Insulin secretion and insulin sensitivity on the oral glucose tolerance test (OGTT) in middle-aged Japanese

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Abstract. The aim of this study was to assess the changes in insulin secretion and insulin sensitivity in relation to fasting and 2-hour plasma glucose (PG) levels and to assess the independent contributions of their impairments to non-diabetic hyperglycemia. A total of 2157 Japanese workers (mean age 52.6±7.3 years and mean BMI 23.9±3.2 kg/m²) underwent an oral glucose tolerance test (OGTT). Of these subjects, 1125 had normal glucose tolerance (NGT), 525 subjects had isolated impaired fasting glucose (IFG), 159 subjects had isolated impaired glucose tolerance (IGT), 263 subjects had combined IFG and IGT, and 85 subjects had newly diagnosed type 2 diabetes. Insulinogenic index and Matsuda insulin sensitivity index (ISI) were significantly attenuated in subjects with normal but slightly elevated fasting PG, or in subjects with normal but slightly elevated 2-hour PG. Whereas, InsAUC120/GluAUC120 was not significantly decreased in those subjects, and significant decrease of it was observed exclusively in subjects with abnormal fasting PG (≥ 106 mg/dL) or abnormal 2-hour PG (≥ 221 mg/dL). Using multiple regression analyses, both Matsuda ISI and insulinogenic index were independently correlated with PG concentrations in subjects with IFG and/or IGT, while Matsuda ISI alone was independently correlated with fasting PG concentrations in normoglycemic subjects. In conclusion, both insulinogenic index and Matsuda ISI were significantly attenuated in subjects with normal but slightly elevated PG. Lowering of Matsuda ISI was likely to be a strong contributor to ‘elevation of fasting PG within the normal range’ in this population.

Key words: Impaired fasting glucose (IFG), Impaired glucose tolerance (IGT), Oral glucose tolerance test (OGTT)

INSULIN resistance and impaired insulin secretion are considered the primary pathophysiological factors in the development of type 2 diabetes [1]. Although hyperglycemic and euglycemic clamp studies are well-established methods of assessing insulin secretion and insulin sensitivity [2, 3], the oral glucose tolerance test (OGTT) is a simpler and less expensive method that provides estimates of both factors. As a measure of insulin secretion, insulinogenic index is highly correlated with the acute insulin response (AIR) on the intravenous glucose tolerance test (IVGTT) in non-diabetic subjects [4, 5], and it has been widely used as an index of early-phase insulin secretion in clinical studies [6-11]. The ratio of the area-under-the-insulin-curve to the area-under-the-glucose-curve in the 120 min of the OGTT (InsAUC120/GluAUC120) has been used as a measurement for total insulin secretion during the OGTT [11-13]. As a measure of insulin sensitivity, Matsuda insulin sensitivity index (ISI) has been validated against measurements obtained by the euglycemic hyperinsulinemic clamp test [14]. Recent studies have demonstrated that Matsuda ISI is better correlated with the clamp-derived M_{LBM}/I value than the indices derived from fasting measurements, such as homeostatic model assessment of insulin resistance (HOMA-IR) [12, 15].

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are intermediate categories between normal glucose metabolism and diabetes, which only partially overlap and are considered different in pathophysiology [16]. To date, in OGTT-based studies
on insulin secretion and insulin sensitivity, some studies have demonstrated that subjects with isolated IFG were more insulin resistant, and subjects with isolated IGT exhibited a more severe deficit in insulin secretion [7, 9, 11]. Other studies, including some conducted in Asian populations, have reported that both subjects with isolated IFG and those with IGT had defects in insulin secretion [6, 8, 10, 12], with higher [6, 10, 12] or comparable [8] levels of insulin resistance compared with subjects with normal glucose tolerance (NGT). These conflicting results are likely due to differences in the methods of measurements, differences in the study subjects, and failure to account for confounding factors such as body mass index (BMI).

