Relative Contribution of Insulin Secretion and Sensitivity at Different Stages of Glucose Tolerance: Non-obese versus Obese Japanese Subjects

Tadashi Iwao, Kenji Sakai and Eiji Ando

Abstract

Objective We examined the relative contribution of insulin secretion and insulin sensitivity at different stages of glucose tolerance in non-obese and obese Japanese subjects.

Methods A total of 641 subjects who underwent 75-g glucose tolerance testing were divided into two groups: 436 non-obese subjects (body mass index: BMI <25) and 205 obese subjects (BMI ≥25). The subjects were further divided into four groups: those with normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes. We compared insulin secretion and sensitivity indices, such as the insulinogenic index (IGI), homeostatic model insulin resistance (HOMA-IR), homeostatic model assessment of β-cell (HOMA-β) and insulin sensitivity index (ISI).

Results In a univariate analysis, the obese subjects had higher levels of HOMA-IR, HOMA-β and IGI associated with lower ISI values in comparison with that observed in the non-obese subjects at different stages of glucose tolerance. A multiple logistic regression analysis showed that the HOMA-IR was a significant independent factor between the non-obese and obese subjects; the odds ratio (OR) (95% confidential interval: CI) was 3.78 (2.04-7.01; p<0.01) in the NGT group, 4.91 (2.06-11.72; p<0.01) in the IGT group and 2.02 (1.22-3.34; p<0.01) in the diabetes group. Although a similar trend was also observed in the IFG group (OR = 15.83), the difference did not reach a level of statistical significance (p = 0.066).

Conclusion These data suggest that obese subjects are characterized by increased insulin resistance rather than reduced insulin secretion at all stages of glucose tolerance. Therefore, non-obese subjects and obese subjects are distinct entities at all stages of glucose tolerance.

Key words: insulin secretion, insulin sensitivity, obesity

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Introduction

Diabetes is a metabolic disease that is diagnosed based on the presence of sustained hyperglycemia. Both insulin sensitivity and impaired insulin secretion are independent determinants of conversion to diabetes in different ethnic groups (1, 2). In a study of Pima Indians and Mexicans, insulin resistance was found to induce the development of type 2 diabetes (3, 4). Similarly, a progressive decline in insulin sensitivity has been described when moving from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) in various subjects with diabetes, whereas insulin secretion exhibits an inverted U-shaped pattern in Caucasian subjects (5-7).

In contrast, the deterioration of IGT and the pathogenesis of diabetes in the Japanese population may be quite different. Indeed, it has been shown that a decrease in early-phase insulin secretion plays an important role in the development of IGT and diabetes (8-10). Although the impact of obesity on glucose metabolism has been studied (8-10), there are conflicting interpretations. On the one hand, Matsumoto et al. (8) reported that the insulinogenic index (IGI), an index of early-phase insulin secretion (11-14), is decreased in both
non-obese and obese subjects with either IGT or diabetes. On the other hand, Iwahashi et al. (10) recently reported that the IGI values were higher in obese Japanese subjects than in non-obese subjects among both those with IGT and diabetes, similar to that observed in Caucasian subjects. Unfortunately, in these studies, the analyses were based on univariate analyses. Therefore, the relative contributions of insulin secretion and insulin sensitivity are not fully understood in Japanese subjects with and without obesity.

This study was designed to answer these questions. For this purpose, we measured insulin secretion and sensitivity indices in a large number of Japanese subjects with and without obesity and analyzed the results using a multiple logistic regression analysis.

Materials and Methods

Construction of the database

In September 1998, we began to construct a hospital-based database concerning 75-g OGTT. The database consisted of the date of investigation, age, gender, height, weight, biochemical data, HbA1c, fasting and post-load plasma glucose and immunoreactive insulin. 75-g OGTT was performed if the presence of diabetes was suspected (e.g., a FPG level ranging from 100 mg/dL to 125 mg/dL, the presence of a family history of diabetes, a secondary examination suspicious of diabetes on a medical checkup and/or obesity). Up to January 2013, we performed 75-g OGTT in a total of 1,005 subjects. Before the performance of 75-g OGTT, informed consent was obtained from each individual. This study was conducted in accordance with local institutional review board approval and the Declaration of Helsinki.

