Impaired glucose regulation (IGR) is a risk factor for both developing diabetes mellitus and coronary heart disease (CHD) [1-3]. Based on World Health Organization (WHO) 1999 criteria for diabetes, the DECODE Study Group demonstrated that impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are both associated with an increased incidence of CHD and increased total mortality; and the multivariate-adjusted analysis showed that IGT is an independent risk factor for CHD and total mortality, while IFG was not [4]. Also, IGT is usually more prevalent than IFG [1, 2]. For these reasons, there was a concern about underestimating the number of people at risk of CHD and diabetes when IGR was diagnosed on the basis of the fasting plasma glucose (FPG) value alone.

The growing prevalence of diabetes and need for primary prevention of CHD [5] have led to an increasing demand for a simple diagnostic procedure for a combination of risk factors for CHD, called metabolic syndrome [6, 7]. In 2003, the American Diabetes Association (ADA) lowered the FPG cut-off point for IFG from 110 mg/dL (6.1 mmol/L) to 100 mg/dL (5.6 mmol/L) [8], and several versions of definition of the metabolic syndrome have adopted the new ADA crite-
rion for the cut-off value of FPG [7, 9, 10].

The current cut-off values applied in Japan for diagnostic test values for diabetes and IGR are the same as the values recommended by the WHO [11], and an abnormal FPG value is defined as 110 mg/dL or more. However, DECODA Study Group demonstrated that when the WHO-recommended cut-off values were used, the 2-hour plasma glucose (PG) values were better predictors of both CHD mortality and total mortality in Asian populations than FPG values were [12]. Since the findings in the DECODA study also suggested that diagnosis of IGR on basis of FPG values alone (110-125 mg/dL) would underestimate the prevalence of IGR in Asian ethnic groups [13], revision of the FPG cut-off value for Japanese would be considered to establish an effective screening method for IGR.

Several papers which investigated the FPG cut-off value on the basis of diabetes incidence among Japanese have been published recently [14-16]. In this study we analyzed the relationship between the subjects’ FPG values at baseline and the incident diabetes at the time of the 5-year follow-up survey, and attempted to identify the optimal FPG cut-off value for predicting future diabetes in a population-based Japanese cohort.

**Study Design and Method**

**Study population**

The Japan Public Health Center-based Prospective Study (JPHC Study) was launched in 1990 for a sub-cohort (Cohort I) and in 1993-1994 for another sub-cohort (Cohort II), which targeted all registered Japanese inhabitants in 11 public health center (PHC) areas aged 40-59 years old in Cohort I and 40-69 years old in Cohort II at the beginning of each baseline survey. The details of the study design have been described elsewhere [17].

In 1998-1999, a survey of diabetes (the JPHC Diabetes Study) was initiated in Cohort II (excluding one PHC area, where the health checkup schedule differed from the schedule in the other areas), and in 2000 it was started in Cohort I. The target population of the surveys of diabetes was inhabitants who received the annual health checkups in each PHC-administered area, and a self-administered questionnaire specific to diabetes research and measurement of HbA1c were added to their routine health checkup examination [18]. The 5-year follow-up survey of Cohort II was conducted in the same manner in 2003-2004, and it was conducted in Cohort I in 2005. The data from one PHC area were not included in the present study, because the participants in the study in that area were exceptionally limited to examinees in a health checkup that was especially designed for inhabitants 40 or 50 years old. The data from another one PHC area were also excluded because the follow-up survey was performed with one-year delay (in 2005).

The age ranges of the two sub-cohorts differed at the time of the baseline and the follow-up surveys of diabetes, and we included only those who were 51 to 70 years of age at the time of the baseline survey of diabetes in the analysis. At the time of the baseline survey, 8,214 men and 14,173 women aged 51 - 70 years old across the 8 PHC areas, who had been registered to the cohort, received the annual health checkup of their own free will and gave written informed consent to participate in this study. Of these, 3,487 men and 6,886 women received the 5-year health checkup.