Therefore, the aim of this study was to assess the changes in insulin secretion and insulin sensitivity in relation to fasting and 2-hour plasma glucose (PG) levels and to assess the independent contributions of their impairments to non-diabetic hyperglycemia. To this end, we measured the insulogenic index (early-phase insulin secretion), InsAUC$_{120}$/GluAUC$_{120}$ (total insulin secretion), and Matsuda ISI (insulin sensitivity) and analyzed the influences of relevant variables, such as BMI, age, and sex.

**Subjects and Methods**

**Study sample**
Hokuriku Central Hospital has a designated department where public school employees receive routine medical checkups. Annual medical checkups are mandated by law and are funded by the employees’ mutual aid association. Of those who received a regular checkup between April 2006 and March 2010, 2348 individuals voluntarily underwent an OGTT. All of the subjects were Japanese men and women aged 30–65 years without a known history of diabetes. Complete medical histories were obtained for 2340 of these individuals. Those who had HbA1c values ≥ 6.5% (Japan Diabetes Society value) (n=42), who had undergone gastrectomy (n=32), who were taking steroids (n=1), or who were taking anticancer drugs (n=1) were excluded. Finally, 107 subjects whose insulogenic index values were ≤ 0 were excluded; 2157 subjects (1471 men and 686 women) were ultimately enrolled in this study. Family history of diabetes was assessed by asking questions about parents’ and siblings’ histories of diabetes. All participants signed informed consent forms, and the hospital review board approved the study protocol.

**Study protocol and assays**
All subjects were asked to visit the hospital between 8:00 a.m. and 9:00 a.m. after an overnight fast. Then an OGTT (75 g dextrose monohydrate in 250 mL water) was performed with 0-, 30-, 60-, and 120-min sampling to establish plasma glucose and insulin levels. PG was assessed using the glucose oxidase method (Automatic Glucose Analyzer ADAMS Glucose GA-1160, Arkray, Kyoto) at the hospital laboratory. Insulin concentration assays were performed by the chemiluminescence immunoassay method at a commercial laboratory (BML, Inc. Tokyo, Japan). Height and weight were measured, and BMI was calculated by dividing weight (kg) by height squared (m$^2$).

**Classification of glucose tolerance**
Using the 2003 American Diabetes Association (ADA) criteria [16], subjects were categorized as having NGT (fasting PG < 100 mg/dL and 2-hour PG < 140 mg/dL), isolated IFG (fasting PG = 100-125 mg/dL and 2-hour PG < 140 mg/dL), isolated IGT (fasting PG < 100 mg/dL and 2-hour PG = 140-199 mg/dL), combined IFG and IGT (IFG+IGT) (fasting PG = 100-125 mg/dL and 2-hour PG = 140-199 mg/dL), or newly diagnosed diabetes (fasting PG ≥ 126 mg/dL and/or 2-hour PG ≥ 200 mg/dL).

**Calculations**
The following indices of insulin secretion and insulin sensitivity or resistance were calculated in this study: insulogenic index = ($\text{Ins}_{30}-\text{Ins}_{0}$)/($\text{Glu}_{30}-\text{Glu}_{0}$), where $\text{Ins}_{y}$ and $\text{Glu}_{y}$ represent values at time $y$ min during the OGTT [4,5]; InsAUC$_{120}$/GluAUC$_{120}$, which is the ratio of area-under-the-curve for insulin (InsAUC) to area-under-the-curve for glucose (GluAUC) calculated by applying the trapezoid rule; Matsuda insulin sensitivity index (ISI) = 10000/($\text{Glu}_{0} \times \text{Ins}_{0} \times \text{Glu}_{120} \times \text{Ins}_{120}$)$^{0.5}$ [17]; and HOMA-IR = $\text{Glu}_{0} \times \text{Ins}_{0}/405$ [18].

