Usefulness of Revised Fasting Plasma Glucose Criterion and Characteristics of the Insulin Response to an Oral Glucose Load in Newly Diagnosed Japanese Diabetic Subjects

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OBJECTIVE — To examine the usefulness of the revised criterion for fasting plasma glucose (FPG) in the diagnosis of diabetes recommended by the American Diabetic Association (ADA) (126 mg/dl, 7 mmol/l), and to characterize insulin response during the 75-g oral glucose tolerance test (OGTT) in newly diagnosed Japanese diabetic subjects.

RESEARCH DESIGN AND METHODS — A series of 2,121 Japanese subjects underwent a 75-g OGTT (0–3 h) and were divided into three groups (normal glucose tolerance [NGT], impaired glucose tolerance [IGT], and diabetes mellitus [DM]) according to the current World Health Organization criteria. After the cutoff values of FPG that distinguish NGT and IGT from diabetes were analyzed, the usefulness of the ADA criterion for FPG was examined by comparing diagnostic parameters (sensitivity, specificity, and accuracy) with those for the cutoff value of 140 mg/dl. To assess insulin response, both the insulinogenic index (Islx), a marker of early secretion, and the area under the insulin response curve (AUC_{Ins}), a marker of total secretion, were compared between the DM, NGT, and IGT groups.

RESULTS — First, the FPG cutoff value distinguishing NGT from diabetes was 109 mg/dl. An FPG of 126 mg/dl showed a higher sensitivity (0.52 vs. 0.31), the same specificity (1.00), and a higher accuracy (0.82 vs. 0.74) than an FPG of 140 mg/dl, and it had a higher specificity (1.00 vs. 0.86) with a slightly lower accuracy (0.82 vs. 0.85) than an FPG of 109 mg/dl. Second, the FPG cutoff value differentiating IGT from diabetes was 113 mg/dl. An FPG of 126 mg/dl showed a higher sensitivity (0.52 vs. 0.31) and accuracy (0.80 vs. 0.74) and a similar specificity (0.97 vs. 1.00) compared with an FPG of 140 mg/dl, and it had a higher specificity (0.97 vs. 0.82) with the same accuracy (0.80) as an FPG of 113 mg/dl. Third, the DM group showed the lowest Islx among the three groups at all FPG values. The AUC_{Ins} in the DM group increased along with FPG, reached the maximum level at an FPG of 110 mg/dl, and declined thereafter. AUC_{Ins} was higher in the DM group than in the NGT group at FPG values ≥100 mg/dl.

CONCLUSIONS — The revised ADA criterion for FPG of 126 mg/dl may improve diagnostic sensitivity without loss of specificity in Japanese diabetic subjects when compared with an FPG criterion of 140 mg/dl. Although early insulin secretion was impaired, total insulin secretion did not seem to be reduced in newly diagnosed Japanese diabetic subjects.

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Abbreviations: ADA, American Diabetes Association; AUC_{Ins}, area under the insulin response curve; DM, diabetes mellitus; FPG, fasting plasma glucose; IGT, impaired glucose tolerance; Islx, insulinogenic index; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; WHO, World Health Organization.

Current Japanese fasting plasma glucose (FPG) criteria for the upper limit of normal and for the diagnosis of diabetes were defined as 109 mg/dl and 140 mg/dl, respectively, by the Japan Diabetes Society in 1982 (1). Patients in whom diabetes is suspected and whose FPG values are between 110 and 139 mg/dl are encouraged to undergo a 75-g oral glucose tolerance test (OGTT). However, because we often encounter patients with mild diabetes and an FPG <140 mg/dl in the outpatient clinic, we have the impression that the FPG diagnostic criterion should be reduced from 140 mg/dl to an optimum level equivalent to the World Health Organization's (WHO) 2-h plasma glucose (PG) value of 200 mg/dl in the 75-g OGTT. Recently, the American Diabetes Association (ADA) revised the FPG criterion for the diagnosis of diabetes from 140 to 126 mg/dl (7.0 mmol/l), based on the report of the ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, established in 1995 (2). Therefore, we evaluated the usefulness of the new FPG criterion of 126 mg/dl compared with the old value of 140 mg/dl in Japanese subjects.

Regarding the insulin response of Japanese subjects, Kosaka et al. (3) have reported that both early and late insulin secretion during the 100-g OGTT were impaired in diabetic subjects who were defined as having a previous or current FPG >140 mg/dl. However, their study included people undergoing general health checks, and analysis of a large number of subjects suspected of having diabetes and undergoing the 75-g OGTT has not been done in Japan. Accordingly, we evaluated the insulin response during the 75-g OGTT in newly diagnosed diabetic patients compared with normal individuals or those with impaired glucose tolerance (IGT) in 2,121 Japanese subjects suspected of having diabetes.

