Utility of 75-g Oral Glucose Tolerance Test Results and Hemoglobin A1c Values for Predicting the Incidence of Diabetes Mellitus among Middle-aged Japanese Men —A Large-scale Retrospective Cohort Study Performed at a Single Hospital—

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Abstract

Objective The aim of this study was to investigate the associations between the incidence of diabetes and the accumulation of markers of impaired glucose metabolism; i.e., pre-diabetes.

Methods This retrospective cohort study recruited 1,631 men without diabetes at baseline who attended more than two routine health check-ups at our institution between 2006 and 2012. The participants were divided into four groups based on the number of markers of impaired glucose metabolism exhibited at the initial examination. The following markers of impaired glucose metabolism were defined as risk factors for diabetes: a fasting plasma glucose level of ≥110 mg/dL, 2-hour plasma glucose level of ≥140 mg/dL and glycated hemoglobin (HbA1c) value of ≥6.0% (42 mmol/mol). The risk of developing diabetes was assessed using a multivariate analysis.

Results The median examination interval was 1,092 days. The incidence of diabetes rose in association with the number of markers. The subjects with two markers displayed a multivariate-adjusted odds ratio (OR) for diabetes of 19.43 [95% confidence interval (CI): 9.70-38.97] and the subjects with three markers displayed an OR of 48.30 (95% CI: 20.39-115.85) compared with the subjects with one or no markers.

Conclusion The present results demonstrate the impact of accumulating markers of impaired glucose metabolism on the risk of developing diabetes. Anti-diabetes intervention strategies should aim to comprehensively assess an individual’s risk of developing diabetes at the pre-diabetes stage.

Key words: pre-diabetes, 75-g oral glucose tolerance test (OGTT), risk of progression to diabetes

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Introduction

It is estimated that more than 10 million people who have not been diagnosed with diabetes exhibit glycated hemoglobin (HbA1c) values ranging from ≥6.0% (42 mmol/mol) to <6.5% (48 mmol/mol), and (1) such individuals thought to have either diabetes or be at high risk of developing the disease in the near future (2).

Pre-diabetes, which includes various carbohydrate metabolism disorders, is generally viewed as a distinct clinical entity, i.e., an interim condition, and is considered to be a risk factor that presages the development of diabetes (3). Patients with pre-diabetes are usually classified according to their plasma glucose level; i.e., whether they display impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or both. The 75-g oral glucose tolerance test (OGTT) is the standard method for screening for diabetes, employed

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Study population

This was a retrospective cohort study conducted at the Center for Preventive Medicine at the NTT Medical Center, Tokyo from May 2006 to February 2012. Employers in Japan are required by the Industrial Safety and Health Law to commission medical examinations once a year to ensure the health of their employees. We were contracted by NTT, a telecommunications company, to provide medical examinations to their employees based on the requirements of the abovementioned law. The present study was conducted as part of the general health check-up program delivered at our center. Most of the study subjects were volunteers recruited from among the employees of NTT and their families. Our investigation focused on 1,853 men who underwent more than two examinations at our center during the abovementioned period. For participants who underwent several examinations during the study period, their initial and latest data were analyzed. The exclusion criteria were as follows: the presence of diabetes at the initial examination, a history of gastrectomy and lack of OGTT findings. According to the exclusion criteria, 220 of the 1,853 initial study candidates were excluded, including 66 patients with diabetes at the initial examination, 20 patients who had undergone gastrectomy, 111 patients who did not undergo OGTTs at the initial examination and 25 patients without obvious diabetes who did not undergo OGTTs during the latest examination. (Figure) Thirteen individuals who were diagnosed with diabetes using methods other than OGTT at the latest examination were included in the study [seven individuals who had been receiving pharmacotherapy for diabetes and six individuals with an HbA1c value of ≥6.5% (48 mmol/mol)]. Hence, a total of 1,631 subjects were enrolled in this study.

Data collection

All examinations were performed at a single institution, and the results were used for the abovementioned mandated medical employee examinations. Therefore, the precision of the examinations did not vary.

The participants completed self-administered questionnaires regarding their demographic characteristics and medical history, and well-trained staff interviewed any participants who had failed to complete the forms. The examinations were performed on two consecutive days. On the first day, weight and height were measured after the subject removed their shoes and heavy clothing, and blood pressure was measured in the sitting position with an automatic monitor. In addition, serum samples were collected from each participant after overnight fasting and immediately subjected to a biochemical analysis. The serum samples were also used to determine the subjects’ HbA1c values. On the second day, participants without obvious diabetes underwent 75-g OGTT examinations, in which we measured the FPG level and 1-hour and 2-hour post-load plasma glucose and immunoreactive insulin levels. The HbA1c values were determined using high-performance liquid chromatography with an automatic analyzer.