Subjects and assignments

According to the criteria of the American Diabetes Association and our recent observations (15, 16), we divided the subjects into four groups: those with NGT, impaired fasting glucose (IFG), IGT and diabetes. In brief, NGT was defined as a fasting plasma glucose level of <100 mg/dL (15, 16) and a 120-minute post-load plasma glucose level of <140 mg/dL. IFG was defined as a fasting plasma glucose level of 100-125 mg/dL and a 120-minute post-load plasma glucose level of <140 mg/dL. IGT was defined as a fasting plasma glucose level of <126 mg/dL and a 120-minute post-load plasma glucose level of 140-199 mg/dL and diabetes was defined as a fasting plasma glucose level of ≥126 mg/dL and/or a 120-minute post-load plasma glucose level of ≥200 mg/dL (15).

The inclusion criteria were as follows: (1) no anti-diabetic drug or insulin administration; (2) Japanese. A total of 1,005 subjects recruited from September 1998 to January 2013 satisfied these criteria and underwent 75-g OGTT.

In this study, 55 subjects had a fasting plasma glucose level of >140 mg/dL and were excluded because their homeostatic model insulin resistance (HOMA-IR) (17) values were not accurately assessed (18). Therefore, a total of 950 subjects were candidates for this study.

Because specific conditions alter both insulin secretion and insulin sensitivity, we further excluded the following subjects: (1) those with type 1 diabetes (n=2) (who had antibodies to glutamic acid decarboxylase), (2) those with pancreatic disease (n=73) (who had a serum amylase level of ≥135 U/L; the upper limit of serum amylase is 134 U/L at our hospital), (3) those with moderate to severe liver disease (n=79) (who had a platelet count of <14.3×10^9/mm^3 and an impaired liver function, because a reduced platelet count indicates advanced liver fibrosis) (19), (4) those with moderate to severe renal disease (n=41) (who had an estimated glomerular filtration rate (e-GFR) of <45 mL/minute/1.73 m^2; because a reduced glomerular filtration rate indicates advanced renal disease (20) and (5) those with malignancy (n=0), (6) pregnancy (n=0) or (7) missing biochemical data (n=146). The e-GFR was calculated according to the Modification of Diet in Renal Disease study equation modified for Japanese patients (21). Several subjects had overlapping pancreatic, liver, and/or renal disease. For the above-mentioned analysis, 309 subjects were excluded. Therefore, a total of 641 subjects (63.8%) were ultimately enrolled.

Measurements and calculations

The 75-g OGTT examinations were performed after a 12-hour overnight fast. The subjects ingested a carbohydrate equivalent to 75 g of glucose (Torelan-G, Ajinomoto Pharmaceuticals, Tokyo, Japan), and blood samples were obtained at 0, 30, 60, 90 and 120 minutes. The levels of plasma glucose were measured with an automatic analyzer according to the glucose oxidase method, and the immunoreactive insulin index (IRI) was measured with a radioimmunoassay kit. The mean plasma glucose level and mean IRI level were also calculated. The intra-assay coefficient of variation was 0.4% for plasma glucose and 2.0% for IRI.

Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height in meters (m^2). The IGI was defined as the ratio of the increment in insulin to that of plasma glucose 30 minutes after a glucose load (11-14). The basal insulin secretion and resistance were evaluated according to the homeostatic model assessment of β-cell (HOMA-β) and HOMA-IR. The HOMA-β and HOMA-IR were calculated as follows: HOMA-β ( %=360×fasting IRI (μU/mL)/(fasting plasma glucose (mg/dL)-63)), HOMA-IR= fasting plasma glucose (mg/dL)×fasting IRI (μU/mL)/405, respectively (17). The insulin sensitivity index (ISI), which provides an index of whole-body insulin sensitivity, was evaluated (22). In this study, the ISI was calculated as follows: 10,000/√ fasting plasma glucose (mg/dL)×fasting IRI (μU/mL)×120 minutes post-load plasma glucose (mg/dL)×120 minutes post-load IRI (μU/mL). It has been shown that the ISI calculated using the above formula is well correlated (r=0.77 for n=153) to that obtained from measurements at 0, 30, 60, 90 and 120 minutes (23).
Statistical analysis

The data were expressed as the mean±standard deviation. For the univariate analyses, we used the t-test to assess continuous variables and the χ² test to assess a proportion of the discrete variables between the two groups. Age, the plasma glucose levels, the immunoreactive insulin levels, HOMA-IR, HOMA-β, IGI and ISI among the NGT, IFG and diabetes groups were compared using a one-way analysis of variance (ANOVA) between the non-obese subjects and obese subjects, respectively. The proportion of men was compared using Fisher’s exact test. Similarly, this variable was compared between the NGT, IGT and diabetes groups in the non-obese subjects and obese subjects using ANOVA or Fisher’s exact test. The proportions of patients with IFG and IGT in the IGT groups (i.e., IFG, IFG+IGT and IGT) with or without obesity were analyzed using the χ² test. A multiple logistic regression analysis with adjustment for age and gender was then performed using a simple model (model A) and a complicated model (model B). Model A was used to examine whether the HOMA-IR and IGI were independent factors in the non-obese and obese subjects at different stages of glucose tolerance. Model B was used to examine whether the HOMA-IR, HOMA-β, IGI and ISI were independent factors in the non-obese and obese subjects at different stages of glucose tolerance. If significant differences were noted, we calculated the odds ratio (OR) and 95% confidence interval (CI) for each variable.

All p values were two-tailed, and p values of <0.05 were considered to be statistically significant. The statistical analyses were performed using the Excel 2012 statistical software package (version 1.10, Social Survey Research Information Co., Ltd., Tokyo, Japan).

Results

Characteristic of the subjects

The mean age of the 641 subjects (58% men) was 58±14 years. The mean BMI was 23.7±4.0. A total of 436 subjects had a BMI of <25 and 205 subjects had a BMI of ≥25.

Clinical characteristics and insulin secretion and sensitivity indices

Among the NGT patients, there were 177 non-obese subjects and 63 obese subjects. The mean age and proportion of men were similar between the two groups. The fasting plasma glucose and mean plasma glucose levels were similar between the two groups. The fasting IRI, mean IRI, HOMA-IR, HOMA-β and IGI values were significantly higher in the obese subjects than in the non-obese subjects. In contrast, the ISI values were significantly lower in the obese subjects than in the non-obese subjects. The alanine aminotransferase (ALT) levels were significantly higher in the obese subjects than in the non-obese subjects; however, the platelet counts, creatinine levels, e-GFR values and amylase levels were similar between the two groups (Table 1).

Among the IFG patients, there were 39 non-obese subjects and 13 obese subjects. The mean age and proportion of men were similar between the two groups. The fasting plasma glucose and mean plasma glucose levels were similar between the two groups. The fasting IRI values were significantly higher in the obese subjects than in the non-obese subjects and the mean IRI was also higher in the obese subjects than in the non-obese subjects; however, the difference did not reach a level of statistical significance (p=0.077). The HOMA-IR, HOMA-β and IGI values were significantly higher in the obese subjects than in the non-obese subjects. In contrast, the ISI values were lower in the obese subjects than in the non-obese subjects; however, the difference was not significant. The ALT levels, platelet counts, creatinine levels, e-GFR values and amylase levels were similar between the two groups (Table 1).