Table 1—*Characteristics of the Japanese subjects*

	NGT	IGT	DM	Total
n (M/F)	829 (488/341)	809 (516/293)	483 (351/132)	2,121 (1,355/766)
Age (years)	54 ± 0.5 (20–78)	57 ± 0.4 (20–81)	55 ± 0.5 (22–82)	56 ± 0.3 (20–82)

Data for age are means ± SEM (range).

RESEARCH DESIGN AND METHODS

Study population

The data were reviewed for 2,121 serial Japanese subjects (1,355 men and 766 women, aged 20–82 years [mean age at testing, 56 years]) suspected of having diabetes and undergoing the 75-g OGTT for diagnosis at Saiseikai Central Hospital in Tokyo from January 1994 to December 1996. The subjects were divided into three groups, using the current WHO criteria: a normal glucose tolerance (NGT) group (*n* = 829), an IGT group (*n* = 809), and a diabetes mellitus (DM) group (*n* = 483) (4).

Analytic methods

Data are expressed as means ± SEM. The statistical significance of differences in mean values was determined by multiple analysis of variance. Cutoff values for FPG (basal fasting value in the 75-g OGTT), separating NGT and IGT from diabetes, were calculated from the points of intersection of the two cumulative frequency distribution curves, which consisted of the usual positive curve (cumulative frequency distribution of diabetes as FPG increased) of the DM group and the negative curve (cumulative frequency distribution of nondiabetes as FPG increased) of the NGT or the IGT group (5). Diagnostic parameters were calculated as follows: Sensitivity was calculated as the number of true-positive subjects (in whom diabetes was correctly diagnosed in the DM group by some FPG cut point) divided by the total number of subjects in the DM group; specificity was calculated as the number of true-negative subjects (in whom diabetes was correctly excluded in the NGT group or the IGT group by some FPG cut point) divided by the total number of subjects in the NGT group or the IGT group; and accuracy was calculated as the sum of true-positive and true-negative subjects divided by the total number of subjects in the two groups. The insulinogenic index (IsIx), a marker of early insulin secretion, was defined as Δinsulin/ΔPG, or ($Insulin_{30}$ − $Insulin_0$)/(PG_{30} − PG_0) (3). The area under the insulin curve (AUC_{Ins}), a marker of total insulin secretion, was calculated as the total area under the response curve during the 3-h OGTT. In all three groups, IsIx and AUC_{Ins} were plotted at FPG increments of 10 mg/dl. Each datum was calculated in the subjects with an FPG range: $X - 4 \leq X$ (FPG at every 10 mg/dl) $\leq X + 5$ mg/dl, such that FPG values between 116 and 125 mg/dl were regarded as 120 mg/dl.

RESULTS — The clinical characteristics of the three groups are shown in Table 1, and the responses of PG and plasma insulin in the 75-g OGTT are shown in Fig. 1. There were no differences in age or sex among the three groups. Both the FPG and fasting insulin concentrations in the DM group were highest among the three groups (For NGT vs. IGT vs. DM group, respectively [means ± SEM], FPG: 96 ± 1, 103 ± 1, and 136 ± 2 mg/dl; insulin: 6.4 ± 0.1, 7.7 ± 0.2, and 8.7 ± 0.2 μU/ml; $P < 0.01$). Scatterplots of FPG and 2-h PG during the 75-g OGTT in the DM group are shown in Fig. 2. In the subjects with an FPG from 135 to 145 mg/dl, 2-h PG was 277 ± 7 mg/dl (mean ± SEM, *n* = 63), while the FPG of subjects with a 2-h PG from 200 to 210 mg/dl was 116 ± 2 mg/dl (mean ± SEM, *n* = 66). Cumulative distribution curves are shown in Fig. 3. The cutoff FPG separating the NGT and the DM groups was 109 mg/dl, while the cutoff separating the IGT group and the DM group was 113 mg/dl. As shown in Table 2, the sensitivity was 0.84 and 0.78, the specificity was 0.86 and 0.82, and the accuracy was 0.85 and 0.80, for the 109 and 113 mg/dl cut points, respectively. Table 2 shows that in a comparison of parameters between the NGT and the DM groups, 140 mg/dl had the lowest sensitivity (0.31) and accuracy (0.74) despite complete specificity (1.00), whereas 126 mg/dl had a higher sensitivity (0.52) and accuracy (0.82) than 140 mg/dl without loss of specificity (1.00). Although the cutoff FPG of 109 mg/dl separating NGT from diabetes had the highest sensitivity and accuracy, the specificity was the lowest among the three FPG values. Similarly, in a comparison between the IGT and the DM groups, 126 mg/dl also showed a higher sensitivity (0.52) and accuracy (0.80) than 140 mg/dl, with negligible loss of specificity (0.97). While the cutoff FPG of 113 mg/dl also showed the highest sensitivity and the lowest specificity, the accuracy was equal to that of 126 mg/dl.

