Fasting Plasma Glucose Reference Values among Young Japanese Women Requiring 75g Oral Glucose Tolerance Tests

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Objective: Currently there are various discussions on the upper limit of FPG (Fasting Plasma Glucose) levels. In Japan, when abnormal levels of FPG are detected at general health checkups or complete physical examinations, 75g Oral Glucose Tolerance Tests (75g OGTT) are often conducted in follow-up examinations. Therefore we investigated the appropriate upper limit of FPG levels to decide whether 75g OGTT are actually necessary.
Research Design and Methods: Based on the FPG levels of 256,309 women with an age range of 20 to 79, we established the upper limits of FPG levels by 5-year intervals, using a method equivalent to the National Committee for Clinical Laboratory Standards (NCCLS) used in the U. S. [4]. We also obtained the ROC curve from the 75g OGTT results from 160 women aged 20 to 39. We then divided those 160 women into four categories based on their 75g OGTT results, and compared the abnormal rates of their 2-hour post-75g OGTT glucose levels, HOMA-R and Insulin Index using the Kruskal-Wallis test.
Results: The upper limits of FPG levels were 99 mg/dl in the 20–29 age range, 101 mg/dl in the 30–34 age range, and 104 mg/dl in the 35–39 age range. The upper limits of the FPG reference intervals increased almost proportionally up to the age 50, and showed little difference thereafter. The point on the ROC curve where the total value of sensitivity plus specificity reached the highest had an FPG level of 99.5 mg/dl. For 2-hour post-75g OGTT glucose levels and HOMA-R, there was a significant difference in abnormal rates between the categories of FPG ≦ 99 mg/dl and 100 ≦ FPG ≦ 109 mg/dl, but not in Insulin Index.
Conclusions: We believe that 75g OGTT are necessary for Japanese women aged 20 to 39 with FPG levels of 100 mg/dl or above.

Key words: Fasting Plasma Glucose, 75g Oral Glucose Tolerance Tests, ROC curve, Young Japanese Women

BACKGROUND

Since the diagnostic criterion for diabetes was set in 1997, the normal level of FPG in Japan has been determined as 110 mg/dl or under [1]. Diabetes has been diagnosed and treated based on this criterion ever since then. However in 2003, the ADA (American Diabetes Association) announced that IFG (impaired fasting glucose) was 100 mg/dl or above [2]. In response to this, the EDEG (European Diabetes Epidemiology Group) released a statement in 2006 insisting that lowering the criterion would be a problem because it could raise the prevalence rate of diabetes twofold to fivefold [3], and since then there have been heated debates over the IFG criteria. Thus, a consensus has not been reached on the lower limit of IFG levels.

PURPOSE

Most Japanese adults have an annual health checkup conducted by their companies or municipal governments. People aged over 40 are supposed to undergo a checkup under the Health and Medical Service Law for the Aged, and 12,084,000 people underwent one in 2004. In addition, 44,630,000 workers underwent a health checkup under the Occupational Health and Safety Law, and the executing rate of corporate physical examinations was 87.1% in 2005. FPG is often included in these examinations as a means to screen for IGT (impaired glucose tolerance). When an abnormal level of FPG is detected, the examinee is required to have a 75g OGTT in a follow-up examination.

In the past we have conducted a sex-age specific reference value research of upper limit FPG, gathered from health examination data of about 700,000 Japanese (Fig. 1) [4–5]. This research has shown that the upper limit FPG of females in the age groups of 20–24 and 25–29 were 99 mg/dl, 101 mg/dl for the 30–34 age group, and 104 mg/dl for the 35–39 age group. Numbers from these four groups round off to 100 mg/dl, while the upper limit FPG of women over age 40 seem to remain at the standard 110 mg/dl range.

This research indicates the possibility of overlooking early-stage diabetes of women 20 to 39 years of age. We have verified this hypothesis of scientific standard after a 2-hour OGTT in this paper.