Among the IGT patients, there were 110 non-obese subjects and 64 obese subjects. The mean age was significantly higher in the non-obese subjects than in the obese subjects, and the proportion of men was significantly lower in the non-obese subjects than in the obese subjects. The fasting plasma glucose and mean plasma glucose levels were similar between the two groups. The fasting IRI, mean IRI, HOMA-IR and HOMA-β values were significantly higher in the obese subjects than in the non-obese subjects. The IGI values were also higher in the obese subjects than in the non-obese subjects; however, the difference did not reach a level of statistical significance (p=0.084). In contrast, the ISI values were significantly lower in the obese subjects than in the non-obese subjects. The ALT levels were significantly higher in the obese subjects than in the non-obese subjects; however, the platelet counts, creatinine levels, e-GFR values and amylase levels were similar between the two groups (Table 1).

As to the proportion of patients with IFG and IGT among the IGT subjects (i.e., IFG, IFG+IGT and IGT) with or without obesity, the χ² test failed to show any statistically significant differences (p=0.12).

Among the patients with diabetes, there were 110 non-obese subjects and 65 obese subjects. Although the gender distribution was similar, the mean age was significantly lower in the obese subjects than in the non-obese subjects. The fasting plasma glucose and mean plasma glucose levels were similar between the two groups. The fasting IRI, mean IRI, HOMA-IR, HOMA-β and IGI values were significantly higher in the obese subjects than in the non-obese subjects. In contrast, the ISI values were significantly lower in the obese subjects than in the non-obese subjects. The ALT levels were significantly higher in the obese subjects than in the non-obese subjects. The ALT levels were significantly higher in the obese subjects than in the non-obese subjects; however, the platelet counts, creatinine levels, e-GFR values and amylase levels were similar between the two groups (Table 1).

ANOVA showed no statistically significant differences in the ALT levels, platelet counts, creatinine levels, e-GFR values or amylase levels between the non-obese subjects and
obese subjects among the NGT, IFG and diabetes groups or NGT, IGT and diabetes groups. Although ANOVA also showed no statistically significant differences in age among the obese subjects between the NGT, IFG and diabetes groups or NGT, IGT and diabetes groups, a significant difference was noted in the proportion of men between the non-obese and obese subjects among the NGT, IGT and diabetes groups and NGT, IGT and diabetes groups. Fisher’s exact test showed no significant differences in age among the non-obese subjects between the NGT, IGT and diabetes groups or NGT, IGT and diabetes groups. ANOVA showed the progressions of deterioration of glucose tolerance in both the non-obese and obese subjects in the NGT, IFG and diabetes groups and NGT, IGT and diabetes groups. With respect to the fasting and mean plasma glucose levels, ANOVA showed the progression of deterioration of glucose tolerance in both the non-obese and obese subjects among the NGT, IFG and diabetes groups or NGT, IGT and diabetes groups. Indeed, these values corresponded with the stage of disease. ANOVA failed to show any statistically significant differences in the fasting IRI levels between the non-obese and obese subjects among the NGT, IFG and diabetes groups or NGT, IGT and diabetes groups. With respect to the mean IRI values, although ANOVA failed to show any statistically significant differences among the non-obese subjects between the NGT, IGT and diabetes groups (p=0.09), significant differences were noted in both the non-obese and obese subjects among the NGT, IFG and diabetes groups and in the obese subjects among the NGT, IGT and diabetes groups. ANOVA showed significant differences in the HOMA-IR, HOMA-β, IGI and ISI values between the NGT, IFG and diabetes groups and NGT, IGT and diabetes groups with and without obesity (Table 1).