IsIx and AUC_{Ins} values for the three groups at every 10 mg/dl increment of FPG are shown in Fig. 4. The DM group had the lowest IsIx among the three groups (<0.5 at all FPG values), suggesting impaired early insulin secretion. The IGT group also showed a lower IsIx compared with the NGT group. In both the NGT and the DM groups, AUC_{Ins} increased as FPG rose,

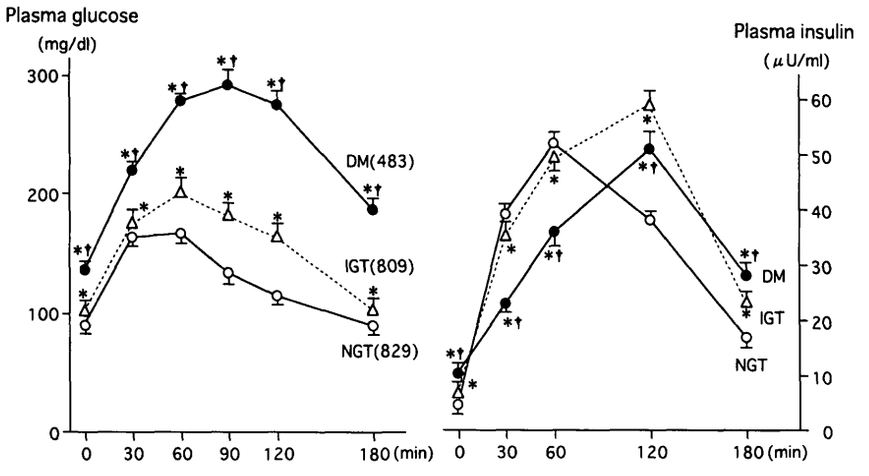

Figure 1—*Responses of PG and plasma insulin during the 75-g OGTT. Values are expressed as means ± SEM. Numbers of subjects are shown in parentheses. *P < 0.01 vs. NGT group; †P < 0.01 vs. IGT group.*

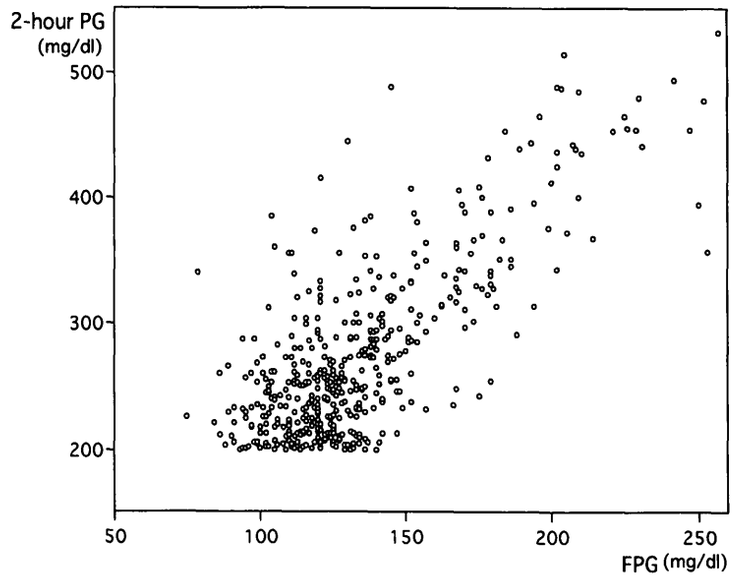

Figure 2—*Scatterplots of FPG and 2-h PG in the diabetic subjects. FPG and 2-h PG were measured before and 2 h after 75-g glucose load.*

reached a maximum at an FPG of 110 mg/dl, and declined thereafter. The AUC_{Ins} of the DM group was higher than that of the NGT group at FPG values ≥100 mg/dl and was similar at FPG values ≤90 mg/dl. The IGT group maintained the highest AUC_{Ins} among all groups at FPG values ≤110 mg/dl, but it decreased thereafter. Thus, total insulin secretion decreased in all three groups at FPG values >110 mg/dl.