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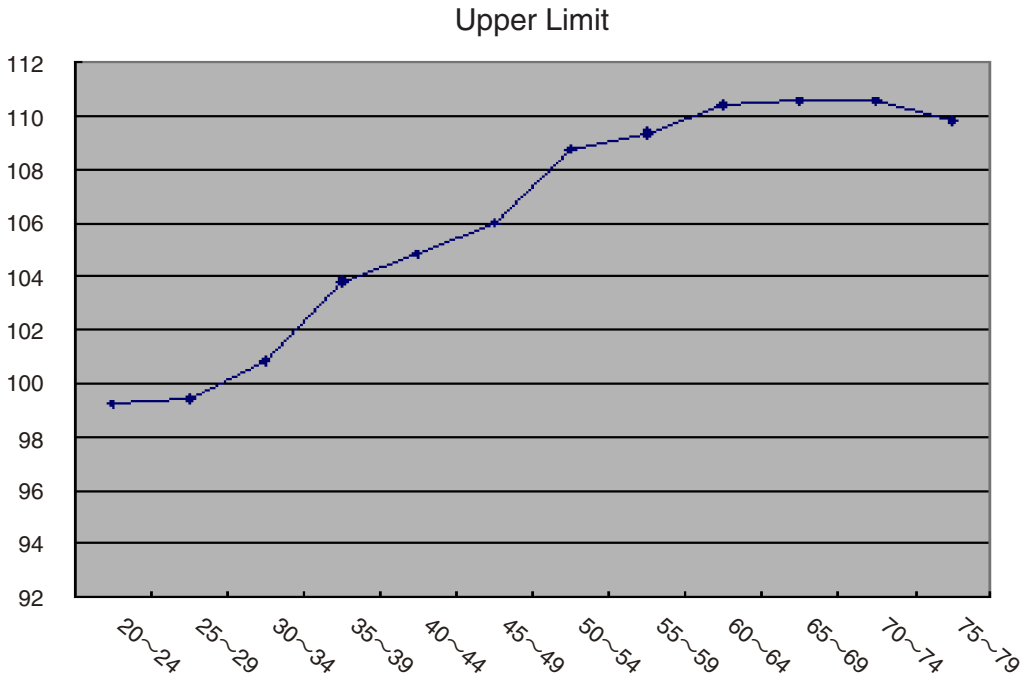

Fig. 1 The upper limits of FPG (Fasting Plasma Glucose) levels by age for women
This graph shows the upper limits of FPG reference intervals for women aged 20 to 79.

METHOD

1. From the 1,049 women (average age ± SD: 53.4 ± 15.1) who underwent 75g OGTT either at Tokai University between May 1998 and February 2006 or at The Health Promotion Foundation of Koriyama between August 2005 and February 2006, we extracted 160 women aged 20 to 39 (average age ± SD: 31.3 ± 4.8) and investigated them.

2. Based on their 2-hour post-75g OGTT glucose levels, we divided the test group into two categories: normal (OGTT < 140 mg/dl) and abnormal (OGTT ≧140 mg/dl). Then we obtained the ROC curve for FPG levels using SPSS (Ver.14.0J).

3. Based on their FPG levels, we divided the test group into four categories; 1) FPG ≦ 99 mg/dl; 2) 100 ≦ FPG ≦ 109 mg/dl; 3) 110 ≦ FPG ≦ 125 mg/dl; and 4) FPG ≧ 126 mg/dl. Then, using the Kruskal-Wallis test with SPSS (Ver.14.0J), we compared abnormal rates in the following three categories: the 2-hour post-75g OGTT glucose level, the index of insulin resistance [HOMA-R: FPG (mg/dl) x fasting insulin concentration (μU/ml)/405], and the insulin secretary capacity [Insulin Index: Δ IRI/ Δ PG; Δ IRI: IRI (immunoreactive insulin) of 30-minute post-75g OGTT glucose level - IRI of 0-minute post-75g OGTT glucose level; Δ PG: 30-minute post-75g OGTT glucose level - 0-minute post-75g OGTT glucose level]. To assess the results of the 75g OGTT, HOMA-R and Insulin Index, we used the following criteria from the Japan Diabetes Society. [6];

- 2-hour post-75g OGTT glucose level (mg/dl): normal type (below 140), intermediate type (140 to 199) and diabetic type (200 and above)
- HOMA-R: normal type (1.6 and below), intermediate type (over than1.6 and less than 2.5) and insulin-resistant type (2.5 and above)
- Insulin Index: normal type (0.4 and above) and low insulin secretion (below 0.4)

RESULTS

1. Fig. 2 shows the ROC curve of 2-hour post-75g OGTT glucose levels. The point on the ROC curve where the total value of sensitivity plus specificity reached the highest had an FPG level of 99.5 mg/dl, and the sensitivity plus the specificity equaled 1.438. The AUC (area under the curve) was 0.702.