**Statistical analysis**
The data are presented as the mean±the standard deviation or the median with the interquartile range for continuous variables or as a frequency for categorical variables. Continuous variables were compared across the glucose tolerance categories using one-way analysis of variance (ANOVA) followed by Scheffe’s post-
Insulin secretion and sensitivity on the OGTT

Results

Basic clinical characteristics

The mean age of the 2157 subjects was 52.6 years, and the mean BMI was 23.9 kg/m². Of these, 1125 subjects (52.2%) had NGT, 525 (24.3%) subjects had isolated IFG, 159 (7.3%) subjects had isolated IGT, 263 (12.2%) subjects had IFG+IGT, and 85 (3.9%) subjects had newly diagnosed type 2 diabetes. As shown in Table 1, subjects with isolated IGT were significantly older than those with NGT. Subjects with any abnormal glucose tolerance had higher BMI compared with those with NGT. The proportion of men was higher in subjects with isolated IFG and those with IFG+IGT but was lower in subjects with isolated IGT compared with those with NGT. Subjects with isolated IFG, those with IFG+IGT, and those with diabetes had a higher proportion of family histories of diabetes than those with NGT.

Insulin secretion and insulin sensitivity in relation to fasting and 2-hour PG concentrations

We evaluated insulin secretion and insulin sensitivity as a function of fasting and 2-hour PG levels after adjusting for BMI, age, and sex. Compared to NFG1, insulinogenic index was significantly decreased in all other five categories of fasting PG (Fig. 1A), and InsAUC_{120}/GluAUC_{120} was significantly decreased in the categories in the range of IFG and diabetes (Fig. 1C). Decreases in these two indices of insulin secretion in the range of IFG remained significant after further adjustment for 2-hour PG (Supplementary Fig. 1A and C). Compared to NGT1, a significant decrease in insulinogenic index was found in all other five categories of glucose tolerance (Fig. 1B), whereas InsAUC_{120}/GluAUC_{120} was not significantly decreased in NGT2.

Table 1 Clinical characteristics of the study subjects by glucose tolerance status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>NGT</th>
<th>Isolated IFG</th>
<th>Isolated IGT</th>
<th>IFG+IGT</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2157</td>
<td>1125</td>
<td>525</td>
<td>159</td>
<td>263</td>
<td>85</td>
</tr>
<tr>
<td>Men (%)</td>
<td>1471 (68.1)</td>
<td>697 (62.0)</td>
<td>423 (80.6)*</td>
<td>97 (61.0)†</td>
<td>192 (73.0)*</td>
<td>62 (72.9)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.6 ± 7.3</td>
<td>51.9 ± 7.6</td>
<td>52.8 ± 7.1</td>
<td>53.6 ± 7.1*</td>
<td>54.4 ± 6.2</td>
<td>53.2 ± 6.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 ± 3.2</td>
<td>23.3 ± 2.9</td>
<td>24.2 ± 3.0*</td>
<td>24.5 ± 3.8*</td>
<td>25.0 ± 3.7*†</td>
<td>24.9 ± 3.7*</td>
</tr>
<tr>
<td>BMI ≥ 25.0 kg/m² (%)</td>
<td>686 (31.8)</td>
<td>276 (24.5)</td>
<td>192 (36.6)*</td>
<td>63 (39.6)*</td>
<td>112 (42.6)*</td>
<td>43 (50.6)*</td>
</tr>
<tr>
<td>Positive family history of diabetes (%)</td>
<td>390 (18.1)</td>
<td>157 (14.0)</td>
<td>105 (20.0)*</td>
<td>34 (21.4)</td>
<td>71 (27.0)*</td>
<td>23 (27.1)*</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation or n (%). Characteristics among groups were compared using one-way ANOVA with Scheffe’s post-hoc tests for continuous variables and chi-square tests for categorical variables. *p<0.05 compared to NGT, †p<0.05 compared to isolated IFG.
Independent associations of insulin secretion and insulin sensitivity with PG concentrations