Table 1. Clinical Characteristic, Plasma Glucose and Immunoreactive Insulin, Indices of Insulin Secretion and Insulin Sensitivity of Subjects with Normal Glucose Tolerance, Those with Impaired Fasting Glucose, Those with Impaired Glucose Tolerance Test, and Those with Diabetes between Non-obese Subjects and Obese Subjects

<table>
<thead>
<tr>
<th>Normal glucose tolerance</th>
<th>Impaired fasting glucose</th>
<th>Diabetes mellitus</th>
<th>ANOVA or Fisher’s exact test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25</td>
<td>BMI ≥ 25</td>
<td>BMI &lt; 25</td>
<td>BMI ≥ 25</td>
</tr>
<tr>
<td>Number</td>
<td></td>
<td>177</td>
<td>63</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>58 ± 16</td>
<td>55 ± 17</td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td></td>
<td>23 ± 14</td>
<td>39 ± 28**</td>
</tr>
<tr>
<td>Creatinin (mg/dL)</td>
<td></td>
<td>0.78 ± 0.16</td>
<td>0.77 ± 0.15</td>
</tr>
<tr>
<td>e-GFR (mL/min)</td>
<td></td>
<td>75 ± 20</td>
<td>78 ± 23</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td></td>
<td>88 ± 23</td>
<td>83 ± 24</td>
</tr>
<tr>
<td>Fasting PG (mg/dL)</td>
<td></td>
<td>87 ± 8</td>
<td>88 ± 7</td>
</tr>
<tr>
<td>Mean PG (mg/dL)</td>
<td></td>
<td>120 ± 17</td>
<td>122 ± 16</td>
</tr>
<tr>
<td>Fasting IRI (μU/mL)</td>
<td></td>
<td>4.6 ± 2.7</td>
<td>9.5 ± 5.4**</td>
</tr>
<tr>
<td>Mean IRI (μU/mL)</td>
<td></td>
<td>32.3 ± 19.0</td>
<td>61.3 ± 41.2**</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td></td>
<td>0.99 ± 0.59</td>
<td>2.06 ± 1.19**</td>
</tr>
<tr>
<td>HOMA-β (%)</td>
<td></td>
<td>81 ± 70</td>
<td>167 ± 169**</td>
</tr>
<tr>
<td>IGI</td>
<td></td>
<td>0.84 ± 1.77</td>
<td>1.31 ± 1.32*</td>
</tr>
<tr>
<td>ISI</td>
<td></td>
<td>13.5 ± 9.2</td>
<td>6.9 ± 9.0**</td>
</tr>
</tbody>
</table>


Plasma glucose and IRI levels before and after 75-g OGTT

The fasting and post-load plasma glucose levels were similar in the patients at all stages of glucose tolerance with or without obesity (Fig. 1). In contrast, the IRI levels were significantly higher in the obese subjects than in the non-obese subjects in the NGT, IGT and diabetes groups at all
impaired in patients with type 1 diabetes, such as adults

50 100 150 200 250 300
Plasma glucose (mg/dL)

Fasting 30 min 60 min 120 min

Due to such strict exclusion criteria, among a total of 1,005

points measured. In the IFG group, a similar trend was ob-

erved; however, the IRI levels at 30 and 60 minutes did not

reach a level of statistical significance (Fig. 2).

**Multivariate logistic analyses of insulin secretion and sensitivity indices**

In Model A, a multiple logistic regression analysis

showed that the HOMA-IR was an independent factor in the

NGT, IGT and diabetes groups between the non-obese and

obese subjects. The odds ratios ranged from 2.30 to 5.77 for

the HOMA-IR (p<0.01). In the IFG group, neither the

HOMA-IR nor ISI were found to be significant independent

factors between the non-obese and obese subjects (Table 2).

In Model B, a multiple logistic regression analysis

showed that the HOMA-IR was an independent factor in the

NGT, IGT and diabetes groups between the non-obese and

obese subjects. The odds ratios ranged from 2.02 to 4.91 for

the HOMA-IR (p<0.01). In the IFG group, the differences

in HOMA-IR (odds ratio 15.83) and IGI (odds ratio 4.25)
did not reach a level of statistical significance (p=0.066, p= 0.062, respectively) (Table 3).

