Fasting Plasma Glucose Cutoff for Diagnosis of Diabetes in a Japanese Population

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Objective: We examined the relationship between fasting plasma glucose (FPG) and 2-h post-load glucose (PG) levels, and the optimal FPG cutoff level to correspond to a 2-h PG of 11.1 mmol/liter, the gold standard diagnostic criterion, in a general Japanese population.

Design: Cross-sectional study populations of 2421 subjects in 1988 and 2698 subjects in 2002, aged 40–79 yr and without antidiabetic medication, were tested with an oral glucose tolerance test. The relationship between FPG and 2-h PG was investigated by various regression models and a receiver operating characteristic curve.

Results: The best-fit model for the relationship between FPG and 2-h PG was a quadratic regression model. The FPG cutoff levels corresponding to the 2-h PG of 11.1 mmol/liter by this model were 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002. In the combined populations, the FPG cutoff point was 6.3 mmol/liter; the sensitivity and specificity of this cutoff point for detecting a 2-h PG of 11.1 mmol/liter were 75.2 and 88.6%, respectively. The receiver operating characteristic curve analysis confirmed that the corresponding FPG point was 6.2 mmol/liter in both the 1988 and 2002 populations. In a stratified analysis, the FPG cutoff level increased with increasing body mass index levels; however, even in subjects with body mass index more than or equal to 30 kg/m², the FPG cutoff level was lower than 7.0 mmol/liter.

Conclusions: Our findings suggest that the FPG cutoff level corresponding to the 2-h PG of 11.1 mmol/liter in the general Japanese population is lower than the current diagnostic criterion. (J Clin Endocrinol Metab 93: 3425–3429, 2008)

2-h post-load glucose (PG) cutoff level of 11.1 mmol/liter is considered to be the gold standard diagnostic criterion for diabetes mellitus. This cutoff point was originally adopted for several reasons (1). First, 11.1 mmol/liter has been found to approximate the cutoff point separating the two components of the bimodal distribution of 2-h PG levels. Second, according to several epidemiological studies, including our own, the prevalence of microvascular disease sharply increases in patients having a 2-h PG above 11.1 mmol/liter (1–4). Third, a great number of clinical and epidemiological studies have used this criterion. By contrast, fasting plasma glucose (FPG) has not been adequately justified as a diagnostic criterion. The FPG cutoff point for diagnosing diabetes was revised by the Expert Committee of the American Diabetes Association (ADA) (1) in 1997; namely, the cutoff point defining diabetes was reduced from more than or equal to 7.8 mmol/liter to more than or equal to 7.0 mmol/liter, though the ADA itself has recognized that this new cutoff point is not the best equivalent of the 2-h value of 11.1 mmol/liter (1, 5). The World Health Organization adopted an FPG of 7.0 mmol/liter as a diagnostic criterion of diabetes in 1998 (6). This lowering was based on the following findings from several studies, primarily with cohorts of high body mass index (BMI) subjects: 1) the prevalence and incidence of diabetic retinopathy increased at an FPG of approximately 7.0 mmol/liter (1, 3, 4); 2) the discrepancy in the detection rate of diabetes between FPG and 2-h PG values was reduced when an FPG of 7.0 mmol/liter was

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, post-load glucose; ROC, receiver operating characteristic.
used; and 3) the prevalence of diabetes by a 2-h PG cutoff point of 11.1 mmol/liter was identical to that of an FPG of approximately 7.0 mmol/liter in several populations. However, the Diabetes Prevention Program Research Group has recently shown that the retinopathy characteristic of diabetes was present in persons whose FPG was below the diabetic range and who had no known history of diabetes (7). Furthermore, an integrated study of three general populations suggested that although the prevalence of retinopathy increased with FPG concentration, there was no clear diagnostic cutoff (8). These findings imply that data of diabetic retinopathy alone are not adequate to determine an FPG cutoff point. Thus, another approach, such as a regression analysis, is needed to validate the FPG cutoff point.

On the other hand, it remains controversial whether the FPG of 7.0 mmol/liter is adequately diagnostic for diabetes in Asian populations, which tend to be leaner than Western populations. For instance, FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter were also lower than 7.0 mmol/liter in other Asian populations (9–11). There have been very few reports on this issue in the Japanese population, in which the prevalence of diabetes has been increasing rapidly in recent years. The purposes of this study were to determine the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter, and to check whether this cutoff value varied according to changes in the society over time by examining the relationship between FPG and 2-h PG values in a general Japanese population at two different time points separated by an interval of 14 yr.