We conducted multiple regression analyses for fasting PG and 2-hour PG concentrations using indices of insulin secretion and insulin sensitivity as independent variables. As shown in Table 2, Matsuda ISI, insulinogenic index, and InsAUC_{120}/GluAUC_{120} were independently correlated with fasting PG and 2-hour PG concentrations in whole study subjects ($p<0.05$). In subjects with NFG, Matsuda ISI but not insulinogenic IGT1, or diabetes1 (Fig. 1D). Even after further adjustment for fasting PG, these findings remained essentially the same (Supplementary Fig. 1B and D). Matsuda ISI was the highest in NFG1 among six categories of fasting PG and the highest in NGT1 among six categories of 2-hour PG. It was significantly decreased in NFG2 and NGT2 and was progressively decreased in higher categories both for both fasting PG and 2-hour PG (Fig. 1E and F).
Insulin secretion and sensitivity on the OGTT

Insulin secretion and insulin sensitivity across categories of glucose tolerance

As shown in Table 3, insulinogenic index, an index of early-phase insulin secretion, was significantly lower in subjects with isolated IFG and in those with isolated IGT compared with those with NGT. This index was even lower in subjects with IFG+IGT compared with those with isolated IFG or isolated IGT. InsAUC_{120}/GluAUC_{120}, an index of total insulin secretion during the OGTT, was significantly lower in subjects with isolated IFG, IFG+IGT, and diabetes, but it was not significantly different in subjects with isolated IGT compared with those with NGT. Matsuda ISI was significantly decreased in subjects with any abnormal glucose tolerance compared with those with NGT. A decrease in Matsuda ISI was more severe in subjects with isolated IGT, IFG+IGT, and diabetes compared with those with isolated IFG. When insulin resistance was assessed with HOMA-IR, subjects with isolated IFG, IFG+IGT, and diabetes had a higher HOMA-IR than those with NGT, but subjects with isolated IGT did not.

Disposition index (DI) across categories of glucose tolerance

Finally, we calculated DI by InsAUC_{120}/GluAUC_{120}×Matsuda ISI because these paired indices of insulin secretion and insulin sensitivity on the OGTT have been validated against DI calculated by IVGTT [19]. It was significantly lower in subjects with any glucose intolerance than in those with NGT, and this measure was even lower in subjects with isolated IGT, IFG+IGT, and diabetes compared with those with IFG.

Discussion

This is a cross-sectional study of insulin sensitivity and insulin secretion based on the OGTT in middle-aged Japanese with a wide range of glucose tolerance. Significant changes in insulinogenic index (early-phase insulin secretion), InsAUC_{120}/GluAUC_{120} (total insulin secretion), and Matsuda ISI (insulin sensitivity) were observed with increasing levels of fasting PG and 2-hour PG, and their independent associations with fasting and 2-hour PG concentrations were assessed. We also clarified the difference in the OGTT-derived indices of insulin sensitivity and insulin secretion among three non-diabetic categories, isolated IFG, isolated IGT, and combined IFG+IGT.

There is disagreement in the literature as to whether insulinogenic index is reduced only in subjects with IGT [7, 9, 11] or in both subjects with IGT and those with IFG [6, 8, 10, 12]. In this study, insulinogenic index was significantly reduced not only in subjects with isolated IGT but also in those with isolated IFG compared with those with NGT (Table 3). The decline in insulinogenic index in the IFG range of fasting PG remained significant even after further adjustment for the 2-hour PG level (Supplementary Fig. 1A). Prior studies based on the OGTT have reported that a significant decline in early-phase insulin secretion associated with small increases in fasting PG starts within the NFG range in a Japanese population [20] and in Mexican-Americans [21]. Similar results have also been demonstrated in studies based on the IVGTT [22, 23]. It may be possible that impaired early-phase insulin secretion related to an elevated fasting PG level contributes to the development of diabetes in subjects with isolated IFG. Follow-up studies are needed to confirm this hypothesis.