2. Fig. 3 is a graph that shows the abnormal rates of 2-hour post-OGTT glucose levels in the four categories of FPG levels. In the category of FPG ≦ 99 mg/dl, the intermediate type of 2-hour post-OGTT glucose levels was 22% and the normal type was 78%. In the category of 100 ≦ FPG ≦ 109 mg/dl the diabetic type of 2-hour post-OGTT glucose levels was 10%, the intermediate type was 55% and the normal type was 35%. In the category of 110 ≦ FPG ≦ 125 mg/dl, the diabetic type of 2-hour post-OGTT glucose levels was 25% and the intermediate type was 75%. In the category of FPG ≧ 126 mg/dl, the diabetic type of 2-hour post-OGTT glucose levels was 100%. Between the categories of FPG ≦ 99 mg/dl and 100 ≦ FPG ≦ 109 mg/dl, there was a significant difference in the abnormal rates of 2-hour post-OGTT glucose levels ($P < 0.001$).

3. Fig. 4 is a graph that shows the abnormal rates of HOMA-R in the four categories of FPG levels. In the category of FPG ≦ 99 mg/dl, the insulin-resistant type was 11%, the intermediate type was 18% and the

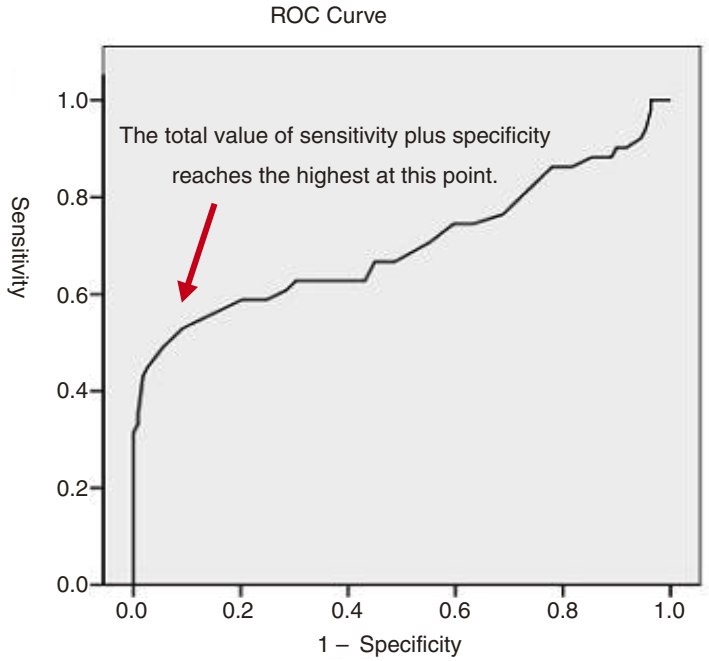

Fig. 2 The ROC curve for FPG to distinguish abnormal 2-hour post-OGTT glucose levels
The FPG level was 99.5 mg/dl at the point where the total value of sensitivity plus specificity reaches the highest (1.438). The AUC (area under the curve) was 0.702.