The subjects’ clinical data were retrospectively retrieved from an institutional database. Before each examination, the participants were informed that the clinical data obtained worldwide. However, the American Diabetes Association (ADA) has recently proposed that the HbA1c value can also be used to diagnose pre-diabetes (4). During health check-ups involving subjects from whom it is difficult to collect blood during fasting, glucose metabolism is often only evaluated based on the HbA1c value. In addition, OGTTs are often not performed during general health check-ups. Regarding the evaluation of glucose tolerance, assessing only the fasting plasma glucose (FPG) level is considered to be insufficient for screening for diabetes in Asian subjects (5). Furthermore, it is widely known that the groups of patients exhibiting IFG and IGT do not overlap completely, and the same applies for the groups of patients displaying IFG and a high HbA1c value. Therefore, assessing pre-diabetes based on a single marker is of limited use. Moreover, the coexistence of IFG and IGT is associated with a higher risk of developing diabetes than the presence of IFG or IGT alone (6). Moreover, previous reports have suggested that the combination of a high FPG level and HbA1c value is associated with an increased risk of developing diabetes (7, 8). OGTTs are thus considered to be useful for accurately predicting an individual’s risk of developing diabetes, and a combination of the abovementioned markers should be employed to diagnose pre-diabetes. However, the association between the presence of both IGT and a high HbA1c value and the incidence of diabetes remains unclear. Namely, it is unknown how the triad of IFG, IGT and a high HbA1c value affects the risk of diabetes progression.

Stratifying individuals with pre-diabetes may help to prevent diabetes. The aim of this study was to determine the impact of the accumulation of markers of impaired glucose metabolism and the presence of different combinations of such markers on an individual’s risk of developing diabetes.

Materials and Methods

Study population

This was a retrospective cohort study conducted at the Center for Preventive Medicine at the NTT Medical Center.

Figure. Inclusion and exclusion flowchart

Initial participants (Japanese, aged 25 or above) 1,853 Subjects
- Participants excluded at the initial examination
  - 66 Subjects: Defined as having diabetes
  - 111 Subjects: The OGTT was not performed
- Participants excluded at the latest examination
  - 25 Subjects: Without obvious diabetes, the OGTT was not performed
- Other excluded participants
  - 20 Subjects: Post-gastrectomy

Final study subjects 1,631 Subjects
during the program may be retrospectively analyzed and published. All of the examinations included in this study were performed as a routine part of the program and none were aimed at specifically collecting data for the current study. The study protocol was approved by the institutional ethics committee.

Data handling

The HbA1c (Japan Diabetes Society; JDS) values were converted to International Federation of Clinical Chemistry (IFCC) values according to National Glycohemoglobin Standardization Program (NGSP) values using the formula developed by the JDS (see below) (9-11).

The following parameters were calculated in this study:

1. \( \text{HbA1c (JDS)} \times 1.02 + 0.25 \)
2. \( \text{HbA1c (IFCC)} = \frac{10.93 \times \text{NGSP} - 23.52}{42} \)
3. Simple Insulin Sensitivity Composite Index (ISI) \((12, 13) = \frac{10,000}{\sqrt{\text{FPG} \times \text{PRG}} \times \text{HbA1c}}\)
4. Homeostasis Model Assessment of Insulin Resistance (HOMA-R) \((14, 15) = \frac{\text{FPG} \times \text{PRG}}{405} \)

Diabetes was defined in accordance with the JDS criteria and ADA guidelines as an FPG level of ≥126 mg/dL, 2-hour plasma glucose level during a 75-g OGTT of ≥200 mg/dL, HbA1c value of ≥6.5% (48 mmol/moL) or self-reported diagnosis of diabetes. The subjects with an HbA1c value of <6.0% (42 mmol/moL) displayed a higher incidence of diabetes. In comparison with the subjects with an HbA1c value of <6.0% (42 mmol/moL), those with an HbA1c value of ≥6.0% (42 mmol/moL) tended to exhibit higher HOMA-R values than the isolated IGT subjects. For example, the isolated IFG subjects displayed less favorable ISI and HOMA-R values than the isolated IGT subjects. The pre-diabetes subjects exhibited less favorable ISI and HOMA-R values than the NGT subjects. However, various differences were detected between the isolated IFG and isolated IGT subjects. For example, the isolated IFG subjects tended to exhibit higher HOMA-R values than the isolated IGT subjects (p<0.1). On the other hand, the mean ISI value among the isolated IGT subjects was significantly worse than among the isolated IFG subjects.