Subjects and Methods

A population-based prospective study of cardiovascular disease has been underway since 1961 in the Town of Hisayama, a suburb in the Fukuoka metropolitan area on Kyushu Island, in Japan. Based on data from the national census, the age and occupational distributions for Hisayama have been almost identical to those of Japan as a whole from 1961 to the present. As a part of this study, two cross-sectional diabetes surveys of Hisayama residents were conducted in similar fashion in 1988 and 2002. A detailed description of the surveys has been published previously (12, 13); briefly, of the total of 3227 residents in 1988 aged 40–79 yr in the town registry, 2587 (participation rate 80.2%) consented to take part in the study. In 2002, we established another study population of 2698 (1162 men and 1536 women) using the same methods and criteria. In both the 1988 and 2002 surveys, clinical evaluation and laboratory measurements were performed in a similar manner. The study subjects underwent the OGTT between 0800 and 1030 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h post-load, and was separated into plasma and blood cells within 20 min. Plasma glucose levels were determined by the glucose-oxidase method. The between-assay and within-assay coefficients of variance of glucose measurement in our laboratory were 0.96 and 0.81% at 5.6 mmol/liter, and 0.81 and 0.56% at 16.7 mmol/liter, respectively. Total cholesterol and triglycerides were determined enzymatically. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the average values were used in the analyses. Hypertension was defined as systolic blood pressure more than or equal to 140 mm Hg and/or diastolic blood pressure more than or equal to 90 mm Hg and/or current treatment with antihypertensive agents. The height and weight of each subject, wearing light clothes without shoes, were recorded, and the BMI (kg/m²) was calculated. The interview investigated smoking habits and alcohol intake. Both were classified as either currently habitual or not. Subjects engaging in sports at least three times per week during their leisure time were classified into a regular exercise group.

SAS (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. Various regression models, including linear, quadratic, logarithmic, inverse, power, and exponential models, without covariates were examined to determine which best fit the relationship between FPG and 2-h PG levels. Furthermore, an FPG cutoff point corresponding to the 2-h PG of 11.1 mmol/liter was calculated from each regression equation. The sensitivity of the FPG cutoff point was defined as its ability to identify correctly individuals who had a 2-h PG of 11.1 mmol/liter or higher, and the specificity was its ability to identify correctly individuals who did not have a 2-h PG of 11.1 mmol/liter or higher. To compare the ability of FPG measurements to detect the presence or absence of a 2-h PG of 11.1 mmol/liter or higher across a range of values, we plotted receiver operating characteristic (ROC) curves. The diagnostic properties of specific cutoff levels of FPG were defined by maximizing the sensitivity and specificity to identify a 2-h PG of 11.1 mmol/liter or higher. This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the participants.

Results

The clinical characteristics of the subjects in 1988 and 2002 are summarized in Table 1. Mean values of age, FPG, 2-h PG, and BMI were higher in 2002 than 1988, whereas the frequency of men was not different between the populations.

To elucidate the relationship between FPG and 2-h PG, we analyzed their interrelationships using the various regression models listed in Table 2. FPG values corresponding to a 2-h PG of 11.1 mmol/liter and R² values were calculated for the combined populations.
of 1988 and 2002. The R² value was larger for the quadratic regression model, indicating that it is a better fit than the other models; the relevant FPG point in this model was 6.3 mmol/liter.

Figure 2 depicts the relationship between the FPG and 2-h PG in 1988 and 2002 considered separately. The quadratic model analyses were still the best fit among the various models for both the 1988 and 2002 populations (data not shown), with R² values of 64.0 in 1988 and 61.3 in 2002. The FPG point corresponding to a 2-h PG of 11.1 mmol/liter was 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002.

To confirm the cutoff point of FPG corresponding to the 2-h PG of 11.1 mmol/liter, we plotted ROC curves and calculated the optimal cutoff points defined as the maximum combination of sensitivity and specificity, and their area under the ROC curves (Fig. 3). In the 1988 subjects, the corresponding FPG point was 6.2 mmol/liter. The sensitivity and specificity of this cutoff point were 81.2 and 88.7%, respectively; and the area under the curve was 91.0%. In the 2002 subjects, the cutoff point was 6.2 mmol/liter; the sensitivity, specificity, and area under the curve were 77.9, 81.3, and 86.7%, respectively.

Finally, we performed a stratified analysis by sex, age, and BMI levels in the combined population using both the quadratic regression model and ROC analysis (Table 3). The FPG level corresponding to the 2-h PG of 11.1 mmol/liter was slightly higher in men than women by both the quadratic regression model and ROC analysis. Higher FPG levels corresponding to a 2-h PG of 11.1 mmol/liter were observed in the younger age groups in the quadratic regression model analysis. However, in ROC analysis there was no association between age and FPG level. The FPG level corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels in both the quadratic regression model and ROC analysis. However, even in subjects with a BMI more than or equal to 30 kg/m², the FPG cutoff level was still lower than the diagnostic criterion of 7.0 mmol/liter.

