.9, and 2.2 mmol/l, while the geometric mean for the group with FPG 6.5–6.9 mmol/l was 1.3 mmol/l, suggesting that the threshold for elevated triglycerides is close to 7.0 mmol/l. No evidence of a threshold was seen for WHR and HDL cholesterol (data not shown). For patients who were normotensive at baseline, the incidence of hypertension (Fig. 2), appeared to rise only at higher levels of FPG, and this was significant when comparing the incidence in all those with FPG ≥ 6.1 mmol/l with the rest (17.5 vs. 11.1%, $P < 0.001$).

Risk of future diabetes

Figure 3 shows the 5-year incidence of diabetes for each FPG group. Below an FPG of 5.0 mmol/l, $<5\%$ of participants progressed to diabetes, whether diabetes was diagnosed by FPG alone or by OGTT (using both FPG and 2-h PG). The incidence of diabetes started to rise in those with FPG >5.0 mmol/l, and was highest in the group with FPG 6.1–6.9 mmol/l. In this group, the incidence was 32% when diabetes was diagnosed by FPG alone and 29% when diabetes was diagnosed by OGTT.

The prevalence of IGT was 19%, and the sensitivity, specificity, and positive predictive value (PPV) for future diabetes were 50, 84, and 24%, respectively. The comparative figures for IFG were 8, 26, 94, and 29%. Using the OGTT for classification at

baseline and follow-up, and lowering the lower limit of IFG to 5.8 mmol/l, these figures became 17, 41, 86, and 22%. Using only the FPG for classification, a lower limit of 5.8 mmol/l for IFG produced 19, 57, 85, and 23% for the same parameters.

From the ROC curves (Fig. 4), the lower limit of the fasting category giving the best combination of sensitivity and specificity for predicting future diabetes (as determined by the point that was the closest to the top lefthand corner of the graph) was 5.5 mmol/l when screening used FPG values only and 5.4 mmol/l using the OGTT.

CONCLUSIONS—IFG has been recently introduced as a category of intermediate glucose metabolism by the ADA and WHO (3,4), both of which define it as fasting values between 6.1 and 6.9 mmol/l (inclusive). The justification for its introduction is evidence that high but not diabetic FPG values are associated with cardiovascular disease and future diabetes (1,2,9–13). Although these studies confirm the risks associated with this condition, the definition of a high fasting glucose has been inconsistent, making it difficult to now select appropriate limits. Not only is it unclear what should be the lower limit, but since several studies used an FPG of 7.7 mmol/l as the upper limit (above which diabetes was diagnosed) (1,12), it is also not certain that results from those studies can be extrapolated to a situation where 6.9 is the upper limit. Presumably, the lowering of the upper limit would remove the most severely affected individuals from the category. Apart from the Rancho Bernardo study (11), all of these studies used dichotomous categories of FPG, in which a variety of high FPG categories were compared with normal (the remainder). This makes it difficult to determine an appropriate threshold. The Rancho Bernardo study examined a range of glucose values, and had similar results to ours with regard to cardiovascular risk factors, which increased in a linear fashion with increasing FPG. The metabolic study by Brunzell et al. (9), which was cited by the ADA committee (3), also examined a range of fasting glucose values and reported that the acute insulin response is lost when the FPG rises above 6.3 mmol/l. However, since this conclusion was based on only three individuals whose FPG was categorized as 6.3–8.2 mmol/l, this result cannot be seen as evidence for a threshold.

The data presented in the current study demonstrate an approximately linear rela-

relationship between fasting glucose and a number of cardiovascular risk factors. This relationship is in keeping with a recent meta-analysis of prospective studies, which found a continuous relationship between baseline fasting glucose and subsequent cardiovascular risk (14). In our study, only triglycerides showed any evidence of a threshold effect, and this threshold was close to the new cutoff for diagnosing diabetes (7.0 mmol/l) rather than to a level that could be used to define IFG.

As far as predicting future outcomes is concerned, a fasting glucose >6.0 mmol/l appeared to define a group at higher risk of developing hypertension, as has been found by others (15). With regard to predicting future diabetes, when FPG alone is used to define diabetes, the risk starts to rise above an FPG of 5.2 mmol/l, but an FPG threshold is not so apparent when diabetes is defined by the OGTT. For 2-h plasma glucose, 7.8 mmol/l has previously been shown to represent a threshold for risk of future diabetes (16). It should of course be noted that those individuals diagnosed by the fasting value are not necessarily the exact same group as are diagnosed by the 2-h plasma glucose.

IGT has now been studied for many years and is currently the subject of a number of intervention studies aimed at preventing progression to diabetes. We have recently shown that in this population, IFG as currently defined carries a slightly higher risk of progressing to diabetes than does IGT (18), but identifies fewer of the total progressors. This observation is now extended by the confirmation that reducing the lower limit of the fasting category increases the total number of progressors that are identified (sensitivity) and makes the group identified more similar to IGT with respect to the risk of future diabetes. The current cutoff of 6.1 mmol/l defines a group that, in comparison to that defined by IGT, is smaller in number but with a relatively greater degree of hyperglycemia, as judged by the higher risk of progressing to diabetes (PPV). Thus, reducing the lower limit of IFG from 6.1 to 5.8 mmol/l nearly doubles its prevalence, and makes its ability to predict diabetes more similar to that of IGT.

The ROC analysis suggests an even lower cutoff for IFG at 5.4 or 5.5 mmol/l. However, this method gives equal weight to false positive and false negative results. Since the costs of these two errors have not been quantified, it is not clear if this

equal weighting is the ideal approach, and it would certainly result in a large proportion of the population being labeled as at risk. Careful consideration of all implications, including financial (costs of repeat testing and close follow-up) and social (distress at being labeled as "ill," insurance implications) as well as medical, would have to be taken before such a low threshold could be introduced.

It should be borne in mind that whatever limits are set for IFG, they will not identify the same people identified as having IGT (5,6), since the median FPG of people with IGT (in this study) is 5.4 mmol/l. Furthermore, IFG appears to be more common among men, while IGT is more common among women.

Pathophysiologically, it is likely that the fasting abnormality defined by IFG differs from the postprandial abnormality of IGT with respect to the relative contributions of insulin secretory defects and of hepatic and peripheral insulin resistance. This difference limits the extent to which IFG can be "matched" to IGT, but since both states are to be used for the same function (i.e., highlighting a person's risk of diabetes and cardiovascular disease), there remains a practical value in approximating the one to the other. In this study, we have chosen to treat IGT as the gold standard, although this is for historical reasons, rather than because of any evidence that it, rather than IFG, represents the "right" risk values.

In summary, these data show that in this population, cardiovascular risk and the risk of progression to diabetes increase continually across most of the range of fasting glucose, and there is therefore no natural threshold of risk for fasting glucose on which to base the definition of IFG. By reducing the lower limit to ~5.8 mmol/l, it may be possible to make a fasting category that is closer to IGT with regard to prevalence and to the risk of future diabetes than is currently the case with the lower limit set at 6.1 mmol/l. These findings need to be tested in other populations, which have different environmental and genetic backgrounds.

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