Collection of a fasting blood sample was not mandatory. We defined a fasting blood sample as a sample collected ≥ 8 hours after the last caloric intake. Otherwise a blood sample was defined as a casual blood sample. We excluded subjects who had given a casual blood sample in any of the two health check-ups and/or any data of whom required for the current analysis were missing. Ultimately, there were a total of 2,392 subjects who completed both the baseline and follow-up surveys for diabetes and from whom a fasting blood sample was collected in both surveys [besides there were 2,430 men (mean FPG value 97.8 mg/dL) and 3,757 women (ditto 95.0 mg/dL) who had only the baseline data and were not included in the analyses because of non-follow up etc. and whose characters were generally similar to those of the analyzed]. After excluding the participants with known diabetes and/or with an FPG value of 126 mg/dL or more at baseline, 2,207 (821 men and 1,386 women) out of 2,392 subjects were included in the present study. The incident cases were considered cases of type 2 diabetes, because the subjects were middle-aged or older and had no signs or symptoms of acute metabolic failure at the time of either health checkup. This study was approved by an ethics committee of the International Medical Center of Japan.

**Questionnaire used for the diabetes survey**

A self-administered questionnaire regarding family history of diabetes, results of previous examinations
for diabetes, physicians’ diagnosis of diabetes, current medication for diabetes, signs of diabetic complications, brief history of body weight changes, physical activity, and history of child birth was distributed at health checkups. In this study “self-reported diabetes” was defined as a reply to the questionnaire that met any of the following criteria: 1) having been told ‘you have diabetes’ by a physician, 2) having received a report of a medical examination suggesting a diagnosis of diabetes, 3) taking medication for diabetes.

**Diabetes**

We defined diabetes and analyzed its development in two ways. In the first way, we defined diabetes as 1) self-reported diabetes and/or 2) an FPG value of 126 mg/dL (7.0 mmol/L) or more, irrespective of the HbA1c value. In the second way, we defined diabetes as [1] and/or [2] and/or 3) an HbA1c value of 6.1% or more. The definition of diabetes by the HbA1c value was based on the announcement by the Japan Diabetes Society (JDS) in 1999 stating that an HbA1c value of 6.1% corresponds to an FPG value of 126 mg/dL and a 2-hr PG value of 200 mg/dL on the 75 g OGTT (oral glucose tolerance test) in the Japanese population under 60 years of age [11]. The linear regression equations for the correlations have already been published [18].

**Examination of HbA1c Levels**

The method of HbA1c measurement differed according to the PHC area. Either high-performance liquid chromatography (HPLC) assay system or immunochromatographic assay system was used in each PHC throughout the study except one PHC that switched from the immunochromatographic system to the HPLC system in the 5-year survey. HbA1c values were standardized in every laboratory to minimize the variation between laboratories. Standard samples (i.e., sets of calibrators), each of which consisted of two calibrators corresponding to HbA1c 5.5% and 10.5%, named “JDS Lot 1”, were provided by Kokusai Shiyaku (Kobe, Japan) at the time of the baseline survey of diabetes, and newer sets of five calibrators corresponding to HbA1c 4.04%, 5.38%, 7.32%, 9.88%, and 12.63% (named “JDS Lot 2”) were provided by HECTEF (Tokyo, Japan) at the time of the 5-year survey. Both calibrator sets were tested and approved by JDS. JDS reported that the HbA1c values standardized by a Lot 2 calibrator set is regarded to be the same as the values standardized by a former Lot 1 set. Relationship between JDS values of HbA1c above described and values of HbA1c determined by standard samples provided by the International Federation of Clinical Chemistry and Laboratory Medicine has been described in a report [19]. The JDS value is by around 0.4% lower than the values determined by the method of the National Glycohemoglobin Standardization Program (NGSP) [20]. Therefore, 6.1% of the JDS value corresponds to 6.5% by calibration of the NGSP method.