CONCLUSIONS — The ADA Expert Committee on the Diagnosis and Classification of Diabetes Mellitus pointed out that the majority of newly diagnosed diabetic subjects with a 2-h PG ≥200 mg/dl in the 75-g OGTT have shown an FPG <140 mg/dl in many previous studies, suggesting that an FPG value of 140 mg/dl identified more severe hyperglycemia than a 2-h PG value of 200 mg/dl (2). Several studies have shown that the FPG cut point equivalent to a 2-h PG of 200 mg/dl was in the range of 120–126 mg/dl and that the FPG threshold for diabetic retinopathy is also 120–130 mg/dl (6–8). Therefore, to avoid unwarranted discrepancy and to facilitate the use of FPG as a test for diagnosing diabetes that is simpler than the OGTT and equally accurate, the ADA adopted a new FPG criterion of 126 mg/dl (7 mmol/l). Since the FPG corresponding to a 2-h PG value of 200–210 mg/dl in the 75-g OGTT was 116 ± 2 mg/dl (mean ± SEM) in the present study and the 2-h PG corresponding to an FPG of 135–145 mg/dl was 277 ± 7 mg/dl (mean ± SEM), a similar discrepancy between FPG and 2-h PG was also seen in newly diagnosed Japanese diabetic subjects. Actually, the present study demonstrated that the FPG cutoff value separating NGT and diabetes was only 109 mg/dl, while that for IGT and diabetes was 113 mg/dl by cumulative distribution curve analysis (Fig. 3). Thus, Japanese patients with mild diabetes may be missed by the current FPG criterion of 140 mg/dl unless the 75-g OGTT is performed.

Although the DM group could be separated from the NGT group by an FPG of 109 mg/dl and from the IGT group by a value of 113 mg/dl, these values should not be adopted as optimal criteria for the diagnosis of diabetes, because the specificity of 0.86 and 0.82, respectively (Table 2), would mean that 14% of NGT and 18% of IGT subjects may be falsely identified as having diabetes. On the other hand, an FPG of 126 mg/dl showed a higher sensitivity with a negligible decrease in specificity compared with 140 mg/dl. Although the diagnostic accuracy of 126 mg/dl was the same as that of 113 mg/dl and only slightly lower than that of 109 mg/dl, only 2.8% of IGT subjects will be falsely identified as having diabetes if 126 mg/dl is adopted as the new criterion. However, the 2-h PG of these false-positive subjects in the IGT group was 192 ± 3 mg/dl (mean ± SEM) in the present study. Therefore, such subjects should now be regarded and treated as having diabetes. Collectively, these findings suggest that the accuracy and sensitivity of diagnosing Japanese diabetic subjects may be increased with a negligible decrease of specificity by changing the FPG criterion from the current 140 mg/dl to the ADA recommendation of 126 mg/dl.

The impaired IsIx of the DM group (<0.5 at all FPG values) in the present study was consistent with the previous report by Kosaka et al. (3). Although we did not examine the correlation between IsIx and clinical parameters, such as family history, BMI, serum lipid profile, exercise, or other factors, Kosaka et al. (9) showed that subjects with a family history of diabetes had a higher prevalence of low IsIx values, and that even normal or IGT subjects with low IsIx values showed a higher incidence of the development of diabetes. Therefore, low IsIx may be partly associated with genetic background, and the

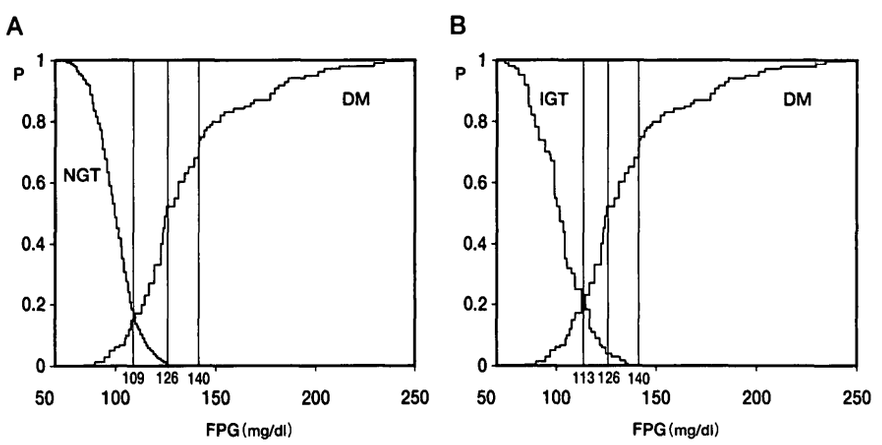

Figure 3—*Cumulative distribution curves.* A: *Comparison of NGT and DM groups.* B: *Comparison of IGT and DM groups. Cumulative distribution curves are explained in* METHODS.