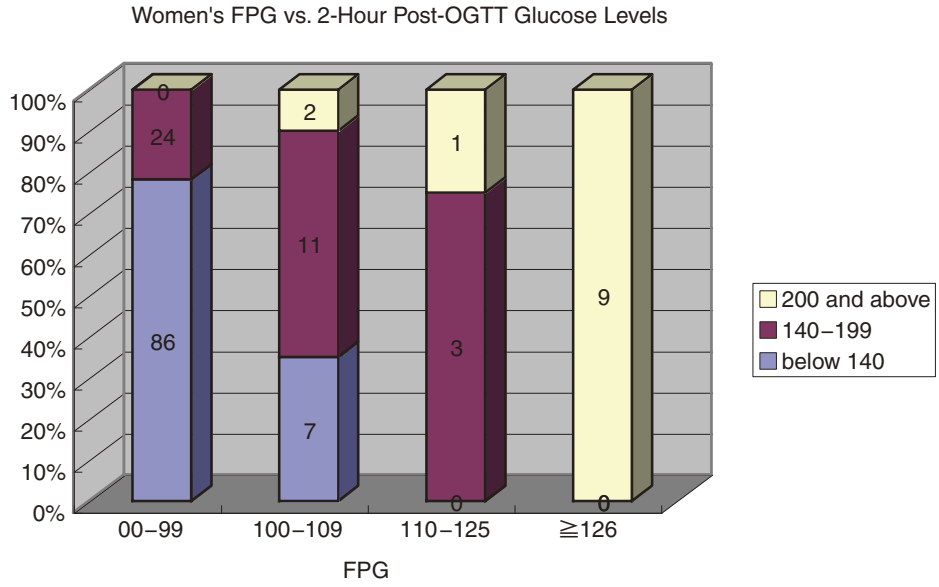

Fig. 3 Rates of three categories of 2-hour post-OGTT glucose levels by FPG level
In comparing the categories of FPG ≦ 99 mg/dl and 100 ≦ FPG ≦ 109 mg/dl, there was a significant difference in the abnormal rates ($P < 0.001$) of 2-hour post-OGTT glucose levels resulting in 140 mg/dl and above.

normal type was 78%. In the category of 100 ≦ FPG ≦ 109 mg/dl, the insulin-resistant type was 55%, the intermediate type was 20% and the normal type was 25%. In the category of 110 ≦ FPG ≦ 125 mg/dl, the insulin-resistant type was 75% and the normal type was 25%. In the category of FPG ≧ 126 mg/dl, the insulin-resistant type was 67%, the intermediate type was 11% and the normal type was 22%. Between the categories of FPG ≦ 99 mg/dl and 100 ≦ FPG ≦ 109 mg/dl, there was a significant difference in the abnormal rates of insulin resistance ($P < 0.001$).

4. Fig. 5 is a graph that shows the abnormal rates of Insulin Index in the four categories of FPG levels. In the category of FPG ≦ 99 mg/dl, the low-insulin type was 20% and the normal type was 80%. In the category of 100 ≦ FPG ≦ 109 mg/dl, the low-insulin type was 45% and the normal type was 55%. In the

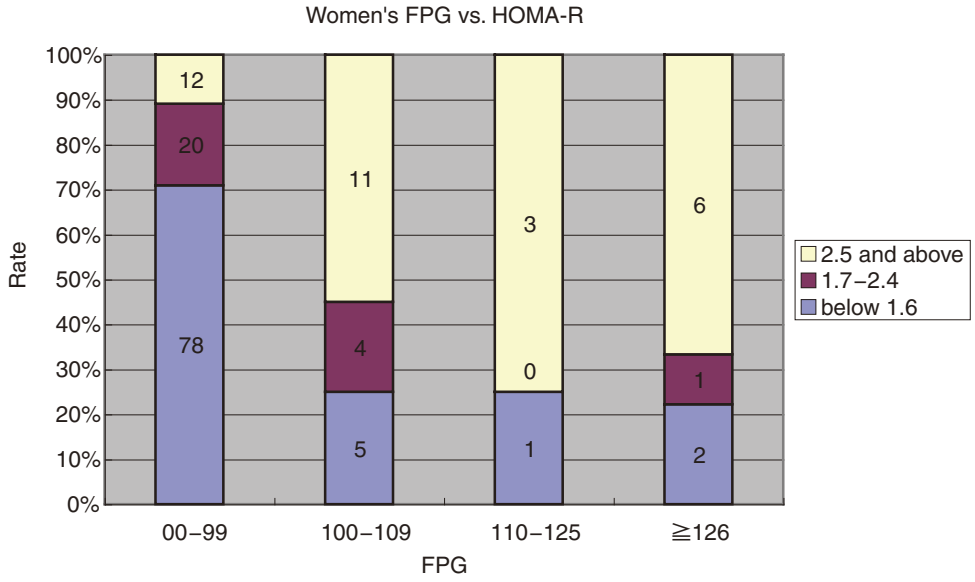

Fig.4 Rates of three categories of insulin resistance (HOMA-R) by FPG level
In comparing the categories of FPG ≦ 99 mg/dl and 100 ≦ FPG ≦ 109 mg/dl, there was a significant difference in the abnormal rates ($P < 0.001$) of HOMA-R resulting in 1.6 and above.