**Discussion**

There is substantial evidence that specific conditions af-

fect insulin secretion and/or sensitivity. Insulin secretion is

impaired in patients with type 1 diabetes, such as adults

with latent autoimmune diabetes (24) and subjects with

chronic pancreatitis (25) and renal failure (26). The rate of

insulin resistance is increased in patients with liver cirrho-

sis (27). For these reasons, we excluded 163 subjects with

type 1 diabetes, pancreatic disease, moderate to severe liver
disease and/or moderate to severe renal disease in addition
to 146 subjects with missing biochemical data. As men-
tioned above, 55 subjects with a fasting plasma glucose
level of >140 mg/dL were also excluded because their

HOMA-IR (17) values were not accurately assessed (18).

Due to such strict exclusion criteria, among a total of 1,005

subjects who underwent 75-g OGTT, only 641 subjects were

enrolled in this study.

In the present study, we demonstrated that both non-obese

and obese subjects have increased HOMA-IR values associ-
ated with decreased HOMA-β, IGI and ISI values, in keep-
ing with the progression of deteriorated glucose tolerance.

Therefore, this finding is in accordance with the results of

other Japanese studies (8-10). Previous studies and the cur-
rent study suggest that decreased insulin secretion and in-
creased insulin resistance contribute to the progression of
glucose tolerance: 177 non-obese subjects (dashed line) and 63 obese subjects (solid line) (upper left panel). The mean values of plasma glucose before and after 75-g OGTT in subjects with impaired fasting glucose: 39 non-obese subjects (dashed line) and 13 obese subjects (solid line) (lower left panel). The mean values of plasma glucose before and after 75-g OGTT in subjects with impaired glucose tolerance: 110 non-obese subjects (dashed line) and 64 obese subjects (solid line) (upper right panel). The mean values of plasma glucose before and after 75-g OGTT in subjects with diabetes: 110 non-obese subjects (dashed line) and 65 obese subjects (solid line) (lower right panel).

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the non-obese subjects in the NGT, IGT and diabetes groups. The magnitude of the difference in IRI between the two groups approximately doubled in each stage, although the difference was a bit weak in the IFG group. These data suggest that obese subjects exhibit increased insulin resistance under fasting conditions.

One interesting finding in this study is that the obese subjects had higher levels of HOMA-IR, HOMA-β and IGI associated with decreased ISI values in comparison with that observed in the non-obese subjects at all stages of glucose tolerance, although the differences between the IGI in IGT and ISI in IFG groups did not reach a level of statistical sig-

Table 2. Multiple Logistic Regression Analyses in Obese Subjects versus Non-obese Subjects at Different Stages of Glucose Tolerance (Model A)

<table>
<thead>
<tr>
<th>Glucose Tolerance</th>
<th>Odds ratio</th>
<th>95% confidential interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.54</td>
<td>2.80-7.36</td>
<td>&lt; 0.01</td>
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<tr>
<td>Insulinogenic index</td>
<td>1.03</td>
<td>0.86-1.24</td>
<td>0.73</td>
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<tr>
<td>Impaired fasting glucose</td>
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<tr>
<td>HOMA-IR</td>
<td>1.61</td>
<td>0.78-3.34</td>
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<td>Insulinogenic index</td>
<td>2.56</td>
<td>0.68-9.71</td>
<td>0.17</td>
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<td>Impaired glucose tolerance</td>
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</tr>
<tr>
<td>HOMA-IR</td>
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<td>3.17-10.50</td>
<td>&lt; 0.01</td>
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<tr>
<td>Insulinogenic index</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>HOMA-IR</td>
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<td>1.62-3.23</td>
<td>&lt; 0.01</td>
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<tr>
<td>Insulinogenic index</td>
<td>1.04</td>
<td>0.25-4.40</td>
<td>0.95</td>
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Table 3. Multiple Logistic Regression Analyses in Obese Subjects versus Non-obese Subjects at Different Stages of Glucose Tolerance (Model B)