The procedure for calibration of HbA1c with JDS Lot 1 at the time of the baseline survey is described elsewhere [18]. The overall intra-assay coefficients of variation (CVs) of the HbA1c 5.5% calibrator ranged from 0.0% to 3.4%, and the CVs for the HbA1c 10.5% calibrator ranged from 0.0% to 2.9% by our hands. The maximal inter-assay CV among laboratories for the 5.5% and 10.5% calibrators was 2.2% and 2.7%, respectively. For calibration by JDS Lot 2 at the time of the 5-year survey, averages of the measured values of each calibrator (HbA1c 4.04%, 5.38%, 7.32%, 9.88%, and 12.63%) were calculated by the same procedure as for the baseline survey [18]. The maximal intra-assay CV and maximal inter-assay CV of these five standard samples among laboratories were 2.3% and 2.8%, respectively. The averages for these 5 standards were used to compute a linear regression equation by the least squares method, and the actual values were calibrated by the regression equation obtained.

**Statistical Analysis**

The crude incidence of diabetes during the next 5 years according to FPG increments by 5 mg/dL was calculated. The receiver operating characteristic (ROC) curve for prediction of the development of diabetes accordingly to the baseline FPG values was plotted using Stata version 8 for Windows (Stata Corp., Texas, USA) in order to identify the optimal cut-off value of FPG. The cut-off value that gave the maximum of sensitivity + specificity was chosen as the optimal cut-off value for the prediction.

**Results**

The baseline characteristics of the subjects are shown in Table 1, and the distribution of the FPG values according to gender and age are shown in Fig. 1. We used two ways of definition of diabetes as described in the “Study Design and Methods” section, and first we will report the data for the development of
As also shown in Fig. 2, the incidence rate began to increase at an FPG value of around 100 mg/dL in both age groups, suggesting that the cut-off value for FPG is not different between these two age groups. We used ROC analysis to identify an optimal cut-off value of FPG for predicting future diabetes. In men, an FPG value of 103 mg/dL was optimal, while the optimal cut-off value for women was 101 mg/dL. In all subjects combined, the optimal cut-off value for FPG was 102 mg/dL (Fig. 3). By performing analyses in the same manner the optimal cut-off value for FPG was 101 mg/dL for the 51- to 60-year-old group and 102 mg/dL for the 61- to 70-year-old group. Thus, the optimal FPG cut-off values for predicting future diabetes in both age groups was very similar. If the FPG cut-off value for IFG were reduced from 110 mg/dL to 100 mg/dL as announced by the American Diabetes Association in 2003, the prevalence of IFG among the subjects in the present study would increase from approximately 7% to 25% (Fig. 1).

To evaluate whether cut-off value for FPG should be defined according to specific age groups, we stratified the subjects into two groups by age and performed analysis for each group in the same manner. As also shown in Fig. 2, the incidence rate began to increase at an FPG value of around 100 mg/dL in both age groups, suggesting that the cut-off value for FPG is not different between these two age groups. We used ROC analysis to identify an optimal cut-off value of FPG for predicting future diabetes. In men, an FPG value of 103 mg/dL was optimal, while the optimal cut-off value for women was 101 mg/dL. In all subjects combined, the optimal cut-off value for FPG was 102 mg/dL (Fig. 3). By performing analyses in the same manner the optimal cut-off value for FPG was 101 mg/dL for the 51- to 60-year-old group and 102 mg/dL for the 61- to 70-year-old group. Thus, the optimal FPG cut-off values for predicting future diabetes in both age groups was very similar. If the FPG cut-off value for IFG were reduced from 110 mg/dL to 100 mg/dL as announced by the American Diabetes Association in 2003, the prevalence of IFG among the subjects in the present study would increase from approximately 7% to 25% (Fig. 1).