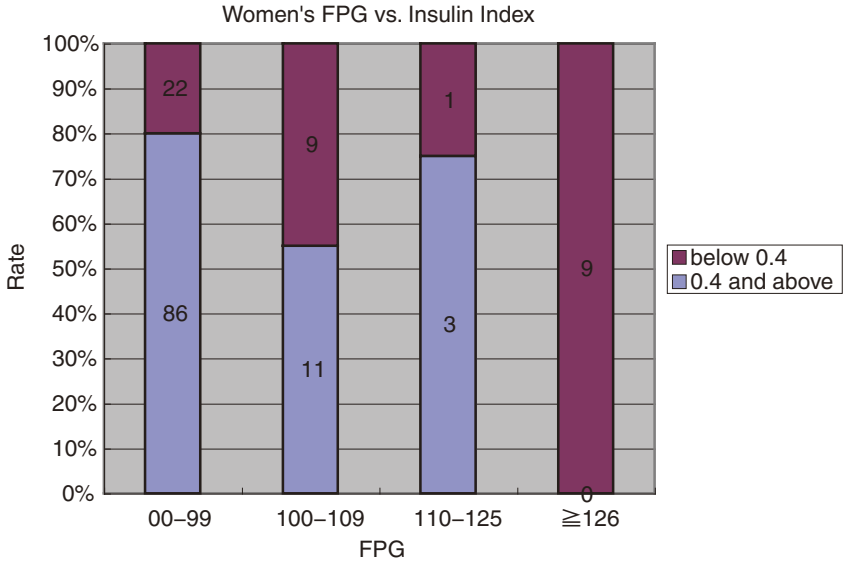

Fig. 5 Rates of two categories of low-insulin index by FPG level
In comparing the three categories of FPG ≦ 99 mg/dl, 100 ≦ FPG ≦ 109 mg/dl, and 110 ≦ FPG ≦ 125 mg/dl, there was no significant difference in the abnormal rates of Insulin Index.

category of 110 ≦ FPG ≦ 125 mg/dl, the low-insulin type was 25% and the normal type was 75%. In the category of FPG ≧ 126 mg/dl, the low-insulin type was 100%. Among the three categories of FPG ≦ 99 mg/dl, 100 ≦ FPG ≦ 109 mg/dl and 110 ≦ FPG ≦ 125 mg/dl, there was no significant difference in the abnormal rates.

DISCUSSION

The ADA and WHO (World Health Organization) revised the diagnostic criteria for FPG in 1979 and 1980 respectively. The latest criterion is similar to that used to diagnose IGT. They announced that people with FPG levels of 100–126 mg/dl would be considered abnormal under the 75g OGTT, and defined them as IFG (impaired fasting glucose) [7–8]. At this point, however, the boundary value between normal and IFG became somewhat arbitrary. Sensitivity and specificity are important in predicting currently undiagnosed diabetes that will develop in the future. It was proven later on in several studies that the level 100 mg/dl is appropriate as the lower limit of IFG, it having the highest total value of sensitivity plus specificity. In Australia, 98 mg/dl is used as the upper limit of

FPG in recommending 75g OGTT [9]. In response to this, the ADA solicited the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus to reinvestigate whether 110 mg/dl was the optimum lower limit of IFG for diabetes screening [10]. Having completed four studies, the Committee announced in 2003 that 100 mg/dl and above was the optimum IFG to predict the future onset of diabetes [2]. Based on this announcement, the EDEG reviewed the lower limit of IFG in 2006. As a result, the EDEG objected to the ADA's definition, insisting that lowering the lower limit of IFG from 110 mg/dl to 100 mg/dl would make no difference in the overall death rate and the rate of CVD (Cardiovascular Disease) but would just raise the prevalence rate twofold to fivefold. Thus, there have been heated debates over appropriate IFG levels.

75g OGTT are essential in confirming the diagnosis of diabetes. Currently, though, it is FPG tests that are most frequently used for diabetes screening. Since FPG tests can be performed in a short time and the procedure is simple and inexpensive, they are often administered during health checkups and other examinations. In Japan, instead of OGTT, FPG tests are used extensively at general health checkups and complete physical examinations. The 75g OGTT required more time and cost than the FPG test. Presently, FPG are used for the screening of diabetes and 75g OGTT are performed when the results of the FPG levels are abnormal [11]. Therefore it is advisable to set an appropriate value for the upper limit of FPG levels. In this study, we discussed the criteria for the upper limit of FPG levels to need 75g OGTT.

According to the cross-sectional study described in Fig. 1, the upper limits of the FPG reference interval for women aged 20 to 39 ranged from 99 mg/dl to 104 mg/dl and a continuous, fairly straight line appeared in the graph. Thus FPG levels can be considered to increase almost in proportion to age. Under normal circumstances, it is preferable to categorize the test groups by 5-year intervals, dividing them into age groups of 20 to 24; 25 to 29; 30 to 34 and 35 to 39, and to investigate each category. In this study though, since there were not so many people who took OGTT, we obtained the ROC curve for people aged 20 to 39 all together.