Table 2—*Diagnostic parameters for various FPG cut points*

Diagnostic parameters	FPG cut point (mg/dl) 109	113	126	140
Sensitivity				
NGT-DM	0.84	—	0.52	0.31
IGT-DM	—	0.78	0.52	0.31
Specificity				
NGT-DM	0.86	—	1.00	1.00
IGT-DM	—	0.82	0.97	1.00
Accuracy				
NGT-DM	0.85	—	0.82	0.74
IGT-DM	—	0.80	0.80	0.74

See METHODS for definitions of diagnostic parameters.

acquired factors affecting IsIx should also be elucidated in further studies.

As shown in Fig. 4*B*, although total insulin secretion increased as FPG rose, insulin secretion declined once FPG exceeded 110 mg/dl. Interestingly, this phenomenon was also observed in both the NGT and the IGT groups. Although total insulin secretion in the IGT group was constantly higher than the NGT group and the DM group at FPG values ≤100 mg/dl, it similarly declined at FPG values ≥110 mg/dl. Our results are consistent with the previous reviews by DeFronzo (10,11), who stated that the relationship between FPG and the mean insulin response during the OGTT in subjects with diabetes and IGT showed an inverted U shape with a peak insulin response at an FPG value of 120 mg/dl. This finding suggests that pancreatic β-cells may no longer maintain accelerated insulin secretion at FPG values >110 or 120 mg/dl, regardless of the diagnostic category or ethnic differences of the subjects.

The ADA defined a new category—"impaired fasting glucose" (110–125 mg/dl)—which is a risk factor for future diabetes or cardiovascular disease. The present study showed that the FPG cut point separating NGT and diabetes was 109 mg/dl, while that separating IGT and diabetes was 113 mg/dl, and that the insulin response decreased at FPG values ≥110 mg/dl in all groups. Therefore, because Japanese subjects with an FPG from 110 to 125 mg/dl show impaired glucose homeostasis, careful follow-up or medical intervention may be necessary.

As shown in Table 1, male subjects were predominant in all groups, and this trend was most marked in the DM group. The prevalence is higher in men than in women in Japan (12), whereas the U.S. population shows the opposite trend (13). Because the factors associated with this ethnic discrepancy in gender are unclear, further studies on the incidence of diabetes in NGT and IGT subjects in the present study may be required.

In conclusion, the present study demonstrated the following characteristics of newly diagnosed Japanese diabetic subjects: *1*) An FPG of 126 mg/dl may be useful for the diagnosis of diabetes, and 2) total insulin secretion was maintained despite the decrement of early secretion. The present study suggested the need to reexamine diagnostic criteria and characterize glucose-stimulated insulin secretion in Japanese subjects; therefore, large-scale cross-sectional and prospective studies will be needed to clarify these points.

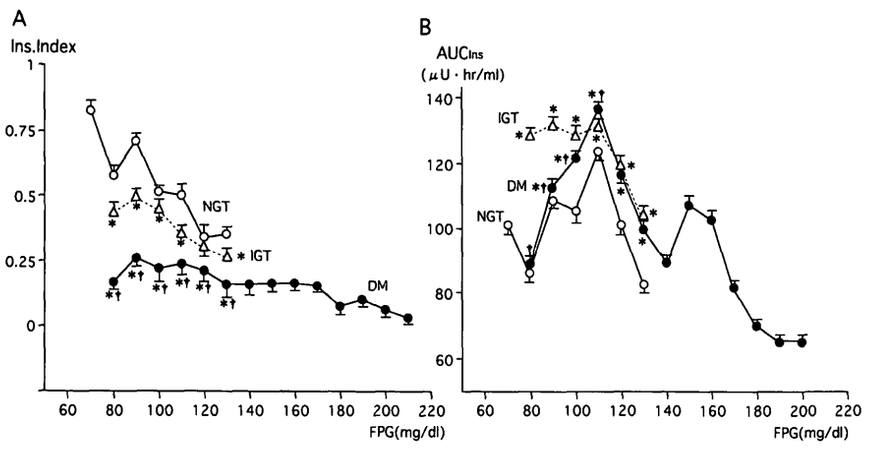

Figure 4—*Insulin response during the 75-g OGTT. Ins. Index, insulinogenic index. (Insulinogenic index and AUC_{Ins} are explained in METHODS.) Values are expressed as means ± SEM. *P < 0.01 vs. NGT group; †P < 0.01 vs. IGT group.*

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