InsAUC_{120}/GluAUC_{120}, an index of total insulin secretion during the OGTT, was not significantly decreased in subjects with IGT, but not in those with normal but slightly elevated 2-hour PG in whom insulinogenic index was clearly lowered (Fig. 2B and D). Cross-group comparisons also showed that subjects with isolated IGT had levels of InsAUC_{120}/GluAUC_{120} that were comparable with the insulin secretion levels in subjects with NGT, despite having significantly reduced insulinogenic index (Table 3). A previous study conducted in 6414 Finish men also demonstrated that InsAUC_{120}/GluAUC_{120} was not significantly changed in individuals with isolated IGT compared with those with NGT [12]. It has been reported that subjects with IGT showed a delayed insulin peak during OGTT compared to subjects with NGT and those with IFG, who showed a peak occurred 30–60 min after glucose administration [10]. This delayed hyperinsulinemia may account for the increased total insulin secretion in subjects with isolated IGT. In contrast, in subjects with IFG+IGT, this compensatory hyperinsulinemia appeared to be attenuated or missing.

Matsuda ISI alone was an independent correlate with
However, even in their study, insulin resistance assessed by the reciprocal of fasting insulin was significantly different between the lower NFG group and the higher NFG group. Impairment in insulin sensitivity may have some contribution to the normal range of increase in PG concentrations also in Japanese population.

Cross-group comparisons of insulin resistance using Matsuda ISI and HOMA-IR yielded inconsistent elevation of fasting PG within the normal range in this study. This finding is consistent with the results that insulin sensitivity assessed by Matsuda ISI was significantly decreased at low PG levels within the normal range where impairment in insulin secretion was not marked in Finnish men [12]. In a Japanese population, Sato et al. have reported that insulin secretory function starts to decrease during normoglycemia [20]. However, even in their study, insulin resistance assessed by the reciprocal of fasting insulin was significantly different between the lower NFG group and the higher NFG group. Impairment in insulin sensitivity may have some contribution to the normal range of increase in PG concentrations also in Japanese population.

Cross-group comparisons of insulin resistance using Matsuda ISI and HOMA-IR yielded inconsis-

Table 2: The associations of fasting PG (upper column) and 2-hour PG (lower column) concentrations with indices of insulin secretion and insulin sensitivity, in all subjects and nondiabetic subjects.

<table>
<thead>
<tr>
<th>Dependent variable: fasting PG</th>
<th>All subjects (n=2157)</th>
<th>NFG (n=1291)</th>
<th>IFG (n=842)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variable</td>
<td>Standardised β</td>
<td>t-statistic</td>
<td>p value</td>
</tr>
<tr>
<td>Matsuda ISI</td>
<td>-0.24</td>
<td>-11.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>insulinogenic index</td>
<td>-0.27</td>
<td>-10.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>InsAUC$<em>{120}$/GluAUC$</em>{120}$</td>
<td>-0.06</td>
<td>-2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Independent variable</td>
<td>Standardised β</td>
<td>t-statistic</td>
<td>p value</td>
</tr>
<tr>
<td>Matsuda ISI</td>
<td>-0.33</td>
<td>-16.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>insulinogenic index</td>
<td>-0.44</td>
<td>-17.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>InsAUC$<em>{120}$/GluAUC$</em>{120}$</td>
<td>0.08</td>
<td>2.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

All models were adjusted for BMI, age, and sex.

Table 3: Indexes of insulin secretion and insulin sensitivity across categories of glucose tolerance