### Results

Table 1 shows the characteristics of the study subjects at the initial examination. The median examination interval was 1,092 days, and the median age of the subjects was 49 years. At the last examination, 3.6% (58/1,631) of the subjects had been diagnosed with diabetes. The subjects were classified into four categories according to the FPG and 2-hour plasma glucose levels, as follows: NGT=1,296 subjects, isolated IFG=83 subjects, isolated IGT=185 subjects, and IFG plus IGT=67 subjects. Among these patients, 45 (3.5%) NGT subjects, 19 (22.9%) isolated IFG subjects, 28 (15.1%) isolated IGT subjects and 33 (49.3%) IFG plus IGT subjects had an HbA1c value of ≥6.0% (42 mmol/moL). In comparison with the subjects with an HbA1c value of <6.0% (42 mmol/moL), those with an HbA1c value of ≥6.0% (42 mmol/moL) displayed a higher incidence of diabetes. The pre-diabetes subjects exhibited less favorable ISI and HOMA-R values than the NGT subjects. However, various differences were detected between the isolated IFG and isolated IGT subjects. For example, the isolated IFG subjects tended to exhibit higher HOMA-R values than the isolated IGT subjects (p<0.1). On the other hand, the mean ISI value among the isolated IGT subjects was significantly worse than among the isolated IFG subjects.
Table 1. Demographic Characteristics according to HbA1c Level at the Initial Examination with the Incidence of Diabetes at the Latest Examination

<table>
<thead>
<tr>
<th>HbA1c Level at the Initial Examination</th>
<th>Median (minimum, maximum)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&lt;6.0%)</td>
<td>5.0 (4.0, 6.0)</td>
<td></td>
</tr>
<tr>
<td>Prediabetes (6.0% - &lt;6.0%)</td>
<td>5.5 (4.0, 6.4)</td>
<td></td>
</tr>
<tr>
<td>Diabetes (≥6.0%)</td>
<td>6.6 (6.0, 6.4)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 shows the associations between the number of markers of impaired glucose metabolism and the subjects’ clinical characteristics. As the number of markers increased, the plasma glucose level rose and the ISI and HOMA-R values fell. As a result, the incidence of diabetes increased in association with the number of markers.

Table 3 shows the risk factors found to be significantly associated with the incidence of diabetes. In Model 1, the subjects with an HbA1c value of ≥6.0% (42 mmol/mol) displayed a multivariate-adjusted odds ratio (OR) for diabetes of 9.94 (95% CI: 5.59-17.70) compared with the subjects with an HbA1c value of <6.0% (42 mmol/mol). In addition, the subjects with a FPG level of ≥110 mg/dL exhibited a multivariate-adjusted OR for diabetes of 26.72 (95% CI: 11.80-61.01) compared with the other subjects. Finally, the subjects with a 2-hour plasma glucose level of ≥140 mg/dL demonstrated a multivariate-adjusted OR for diabetes of 14.01 (95% CI: 7.72-26.62). In Model 2, the subjects with two markers of impaired glucose metabolism displayed a multivariate-adjusted OR for diabetes of 19.43 (95% CI: 9.70-38.97) compared with the subjects with one or no markers. Furthermore, the subjects with three markers of impaired glucose metabolism exhibited an OR for diabetes of 48.30 (95% CI: 20.39-115.85) compared with the subjects with one or no markers. Moreover, the subjects with two markers of impaired glucose metabolism exhibited the following ORs for diabetes compared with the subjects with one or no markers: FPG ≥110 mg/dL and HbA1c ≥6.0% (42 mmol/mol)=10.98 (2.34-38.28) (n=19), FPG ≥110 mg/dL and 2-hour plasma glucose level of ≥140 mg/dL=24.78 (9.27-62.26) (n=28). The OR for diabetes among the subjects who possessed two markers, including a 2-hour plasma glucose level of ≥140 mg/dL, appeared to be higher than that of the isolated IFG subjects (p<0.01). Furthermore, the IFG plus IGT subjects displayed both the highest plasma glucose level sums and worst ISI and HOMA-R values. In addition, these subjects exhibited the highest incidence of diabetes.