**Table 1** Baseline characteristics of the subjects.

<table>
<thead>
<tr>
<th></th>
<th>Men (n=821)</th>
<th>Women (n=1,386)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.4 ± 5.4</td>
<td>61.5 ± 5.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.1 ± 3.0</td>
<td>24.2 ± 3.2</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>96.5 ± 9.7</td>
<td>93.0 ± 8.9</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.0 ± 0.4</td>
<td>5.1 ± 0.4</td>
</tr>
</tbody>
</table>

Data are means ± standard deviation. BMI, body-mass index; FPG, fasting plasma glucose.

**Fig. 1** Distribution of baseline fasting plasma glucose values by gender and age. A) Distribution of baseline fasting plasma glucose (FPG) values by gender. B) Distribution of baseline FPG values in the 51- to 60-year-old group and 61- to 70-year-old group. To convert the FPG values to mmol/L units, multiply by 0.0556.
### Table 2
Number of subjects, cases, incidence rate, and its 95% CI in each baseline FPG category. Diabetes was defined by self-report and FPG value.

<table>
<thead>
<tr>
<th>FPG</th>
<th>All n cases rate* (95%CI)</th>
<th>Men n cases rate* (95%CI)</th>
<th>Women n cases rate* (95%CI)</th>
<th>51-60 years n cases rate* (95%CI)</th>
<th>61-70 years n cases rate* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>71 1 2.8 (0.1-15.2)</td>
<td>25 0 0.0 (0.0-27.4)</td>
<td>46 1 4.3 (0.1-23.1)</td>
<td>30 0 0.0 (0.0-23.1)</td>
<td>41 1 4.9 (0.1-25.7)</td>
</tr>
<tr>
<td>80-84</td>
<td>221 1 0.9 (0.0-14.5)</td>
<td>49 0 0.0 (0.0-14.5)</td>
<td>172 1 1.2 (0.0-6.4)</td>
<td>107 0 0.0 (0.0-6.4)</td>
<td>114 1 1.8 (0.0-9.6)</td>
</tr>
<tr>
<td>85-89</td>
<td>433 8 3.7 (1.6-7.2)</td>
<td>120 3 5.0 (1.0-14.3)</td>
<td>313 5 3.2 (1.9-7.4)</td>
<td>165 1 1.2 (0.0-6.7)</td>
<td>268 7 5.2 (2.1-10.6)</td>
</tr>
<tr>
<td>90-94</td>
<td>496 7 2.8 (1.1-5.8)</td>
<td>177 4 4.5 (1.2-13.4)</td>
<td>319 3 1.9 (0.4-5.6)</td>
<td>193 4 4.1 (1.1-10.4)</td>
<td>303 3 2.0 (0.0-5.7)</td>
</tr>
<tr>
<td>95-99</td>
<td>428 13 6.1 (3.3-10.3)</td>
<td>169 6 7.1 (2.6-15.1)</td>
<td>259 7 5.4 (2.2-11.0)</td>
<td>148 3 4.1 (0.8-11.6)</td>
<td>280 10 7.1 (3.5-12.9)</td>
</tr>
<tr>
<td>100-104</td>
<td>260 15 11.5 (6.5-18.7)</td>
<td>120 6 10.0 (3.7-21.1)</td>
<td>140 9 12.9 (6.0-23.7)</td>
<td>89 5 11.2 (3.7-25.3)</td>
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</tr>
<tr>
<td>105-109</td>
<td>145 22 30.3 (19.5-44.1)</td>
<td>82 12 29.3 (15.6-48.3)</td>
<td>63 10 31.7 (15.8-54.5)</td>
<td>49 5 40.0 (19.2-94.0)</td>
<td>100 13 26.0 (14.2-42.4)</td>
</tr>
<tr>
<td>110-114</td>
<td>76 20 52.6 (33.7-75.4)</td>
<td>37 9 48.6 (23.5-82.4)</td>
<td>29 11 56.4 (30.0-89.7)</td>
<td>23 7 60.9 (26.4-105.8)</td>
<td>53 13 49.1 (27.5-76.6)</td>
</tr>
<tr>
<td>115-119</td>
<td>44 19 86.4 (56.7-117.9)</td>
<td>26 8 61.5 (28.7-103.6)</td>
<td>18 11 122.2 (71.5-165.4)</td>
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<td>27 9 66.7 (33.0-107.9)</td>
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<tr>
<td>120-125</td>
<td>33 19 115.2 (78.4-149.0)</td>
<td>16 8 100.0 (49.3-150.7)</td>
<td>17 11 129.4 (76.7-171.6)</td>
<td>11 8 145.5 (78.1-188.0)</td>
<td>22 11 100.0 (56.4-143.6)</td>
</tr>
</tbody>
</table>