<table>
<thead>
<tr>
<th>Variable</th>
<th>NGT</th>
<th>Isolated IFG</th>
<th>Isolated IGT</th>
<th>IFG+IGT</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1125</td>
<td>525</td>
<td>159</td>
<td>263</td>
<td>85</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulinogenic index (mU/l/mg/dL)</td>
<td>0.45 (0.42-0.49)*</td>
<td>0.36 (0.32-0.42)*</td>
<td>0.27 (0.24-0.30)*†‡</td>
<td>0.17 (0.14-0.21)*†‡§</td>
<td></td>
</tr>
<tr>
<td>InsAUC$<em>{120}$/GluAUC$</em>{120}$ (×10⁻²mU/mg)</td>
<td>2.42 (2.34-2.50)</td>
<td>2.11 (2.00-2.23)*</td>
<td>2.26 (2.05-2.47)</td>
<td>1.85 (1.68-2.01)*†‡</td>
<td>1.53 (1.24-1.81)*†‡</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matsuda ISI (mU/l/mg/dL)</td>
<td>14.8 (14.1-15.4)</td>
<td>11.8 (10.8-12.7)*</td>
<td>8.6 (6.9-10.3)*†</td>
<td>8.1 (6.8-9.5)*†</td>
<td>6.7 (4.3-9.0)*†</td>
</tr>
<tr>
<td>HOMA-IR (mU/l, mg/dL)</td>
<td>0.83 (0.81-0.86)</td>
<td>1.06 (1.01-1.11)*</td>
<td>0.86 (0.79-0.93)*†</td>
<td>1.09 (1.02-1.16)*‡</td>
<td>1.18 (1.05-1.32)*‡</td>
</tr>
<tr>
<td>Disposition Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>InsAUC$<em>{120}$/GluAUC$</em>{120}$ ×Matsuda ISI</td>
<td>2.92 (2.79-3.03)</td>
<td>2.07 (1.89-2.24)*</td>
<td>1.48 (1.16-1.80)*†</td>
<td>1.13 (0.89-1.38)*†</td>
<td>0.75 (0.32-1.17)*†</td>
</tr>
</tbody>
</table>

Data are means (95% confidence intervals) adjusted for BMI, age, and sex. Insulinogenic index and HOMA-IR were log-transformed before analysis and calculated values were untransformed after analysis. *p<0.05 compared to NGT, †p<0.05 compared to Isolated IFG, ‡p<0.05 compared to Isolated IGT, and §p<0.05 compared to IFG+IGT.
Several limitations of this study should be considered. First, insulinogenic index has been characterized by marked within-subject variability in previous studies [32]. \( \text{InsAUC}_{30}/\text{GluAUC}_{30} \) rather than insulinogenic index, has been reported to have a stronger correlation with the AIR measured by the IVGTT [12]. The results of the cross-group comparisons by \( \text{InsAUC}_{30}/\text{GluAUC}_{30} \), however, were similar (data not shown). Additionally, we excluded 107 subjects with an insulinogenic index \( \leq 0 \). Some NGT subjects have so high ability to maintain PG concentrations within the normal limits, such that the PG concentrations during the OGTT returns below the fasting levels at 30 min [33]. The exclusion of these subjects might have attenuated the correlation between insulin secretion and PG concentrations, compared to the aforementioned study that included them by assigning a positive value [20].

Second, samples for PG and insulin were drawn up to 120 min after glucose administration. Because insulin secretion is both decreased and delayed in type 2 diabetes, total secretion might be underestimated by \( \text{InsAUC}_{120}/\text{GluAUC}_{120} \). Third, the cross-sectional design does not allow examination of the temporal or causal relationships among different categories of glucose tolerance. Further studies are needed to examine the temporal changes in insulin secretion and sensitivity in the development of diabetes.

In conclusion, both insulinogenic index (early-phase insulin secretion) and Matsuda ISI began to decline significantly in the normal range of fasting and 2-hour PG. Lowering of Matsuda ISI was likely to be a strong contributor to the elevation of fasting PG within the normal range in this population, although both Matsuda ISI and insulinogenic index were independently correlated with non-diabetic hyperglycemia.

Acknowledgements

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Disclosure

The authors declared no conflict of interest.


**Supplementary Fig. 1** Log-transformed Insulinogenic Index (A and B), InsAUC$_{120}$/GluAUC$_{120}$ (C and D), and Matsuda ISI (E and F) in relation to the fasting PG and 2-hour PG levels. Bars represent mean values and brackets represent 1 standard error for each group, adjusted for other glucose measurements (analyses as a function of the fasting PG level were adjusted for the 2-hour PG level, and analyses as a function of the 2-hour PG level were adjusted for the fasting PG level) as well as for BMI, age, and sex.

*p* < 0.05 compared to NFG1 or NGT1.