<table>
<thead>
<tr>
<th>Glucose Tolerance</th>
<th>Odds ratio</th>
<th>95% confidential interval</th>
<th>p value</th>
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<tr>
<td>Normal glucose tolerance</td>
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</tr>
<tr>
<td>HOMA-IR</td>
<td>3.78</td>
<td>2.04-7.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HOMA-β (%)</td>
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<td>1.00-1.01</td>
<td>0.13</td>
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<tr>
<td>Insulinogenic index</td>
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<td>0.85-1.24</td>
<td>0.76</td>
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<tr>
<td>Insulin sensitivity index</td>
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<td>0.71</td>
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<td>Impaired fasting glucose</td>
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</tr>
<tr>
<td>HOMA-IR</td>
<td>15.83</td>
<td>0.83-301.79</td>
<td>0.07</td>
</tr>
<tr>
<td>HOMA-β (%)</td>
<td>0.93</td>
<td>0.85-1.02</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulinogenic index</td>
<td>4.25</td>
<td>0.93-19.42</td>
<td>0.06</td>
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<tr>
<td>Insulin sensitivity index</td>
<td></td>
<td>0.94-1.22</td>
<td>0.32</td>
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<tr>
<td>Impaired glucose tolerance</td>
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<tr>
<td>HOMA-IR</td>
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<td>2.06-11.72</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HOMA-β (%)</td>
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<td>0.99-1.01</td>
<td>0.56</td>
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<td>0.43-1.62</td>
<td>0.58</td>
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<tr>
<td>Insulin sensitivity index</td>
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<td>Diabetes</td>
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<tr>
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<td>1.22-3.34</td>
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<tr>
<td>HOMA-β (%)</td>
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<td>0.99-1.02</td>
<td>0.54</td>
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<tr>
<td>Insulinogenic index</td>
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<td>0.21-4.14</td>
<td>0.92</td>
</tr>
<tr>
<td>Insulin sensitivity index</td>
<td></td>
<td>0.86-1.13</td>
<td>0.81</td>
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Figure 2. The mean values of immunoreactive insulin before and after 75-g OGTT in the subjects with normal glucose tolerance: 177 non-obese subjects (dashed line) and 63 obese subjects (solid line) (upper left panel). The mean values of immunoreactive insulin before and after 75-g OGTT in the subjects with impaired fasting glucose: 39 non-obese subjects (dashed line) and 13 obese subjects (solid line) (lower left panel). The mean values of immunoreactive insulin before and after 75-g OGTT in subjects with impaired glucose tolerance: 110 non-obese subjects (dashed line) and 64 obese subjects (solid line) (upper right panel). The mean values of immunoreactive insulin before and after 75-g OGTT in the subjects with diabetes: 110 non-obese subjects (dashed line) and 65 obese subjects (solid line) (lower right panel). *: p<0.05 subjects with BMI <25 versus subjects with BMI ≥25, **: p<0.01 subjects with BMI <25 versus subjects with BMI ≥25.
nificance. This observation suggests that, when insulin secretion and sensitivity indices are compared between non-obese and obese subjects, obese Japanese subjects are characterized by increased insulin secretion and resistance at all stages of glucose tolerance.

It should be noted that the insulin secretion patterns were similar between the non-obese and obese subjects. Indeed, as shown in Fig. 2, the pattern imitated an inverted U shape in the NGT group, an inverted V shape in the IFG group, an exponential shape in the IGT group and a linear shape in the diabetes group. However, fasting and post-load hyperinsulinemia was noted in our obese subjects at all stages of glucose tolerance despite the finding of similar glucose curves in the two groups, as shown in Fig. 1. This observation supports the results of a recent study (10) in which obese patients exhibited increased early insulin secretion associated with delayed insulin secretion in the IGT and diabetes groups. We have no clear explanations regarding the hyperinsulinemia observed in obese subjects. A possible explanation is the presence of an increased visceral fat volume induced by factors, such as over eating, that result in a larger β-cell capacity (10). Indeed, our obese subjects had higher levels of HOMA-β and IGI than the non-obese subjects, although these indices declined with the progression of deteriorated glucose tolerance. This observation further strengthens the hypothesis that obese subjects have a larger β-cell capacity.