* Incidence rate per 1,000 person-years 95%CI, 95% confidence interval

### Table 3
Number of subjects, cases, incidence rate, and its 95% CI in each baseline FPG category. Diabetes was defined by self-report, FPG, and HbA1c value.

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* Incidence rate per 1,000 person-years 95%CI, 95% confidence interval
Next, we analyzed the incidence of diabetes defined differently from what was described above, in which (second analysis) diabetes was defined as any of the following three; a self-report, an increase in FPG value, and an increase in HbA1c value (described in the “Study Design and Methods” section). Forty of the subjects in the first analysis described above were excluded in the second analysis because they met the HbA1c criterion for diabetes at the baseline. As a result, 2,167 subjects (812 men and 1,355 women) were included. There were 132 (66 men and 66 women) subjects who developed diabetes, and thus the proportion of the subjects of this analysis who developed diabetes during the next 5-year period was slightly higher, 6.1%, as opposed to the 5.7% when the first definition of diabetes was used. Diabetes was diagnosed in 81 out of the 132 newly diagnosed cases based on FPG and/or HbA1c levels. In 30 of the 81 newly diagnosed diabetes cases only FPG criterion was met, and 31 satisfied only the HbA1c criterion (Fig. 5). The incidence rate of diabetes according to the FPG level at baseline was shown in Fig. 4 and Table 3 and the overall trend was the same as when the first definition of diabetes was used. The incidence rate for baseline FPG levels of 95-99, 100-104, 105-109, 110-114, 115-119, and 120-125 mg/dL of all subjects was 8.0, 18.8, 31.9, 48.6, 75.7, and 110.3 per 1,000 person-years, respectively. The results of the ROC analysis indicated that the optimal FPG cut-off value for the 2,167 subjects was 101 mg/dL. When the subjects were divided into two age groups (51 to 60 years old and 61 to 70 years old, respectively), the trend for incidence rate of diabetes (Fig. 4) was similar to the trend when the first definition of diabetes was used. Also, the optimal cut-off value indicated by the ROC analysis was almost the same.

Discussion

A search for a simple and effective screening method to identify people at high-risk for diabetes has been conducted worldwide, and there could be differences in FPG cut-off values among different study populations. An optimal cut-off value of 5.5 mmol/L (99 mg/dL) has been reported in a Mauritius population aged 25 to 74 years [21], and of 92 mg/dL in Korean men aged 30 to 59 years based on the results of a 5-year follow-up [22]. The San Antonio Heart Study reported that by lowering the FPG cut-off value of the metabolic syndrome criteria to 5.4 mmol/L (94 mg/dL) efficacy of the criteria to identify high-risk population for diabetes was improved [23]. Thus, ethnicity might be taken into account when setting FPG cut-off values. Also, the cut-off value, which is selected to distinguish people with much less risk of diabetes from
those at higher risk, should better be based on the incidence of diabetes rather than the prevalence in cross-sectional studies. In 1999 JDS defined normal glucose tolerance as a situation that is not likely to develop diabetes during the next several years of follow-up [11]. The present study has proposed the optimal FPG cut-off values in terms of sensitivity and specificity for prediction of future diabetes by a longitudinal observation of a Japanese population, based on the JDS statement in 1999 above described. The results of the present study indicate that the FPG cut-off value for IFG should be 101 or 102 mg/dL in Japanese people aged 51 to 70 years old. There was almost no difference in cut-off value between men and women, or between subjects 51 to 60 years old and 61 to 70 years old.