Discussion

This retrospective cohort study examined the associations between the results of the 75-g OGTT and/or the HbA1c values and the incidence of diabetes mellitus and found that the incidence of diabetes rose in accordance with the accumulation of the following three risk factors: an FPG level of ≥110 mg/dL, 2-hour plasma glucose level of ≥140 mg/dL and HbA1c value of ≥6.0% (42 mmol/mol). Furthermore, subjects who possessed any combination of two risk factors showed higher ORs for diabetes than those with no or only a single risk factor.

To the best of our knowledge, this is the first study to ex-
Table 2. The Relationships between the Glucose Metabolism-related Characteristics of the Subjects and the Number of Risk Factors for Diabetes Mellitus

<table>
<thead>
<tr>
<th>Numbers of risk factors for diabetes</th>
<th>Median (minimum, maximum) or N (%)</th>
<th>rs</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of participants</td>
<td>1,251</td>
<td>1,099(160,2,033)</td>
<td>81</td>
</tr>
<tr>
<td>Examination interval (days)</td>
<td>25(5,76)</td>
<td>1,099(232,2,071)</td>
<td>266</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.5(3.7, 338.0)</td>
<td>47.5(5.9, 188.0)</td>
<td>58.2(15.3, 645.3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>31.1(2,4, 239.8)</td>
<td>45.7(5.2, 201.0)</td>
<td>50.0(10.9, 225.7)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>104(50, 139)</td>
<td>137(56, 194)</td>
<td>190(113, 276)</td>
</tr>
<tr>
<td>Sum of plasma glucose during the OGTT (mg/dL)</td>
<td>334(216, 464)</td>
<td>415(226, 536)</td>
<td>465(359, 581)</td>
</tr>
<tr>
<td>Immunoreactive insulin</td>
<td>5.2(0.7, 28.1)</td>
<td>6.3(1.2, 30.7)</td>
<td>7.5(1.2, 26.1)</td>
</tr>
<tr>
<td>Fasting immunoreactive insulin (µU/mL)</td>
<td>46.5(3.7, 338.0)</td>
<td>47.5(5.9, 188.0)</td>
<td>55.5(10.0, 188.0)</td>
</tr>
<tr>
<td>1 hour - immunoreactive insulin (µU/mL)</td>
<td>31.1(2,4, 239.8)</td>
<td>45.7(5.2, 201.0)</td>
<td>56.0(10.9, 225.7)</td>
</tr>
<tr>
<td>Sum of immunoreactive insulin during the OGTT (µU/mL)</td>
<td>85.5(14.3, 479.6)</td>
<td>102.8(15.3, 645.3)</td>
<td>126.1(24.2, 406.0)</td>
</tr>
<tr>
<td>Simple insulin sensitivity composite index</td>
<td>8.0(1.4, 0.7)</td>
<td>14.5(0.8, 27.9)</td>
<td>3.7(1.1, 19.2)</td>
</tr>
<tr>
<td>Homeostasis model assessment of insulin resistance</td>
<td>1.2(0.1, 7.1)</td>
<td>1.6(0.3, 7.2)</td>
<td>2.0(0.3, 7.2)</td>
</tr>
</tbody>
</table>

Table 3. Odd’s Ratios for the Development of Type 2 Diabetes according to the Risk Factors at the Initial Examination (Binary Logistic Regression Analysis)

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c ≥6.0% (n=125)</td>
<td>FPG ≥110mg/dL (n=150)</td>
</tr>
<tr>
<td>Incidence of diabetes (%)</td>
<td>24(22.4)</td>
</tr>
<tr>
<td>Univariate hazard ratio for diabetes (95%CI)</td>
<td>14.20 (8.13-24.77)</td>
</tr>
<tr>
<td>Multivariate hazard ratio for diabetes (95%CI)*</td>
<td>11.61 (6.33-21.38)</td>
</tr>
</tbody>
</table>

* Adjusted for age at the initial examination, BMI at the initial examination, and examination interval

Diabetes was defined as an HbA1c level 6.5% or higher, self-reported diabetes under pharmacotherapy, or receiving a diagnosis of diabetes after an OGTT.

