Beta cell dysfunction and its clinical significance in gestational diabetes

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Abstract. The aim of this study is to explore beta cell dysfunction and its clinical significance in gestational diabetes mellitus (GDM). We assessed insulin sensitivity and insulin secretion in a total of 277 Japanese women between 24 and 27 weeks of pregnancy who underwent a 2 h, 75 g oral glucose tolerance test (OGTT) because of an abnormal result on a 1 h 50 g oral glucose challenge conducted as part of a standard screening for GDM. Insulin sensitivity was evaluated by an insulin sensitivity index derived from OGTT (ISOGTT), whereas insulin secretion was calculated as a ratio of the total area under the insulin curve to the total area under the glucose curve (AUC ins/glu). Beta cell function in relation to insulin sensitivity (i.e. disposition index) was derived from the product of insulin sensitivity and insulin secretion (i.e. AUC ins/glu × ISOGTT). In women diagnosed with GDM (n=57), the disposition index was significantly lower than that in those without GDM, irrespective of obesity. The disposition index in women with GDM was significantly correlated with levels of fasting and mean preprandial capillary glucose and HbA1c before initiating insulin therapy (r = -0.45, -0.38, -0.49, respectively). Furthermore, there was a significant correlation between the disposition index and total insulin dosage to achieve glycemic goal (r = -0.41). In conclusion, we demonstrated beta cell dysfunction in Japanese women with GDM irrespective of obesity. The level of beta cell dysfunction in GDM was associated with the severity of glucose intolerance and total insulin dosage required. These findings underpin clinical significance of beta cell dysfunction in GDM.

Key words: Insulin secretion, Insulin sensitivity, Disposition index, Glucose metabolism, Asian
tion, the clinical impact of beta cell dysfunction on the severity of glucose intolerance in women with GDM remains unknown. Therefore, we performed a retrospective cohort study to address the following questions: (i) Does the hyperbolic insulin sensitivity-secretion relationship exist in Japanese pregnant women? (ii) Is beta cell dysfunction present in Japanese women with GDM irrespective of obesity? (iii) Does beta cell dysfunction reflect the severity of glucose intolerance in women with GDM?

Materials and Methods

Subjects

We conducted a retrospective cohort study of 277 consecutive Japanese pregnant women who underwent a diagnostic 2 h, 75 g oral glucose tolerance test (OGTT) because of an abnormal result on a standard 1 h, 50 g oral glucose challenge test (GCT) from 2004 to 2009. All women were cared for at the perinatal unit of Keio University Hospital. Gestational age was confirmed in the first trimester by crown-rump length measurements. Excluded from this study were women with multiple pregnancies and women whose neonates exhibited congenital anomalies. Women with a medical history indicating either impaired glucose tolerance or diabetes mellitus, or the use of medications known to affect glucose metabolism were also excluded. The research was performed in accordance with the Declaration of Helsinki and informed consent was obtained from patients where appropriate. The study was approved by the institutional review board at Keio University School of Medicine.

GDM screening and glucose tolerance status

Preceding the diagnostic OGTT, each subject underwent a standard 50 g GCT between 24 and 27 weeks of gestation as part of a universal screening procedure for GDM. A venous blood sample was obtained 1 h after ingestion of a 50 g oral glucose load, administered without regard for the fasting or fed state. If the GCT result exceeded 140 mg/dL, a 2 h, 75 g OGTT was performed as a diagnostic test [12]. The OGTT was performed after a 12 h overnight fast. Venous blood samples for measurement of plasma glucose levels and insulin concentrations were drawn in the fasting state and at 30 min, 1 h and 2 hrs after ingestion of the glucose drink.

Based on the criteria using the OGTT proposed by the Japan Society of Obstetrics and Gynecology (JSOG), GDM was diagnosed if two or more values reached or exceeded the following thresholds: fasting, 100 mg/dL; 1 h, 180 mg/dL; 2 hrs, 150 mg/dL [13]. Plasma glucose and insulin levels were measured as previously described by a glucose oxidase method and enzyme immunoassay, respectively [14]. The OGTT result was considered normal if plasma glucose levels in the fasting state and at 1 h and 2 hrs during the OGTT were less than the thresholds of the JSOG criteria. The normal glucose tolerance (NGT) group comprised women with normal OGTT results.

Daily glucose profile and management of GDM

All women found to have GDM were hospitalized to undergo dietary management (daily calorie intake: 30 kcal/kg + 350 kcal; if obese, 30 kcal/kg). On Day 3 after admission, daily capillary glucose profiles were obtained seven times a day under dietary management: fasting (7:30), 2 h postbreakfast (10:00), before lunch (11:30), 2 h postlunch (14:00), before dinner (16:30), 2 h postdinner (19:00) and bedtime (21:00). Capillary glucose levels were measured by bedside glucose monitor (Antsense II, HORIBA, Kyoto, Japan). HbA1c levels were measured by HPLC and expressed as an international standard value. Insulin therapy was initiated when dietary treatment did not consistently maintain fasting and premeal capillary glucose ≤100 mg/dL and 2 h postprandial capillary glucose ≤120 mg/dL, respectively. Regular and NPH insulin were used to achieve the glycemic goal and insulin dose was adjusted according to insulin algorithm based on bedside glucose monitor or self-monitoring capillary glucose values. The patients were discharged after titrating the dosage, with the total insulin dosage at discharge being used for analyzing its correlation with beta cell function.