In this study, we investigated the reference value of FPG for Japanese women. From the ROC curve shown in Fig. 2, the FPG level was 99.5 mg/dl on the point where the total value of sensitivity plus sensitivity reached the highest (1.438). And preferable upper limit of normal FPG levels was below 100 mg/dl for Japanese women aged 20 to 39. For both genders aged over 40, however, the FPG level was 107.5 mg/dl at the point where the total value of sensitivity plus specificity reached the highest. These data are not shown in this paper. Therefore we considered that the current criterion for the upper limit of FPG levels, which is 110 mg/dl and below, is appropriate for them. The FPG test can be used for screening since the AUC was 0.702 but we still regard 75g OGTT as necessary to make a definite diagnosis. Based on the result of the ROC curve, we investigated the test groups between these two categories: FPG $\leqq$ 99 mg/dl and 100 $\leqq$ FPG $\leqq$ 109 mg/dl. As shown in Fig. 3 and 4, both 2-hour post-OGTT glucose levels and HOMA-R showed a significant increase ($p < 0.001$) in the abnormal rates of the 100 $\leqq$ FPG $\leqq$ 109 mg/dl category. In regard to 2-hour post-OGTT glucose levels, the intermediate type was 20% in the category of FPG $\leqq$ 99 mg/dl, while in the category of 100 $\leqq$ FPG $\leqq$ 109 mg/dl, the intermediate type was 47.9% and the diabetic type was 8.6%, Which also showed a significant difference ($p < 0.001$). Regarding HOMA-R, the intermediate type was 18% and the insulin-resistant type was 11% in the category of FPG $\leqq$ 99 mg/dl, while in the category of 100 $\leqq$ FPG $\leqq$ 109 mg/dl, the intermediate type was 21% and the insulin-resistant type was 55%, which also showed a significant difference ($p < 0.001$). Thus, for Japanese women aged 20 to 39, it appears that the abnormal rates of impaired glucose tolerance increase when their FPG levels are over 100 mg/dl. However, Fig. 5 showed Insulin Index is no significant difference among the three categories: FPG $\leqq$ 99 mg/dl, 100 $\leqq$ FPG $\leqq$ 109 mg/dl and 110 $\leqq$ FPG $\leqq$ 125 mg/dl. Therefore, we considered that there were no big differences in insulin secretary capacity among these three categories. After all, it seemed that in the category 100 $\leqq$ FPG $\leqq$ 109 mg/dl, impaired glucose tolerance is mainly caused by insulin resistance, and that lifestyle improvement could also improve impaired glucose tolerance.

Unlike IGT, whether or not IFG is an independent factor in the total death rate or the death rate from CVD is a controversial issue. However, IFG is important for the screening of IGT. From this perspective, setting a proper reference value for IFG is necessary for the prevention of diabetes. Danish data indicates that the prevalence rate will increase from 12% to 38% if the lower limit of IFG levels is set below 100 mg/dl [9, 12]. For this reason, the EDEG disapproves of changing the lower limit of IFG levels to below 100 mg/dl, insisting that it will only result in increasing the prevalence rate without adequate grounds. Indeed, the results of this study also showed that for women over the age 40, FPG $\geqq$ 100 mg/dl was 27.4% and FPG $\geqq$ 110 mg/dl and 9.8%. If the upper limit of FPG levels for women over the age 40 is lowered to 100 mg/dl, the prevalence rate will roughly triple. Therefore, if the normal value of FPG levels is lowered to 99 mg/dl and below for all ages, there is a risk of unnecessarily increasing the prevalence rate in the elderly or, according to this study, for people over 40. On the other hand, using the current reference value, there is a good probability of overlooking many people in younger generations with abnormal 2-hour post-75g OGTT glucose levels. Thus, we think that 75g OGTT should be conducted for women aged 20 to 39 with FPG of 100 mg/dl and above.

We think there is a need to set FPG reference values by age and gender to determine if the 75g OGTT is required. We believe that it is necessary to collect more data and to closely compare 2-hour post-75g OGTT glucose levels, HOMA-R and Insulin Index by 5-year intervals. Moreover, we consider that a cohort study should be conducted to compare not only the onset of diabetes but also the overall death rate and the CVD rate.

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