### Discussion

We examined the association between FPG and 2-h PG levels in a general Japanese population at two time points separated by a 14-yr interval, and using the quadratic model, which proved to be the best fit for the data, demonstrated that the FPG level corresponding to a 2-h PG of 11.1 mmol/liter, the gold standard for diagnosis of diabetes, was 6.2 mmol/liter for the 1988 data and 6.3 mmol/liter for the 2002 data. The FPG points derived from the ROC analyses corroborated these findings. It has been reported that the corresponding FPG cutoff level by the quadratic model was 5.7 mmol/liter in Chinese (9) and 6.3 mmol/liter in Taiwanese (10). Together with the findings of these other studies, our results suggest that, in relatively lean Asian populations, including the Japanese, the FPG cutoff level is clearly lower than the FPG value of 7.0 mmol/liter, which is currently used in various diagnostic criteria for diabetes (1, 6), and that this situation did not change over the course of 14 yr in the Japanese population.

Although a method using FPG values corresponding to the gold standard of 2-h PG levels for diagnosis of diabetes has not yet been established, regression analysis appears to be a useful method for detecting the FPG cutoff value. Two previous epidemiological studies determined FPG cutoff points by analyzing the relationship between FPG and 2-h PG using linear or exponential models (14, 15). However, in our study the quadratic model showed the highest positive correlation between FPG and 2-h PG, and, thus, was the best-fitted model. This is consistent with the findings of studies in Taiwanese (9) and Chinese (10) populations.

The ADA recommends the use of the FPG instead of 2-h PG for diagnosing diabetes because it is difficult to perform an OGTT in routine clinical practice (1). Thus, it is very important to determine the appropriate FPG cutoff value for the diagnosis of diabetes in different populations. The FPG of 7.0 mmol/liter for diagnosing diabetes is based on several population studies examining the relationship between the glycemic threshold and diabetic retinopathy (1, 3, 4); however, optimal cutoff levels of plasma glucose for defining diabetes depend on ethnicity. In a Pima Indian study, the ROC curve analysis in a diabetic retinopathy study identified the optimal FPG cutoff level as 6.8 mmol/liter (3). The National Health and Nutrition Examination Survey III study of the U.S. population also reported that the prevalence of retinopathy increased dramatically at FPG levels of 6.7 mmol/liter (1). These findings were apparently confirmed by a similar study in Egypt (4), in which the optimal FPG cutoff level

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**Table 1. Clinical characteristics of subjects: the Hisayama study in 1988 and 2002**

<table>
<thead>
<tr>
<th></th>
<th>1988 (n = 2421)</th>
<th>2002 (n = 2698)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57 (10)</td>
<td>59 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men (%)</td>
<td>43.2</td>
<td>43.1</td>
<td>0.94</td>
</tr>
<tr>
<td>FPG (mmol/liter)</td>
<td>5.7 (1.1)</td>
<td>6.0 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2-h PG (mmol/liter)</td>
<td>7.3 (3.2)</td>
<td>7.7 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 (3.1)</td>
<td>23.3 (3.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are means (SD).

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**Table 2. Relationship between FPG (Y) and 2-h PG (X) in various regression models for the combined population of 1988 and 2002**

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
<th>FPG corresponding to 2-h PG of 11.1 mmol/liter (mmol/liter)</th>
<th>R² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadratic</td>
<td>Y = 0.0149X² − 0.102X + 5.621</td>
<td>6.3</td>
<td>62.3</td>
</tr>
<tr>
<td>Linear</td>
<td>Y = 0.243X + 4.024</td>
<td>6.7</td>
<td>51.8</td>
</tr>
<tr>
<td>Exponential</td>
<td>Y = 2.718(0.032X + 1.511)</td>
<td>6.5</td>
<td>48.6</td>
</tr>
<tr>
<td>Power</td>
<td>Y = 3.512X⁰.²₅₅</td>
<td>6.5</td>
<td>36.6</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>Y = 1.831 logX + 2.277</td>
<td>6.7</td>
<td>35.6</td>
</tr>
<tr>
<td></td>
<td>Log(Y) = 0.255 logX + 1.256</td>
<td>6.5</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>Log(Y) = 0.243 (logX)² − 0.748 logX + 2.260</td>
<td>6.5</td>
<td>50.2</td>
</tr>
<tr>
<td>Inverse</td>
<td>Y = 7.265 − 9.416X</td>
<td>6.4</td>
<td>20.1</td>
</tr>
</tbody>
</table>
for detecting diabetic retinopathy was 6.9–7.2 mmol/liter. However, these three populations have higher BMI levels compared with Asian populations. We previously reported that although the glycemic threshold of 2-h PG for retinopathy in Japanese was 11.1 mmol/liter, that of FPG was only 6.4 mmol/liter (2). Other Asian population studies have reported optimal FPG cutoff levels for retinopathy ranging between 5.6 and 6.0 mmol/liter (16, 17). These findings suggest that FPG cutoff levels are lower in Asian populations than in other populations.