We consider that the three abovementioned risk factors affect the risk of diabetes to different extents. For example, there are differences between the effects of an elevated HbA1c value and plasma glucose level on the risk of diabetes. There are considerable differences in the HbA1c values and plasma glucose levels of populations diagnosed with NGT or pre-diabetes. In fact, in the present study, the subjects who exhibited IFG, IGT or an elevated HbA1c value did not overlap completely. However, the utility of HbA1c as a screening tool for identifying individuals with pre-diabetes is disputed (16). Furthermore, other reports have suggested that the risk of progression to diabetes is continuous and occurs at glucose and HbA1c values lower than those currently used to define pre-diabetes (3, 4, 17-19). We consider that higher HbA1c values and plasma glucose levels are associated with an increased risk of progression to diabetes in individuals exhibiting NGT and pre-diabetes, respectively. In addition, differences were also noted in the current study between the risks associated with the detection of increased FPG and 2-hour plasma glucose levels during the OGTT examinations. Notably, IFG and IGT have different underlying pathophysiological mechanisms (20-23), and it is generally thought that individuals with isolated IFG exhibit severe hepatic insulin resistance, whereas those with isolated IGT display severe muscle insulin resistance. Furthermore, individuals with both IGT and IFG demonstrate steeper reductions in insulin resistance and are at higher risk of developing diabetes than those with NGT, isolated IFG or isolated IGT (24, 25). In the present study, the HOMA-R values, a measurement of hepatic insulin resistance (20), were worse in the subjects with isolated IFG than in those with isolated IGT. On the other hand, the ISI, a measurement of the deterioration of whole-body insulin sensitivity (20), was significantly lower in the subjects with isolated IGT than those with isolated IFG. These findings suggest that patients with isolated IGT suffer from severe peripheral (muscle) tissue insulin resistance. Moreover, the subjects who exhibited both IFG and IGT in the present study demonstrated the highest HOMA-R values and the lowest ISI values, indicating that they were experiencing widespread deterioration in their ability to metabolize insulin. Our findings thus suggest that elevated FPG and 2-hour plasma glu-
cose levels are associated with different carbohydrate metabolism disorders in patients with pre-diabetes. In addition, our data indicate that the risk of diabetes differs between subjects with an elevated FPG level and those with an increased 2-hour plasma glucose level. Namely, an elevated 2-hour plasma glucose level appears to be a stronger risk factor for diabetes than an increased FPG level or HbA1c value. In Japanese individuals, the deterioration of early-phase insulin secretion may result in an elevated post-challenge plasma glucose level. Furthermore, deterioration in early-phase insulin secretion has a great impact on the incidence of type 2 diabetes (26, 27). Hence, an elevated 2-hour plasma glucose level may be important for predicting the development of diabetes in the Japanese population. Accordingly, OGTTs, which can be used to assess the 2-hour plasma glucose level, are an important tool for precisely evaluating the status of pre-diabetes.

The risk of diabetes varies widely among individuals diagnosed with pre-diabetes based on the measurements of a single parameter. Comprehensive risk evaluations, as well as stratifying individuals according to the number of risk factors for diabetes progression and prioritizing management strategies, may help to prevent diabetes in Japanese patients with pre-diabetes.

This study is associated with several limitations. First, there was selection bias, as only men were assessed. In addition, more than 70% of the participants were healthy office workers ranging in age from 40 to 60 years. Hence, the investigated cohort was affected by the healthy worker effect and does not accurately represent the overall Japanese population, and a multicenter study involving a sufficient number of women and elderly subjects is required. Second, it was not possible to estimate the level of early-phase insulin secretion because our participants were not examined at 30 minutes during the OGTT examinations. Moreover, we are unable to comment on the deterioration of early-phase insulin secretion due to a lack of data regarding the immunoreactive insulin and plasma glucose levels at 30 minutes during the OGTTs. As mentioned in the discussion section, the deterioration of early-phase insulin secretion may play an important role in the pathogenesis of abnormal carbohydrate metabolism in Japanese individuals. Third, we did not examine some parameters that are known to play important roles in the development of diabetes, such as lifestyle factors and family history. Therefore, further studies evaluating such information are needed.

Conclusion

Elevated FPG, 2-hour plasma glucose and HbA1c levels may represent different disorders in individuals with pre-diabetes. In the present short-term study, the accumulation of these markers of impaired glucose metabolism was found to be closely associated with the incidence of diabetes mellitus.

Author’s disclosure of potential Conflicts of Interest (COI), Kazutoshi Fujibayashi: Employment, NTT Medical Center Tokyo. Toshiaki Gunji: Employment, NTT Medical Center Tokyo, Noriko Sasabe: Employment, NTT Medical Center Tokyo. Mitsue Okumura: Employment, NTT Medical Center Tokyo. Kimiko Iijima: Employment, NTT Medical Center Tokyo.

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