Several papers which investigated the IFG cut-off value on the basis of diabetes incidence among Japanese have been published recently [14-16]. In a study based on the health checkup data of 11,129 subjects, the optimal FPG cut-off value for IFG was determined to be 5.7 mmol/L (102 or 103 mg/dL) [15]. The results of a study based on the health checkup data of 11,369 subjects showed that the optimal FPG cut-off value for IFG was 101 mg/dL [15]. In these studies the criterion for diagnosis of diabetes was an FPG value ≥ 7.0 mmol/L or diagnosis by physician. In a study based on the data obtained in the Funagata study, the optimal FPG cut-off value for IFG was found to be 5.36 mmol/L (96 or 97 mg/dL) [16]. In this study the diagnosis of diabetes was based on the results of an OGTT, and the diagnosis of diabetes may be more accurate than in the two previous Japanese studies, but the optimal FPG cut-off value was almost the same. All of these three previous studies indicated that the optimal FPG cut-off value for IFG is around 100 mg/dL.

The sensitivity of FPG cut-off value of 110mg/dL and 100mg/dL in the present study was found to be about 35% and 70%, respectively (Fig. 3). One of the main purposes of defining IFG is to detect high risk subjects and lower the number of diabetes patients in the future by intervening. At the FPG cut-off value of 110 mg/dL, about 65% of future cases of diabetes will be missed, and it seems inadequate to achieve the purpose described above. However, the considerable increase in prevalence of IFG when the FPG cut-off value was lowered to the level announced in 2003 by the ADA would be a concern. Lowering the FPG cut-off value would also raise the problem of lower positive predictive value (PPV). While the PPV of a FPG cut-off value of 110 mg/dL is 27.3% for men and 39.6% for women, the PPV of a FPG cut-off value of 100 mg/dL is 14.8% and 18.1%, respectively, and more than 80% of subjects who are designated as IFG would not develop diabetes within five years. That means that subjects with an FPG level 100-125 mg/dL are not at equal risk of developing diabetes, and risk stratification is necessary. Recent reports have suggested that a combination of FPG values and additional information, such as in regard to abdominal obesity and hypertension, can be used to efficiently identify people who are at high risk of CHD and/or diabetes [24]. In addition to risk stratification, future development of effective intervention to IFG, though for the moment essentially no such evidence is reported, is necessary and it will start with the recognition that subjects with FPG value of 100-109 mg/dL are not “normal” but are at high risk of diabetes. In this regard, health check-up system should deal with this and evidence could be built up herein.

Japanese cross-sectional studies have reported higher prevalence of type 2 diabetes among middle- and elderly aged men than women, and that this difference decreases with age[13, 18]. The results of the present study have shown that the FPG values of the women were distributed over a lower range than those of the men (Fig. 1). Thus, the gender difference in prevalence of diabetes over the previous cross-sectional studies in Japan may be attributable to the difference in FPG distribution between the two genders.

The present study has at least two limitations. First, the number of participants who received the baseline and follow-up health checkups was relatively small compared to that of the original whole subjects, and fasting blood samples were collected from only a small proportion of subjects at both baseline and follow-up. As a result, only about 2% of the two sub-cohorts were analyzed in the present study, and this may have caused selection bias. Second, the cut-off value was determined based on the risk of diabetes alone, and the risk of CHD was not considered. In addition, we should be cautious in interpreting the data of incidence rate by the current analyses because we did not have conducted OGTTs, which might have resulted in an underestimation of incidence.

In conclusion, the FPG cut-off value for IFG in the Japanese ethnic group might be reduced to around 100 mg/dL. However, not all subjects with IFG should be
targeted for primary prevention equally, because the subjects with a higher range of IFG values were at much higher risk than those with values in the lower range.

Acknowledgments

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