In our subjects the FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels. However, even in subjects with a BMI more than or equal to 30 kg/m², the FPG cutoff level using the quadratic model was 6.4 mmol/liter, much lower than the diagnostic criterion of 7.0 mmol/liter. It is not clearly understood why FPG cutoff levels differ among ethnic groups. One possible explanation is that the capacity for acute insulin response to glucose load may influence the FPG cutoff level. The acute insulin response is known to be lower in Asian populations than other populations (18). In some clinical studies, the loss of acute insulin response by somatostatin was associated with a marked impairment in the initial suppression of hepatic glucose production, which led to higher 2-h PG concentrations (19, 20). Thus, impairment of acute insulin response may lead to a wide gap between FPG and 2-h PG; in other words, much lower FPG cutoff levels correspond to the 2-h PG diagnostic standard level. These findings might explain why the FPG cutoff level for the diagnosis of diabetes is lower in Asian populations, including ours, even in those with high BMI.

In the present study, the R² value in the quadratic model and the sensitivity, specificity, and area under the curve in the ROC analysis were all lower in 2002 than 1988. Although this phenomenon was not clearly understood, one possible reason may be that individuals in 2002 had more diverse lifestyles compared with those in 1988. Nevertheless, it is noteworthy that the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter was similar in the two populations.

Two limitations of our study should be discussed. First, in our study we determined the FPG cutoff level that corresponded to a 2-h PG of 11.1 mmol/liter, the gold standard for the diagnosis of diabetes, rather than that corresponding directly to diabetic complications. However, our previous study showed that the glycemic threshold of FPG for retinopathy is 6.4 mmol/liter (2), a result very similar to that of the present study. These findings suggest that the quadratic model precisely predicts the relationship between FPG and 2-h PG levels, making the FPG cutoff level nearly as accurate as the 2-h PG level, as well as more useful in clinical settings. Second, it is known that 2-h PG values in a 75-g OGTT have lower reproducibility than FPG (21, 22). It might be reasonable to propose FPG as the “gold standard.” However, in the National Health and Nutrition Examination Survey III, 2-h PG was more specific for diabetic retinopathy than FPG (1). In several epidemiological studies, 2-h PG was also a stronger predictor of cardiovascular disease and total death compared with FPG (23–27). In addition, a 2-h PG of 11.1 mmol/liter was established in some revised processes for the diagnosis of diabetes. Based on these studies, then, a 2-h PG of 11.1 mmol/liter remains the “gold standard.” Nevertheless, the present study found that two cross-sectional populations in 1988 and 2002 had nearly the same cutoff FPG values. This suggests that the high variability in 2-h PG values did not invalidate the present findings.

In conclusion, we have shown that the quadratic regression model is best fitted for the relationship between FPG and 2-h PG in a general Japanese population. The FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/liter was 6.3 mmol/liter, and this result did not change over the course of 14 yr. Furthermore, the FPG cutoff levels were higher in subjects with higher BMI levels. The findings of the present study together with those of previous studies examining diabetic retinopathy sug-

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**FIG. 2.** The relationship between FPG and 2-h PG by a 75-g OGTT in Hisayama residents aged 40–79 yr in 1988 (left panel) and 2002 (right panel). Solid line represents the regression line by the quadratic regression model.

**FIG. 3.** ROC curves for FPG for predicting the 2-h PG of 11.1 mmol/liter using 1988 (left) and 2002 (right) data sets. The arrow shows the optimal cutoff point for detecting the 2-h PG of 11.1 mmol/liter defined as the maximum combination of sensitivity and specificity.
gest that in Asian populations, the FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/l is lower than 7.0 mmol/l, the current diagnostic criterion for diabetes. Considering the growing importance of the FPG test in screening for diabetes, further investigations are required to clarify the optimal FPG cutoff level in Asian and other ethnic populations.

Acknowledgments

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