As to the proportion of patients with IFG and IGT among the IGT subjects (i.e., IFG, IFG+IGT and IGT) with or without obesity, the χ² test failed to show any statistically significant differences (p=0.12). This negative observation may be due to a type 2 error in the statistical analysis. Indeed, there were only 52 subjects with IFG, whereas there were 174 subjects with IGT. However, limited information is currently available concerning the prevalence of obesity in IFG and IGT subjects. Therefore, further studies are required to answer this question.

This is the first study to address the relative contributions of insulin secretion and sensitivity at different stages of glucose tolerance in Japanese subjects with and without obesity. Using a multiple logistic regression analysis, we were able to demonstrate that, after adjusting for age and gender, the HOMA-IR was a significant independent factor in the NGT, IGT and diabetes groups among the non-obese and obese subjects. As shown in Table 2, the odds ratios for HOMA-IR ranged from 2.30 to 5.77 in Model A. On the other hand, the IGI was found to be a less important factor. In the same way, when the HOMA-IR, HOMA-β, IGI and ISI values were analyzed together, a multiple logistic regression analysis again showed that the HOMA-IR was the strongest independent factor in the NGT, IGT and diabetes groups among the non-obese and obese subjects. As shown in Table 3, the odds ratios for HOMA-IR ranged from 2.02 to 4.91 in Model B.

The pathophysiology of IFG with and without obesity deserves comment. In this study, we failed to demonstrate any significant factors in the obese and non-obese subjects. In Model B, although neither the HOMA-IR nor IGI reached a level of statistical significance, the ORs of HOMA-IR and IGI were 15.83 and 4.25, respectively. We therefore hypothesize that insulin resistance also plays a critical role in the development of IFG in subjects with obesity. Again, our negative observation may be due to a type 2 error in the statistical analysis. Therefore, further studies of large numbers of IFG subjects are needed.

In the current study, the platelet counts, which reflect the degree of liver fibrosis (19), creatinine levels, e-GFR values and amylase levels were similar between the non-obese and obese subjects. However, the ALT levels were significantly higher in the obese subjects than in the non-obese subjects. According to updated information, the upper limit of ALT is 30 U/L (28). In this regard, it should be noted that the mean ALT levels were more than 30 U/L in the obese subjects at different stages of glucose tolerance, except for that observed in the IFG subjects. In contrast, the mean ALT levels were less than 30 U/L in the non-obese subjects at different stages of glucose tolerance. The J-SHIPP study demonstrated that the ALT level is an independent determinant of insulin resistance (29). Therefore, the current observation indirectly supports the findings of the J-SHIPP study (29). In other words, the liver plays a critical role in the pathogenesis of insulin resistance at different stages of glucose tolerance.

Ethnic differences in the contribution of insulin secretion and sensitivity to the pathogenesis of diabetes deserve comment. Fukushima et al. reported differences in the pathogenesis of glucose tolerance between Caucasians and Japanese (30). In that study, increased insulin secretion was found to compensate for insulin resistance in Caucasians, whereas decreased insulin secretion was observed in Japanese. Interestingly, the insulin secretion pattern observed in the obese subjects with NGT in this study closely resembles the insulin secretion pattern observed in Caucasians with IGT (30). On the other hand, the insulin secretion patterns observed in the non-obese subjects at different stages of glucose tolerance in the current study were similar to those observed in the Japanese population (30). Therefore, it seems likely that obesity, as well as ethnic factors, has an impact on the pathogenesis of glucose tolerance.

In conclusion, non-obese Japanese subjects and obese Japanese subjects are distinct entities at all stages of glucose tolerance. Therefore, different therapeutic strategies should be considered in subjects with and without obesity.

The authors state that they have no Conflict of Interest (COI).

References