Insulin sensitivity and beta cell function

Insulin sensitivity and insulin secretion were evaluated using measurements from the diagnostic OGTT. The insulin sensitivity was estimated by the whole-body insulin sensitivity index derived from the OGTT (ISOGTT) as proposed by Matsuda and DeFronzo [15-16]. The ISOGTT is calculated by the following formula: 10,000 / square root {Glu0 × Ins0 × (Glu0 + Glu40 × 2 + Glu120) / 2 × (Ins0 + Ins40 × 2 + Ins120) / 2}, where Glu and Ins x and Ins y represent plasma glucose (mg/dL) and insulin values (µU/mL ), respectively, at time x min during...
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Caucasian counterparts, obesity was defined as body mass index (BMI) ≥25 based on weight and height before pregnancy, as proposed by Japan Society for the Study of Obesity [17].

Statistical analysis

Data are presented as mean ± SD in text and tables, and illustrated as mean ± SEM in figures. In Tables 1 and 2, continuous variables were tested for normality of distribution and were compared among four subgroups using the one-way analysis of variance or the Kruskal-Wallis test, followed by Scheffe’s post hoc analysis. In Table 1, categorical variables are presented as proportions and were assessed with the χ² test or Fisher’s exact test. Simple or multiple regres-

Table 1  Maternal demographic characteristics of the subjects stratified by glucose tolerance status and the presence of obesity.

<table>
<thead>
<tr>
<th></th>
<th>Non-obese NGT</th>
<th>Non-obese GDM</th>
<th>Obese NGT</th>
<th>Obese GDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>194</td>
<td>40</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35 ± 5</td>
<td>36 ± 4</td>
<td>36 ± 4</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>Parous (%)</td>
<td>29.4</td>
<td>23.1</td>
<td>42.3</td>
<td>25.0</td>
</tr>
<tr>
<td>Prior GDM (%)</td>
<td>0</td>
<td>7.5</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>7.7</td>
<td>15.0</td>
<td>7.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Gestational weeks at the OGTT</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>28 ± 4</td>
<td>28 ± 4</td>
</tr>
<tr>
<td>Pregravid BMI</td>
<td>20.4 ± 2.0</td>
<td>19.9 ± 2.2</td>
<td>27.6 ± 2.4*</td>
<td>27.6 ± 1.9*</td>
</tr>
<tr>
<td>Pregravid body weight (kg)</td>
<td>51.7 ± 5.6</td>
<td>49.4 ± 7.2</td>
<td>68.3 ± 9.1*</td>
<td>68.6 ± 5.5*</td>
</tr>
<tr>
<td>Body weight at the OGTT</td>
<td>57.1 ± 5.8</td>
<td>54.6 ± 6.4</td>
<td>70.7 ± 7.6*</td>
<td>73.5 ± 6.6*</td>
</tr>
</tbody>
</table>

NGT: normal glucose tolerance; GDM: gestational diabetes mellitus. *: p <0.001, vs. non-obese women with NGT or GDM.

Table 2  75 g OGTT profiles of the subjects stratified by glucose tolerance status and the presence of obesity.

<table>
<thead>
<tr>
<th></th>
<th>Non-obese NGT</th>
<th>Non-obese GDM</th>
<th>Obese NGT</th>
<th>Obese GDM</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>194</td>
<td>40</td>
<td>26</td>
<td>17</td>
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<tr>
<td>OGTT-glucose (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>79 ± 6</td>
<td>83 ± 8*</td>
<td>82 ± 7</td>
<td>93 ± 11§‡</td>
</tr>
<tr>
<td>30 min</td>
<td>132 ± 16</td>
<td>159 ± 20§</td>
<td>132 ± 18¶</td>
<td>157 ± 17‡</td>
</tr>
<tr>
<td>60 min</td>
<td>143 ± 22</td>
<td>193 ± 28§</td>
<td>146 ± 17¶</td>
<td>190 ± 26§‡</td>
</tr>
<tr>
<td>120 min</td>
<td>120 ± 19</td>
<td>167 ± 24§</td>
<td>124 ± 14¶</td>
<td>168 ± 26§‡</td>
</tr>
<tr>
<td>OGTT-insulin (mU/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 min</td>
<td>6.0 ± 2.9</td>
<td>7.0 ± 4.1</td>
<td>9.4 ± 3.7§£</td>
<td>14.6 ± 5.8§¶†</td>
</tr>
<tr>
<td>30 min</td>
<td>51.8 ± 28.1</td>
<td>56.4 ± 28.2</td>
<td>65.6 ± 32.8</td>
<td>68.5 ± 26.9</td>
</tr>
<tr>
<td>60 min</td>
<td>63.0 ± 32.9</td>
<td>73.7 ± 39.2</td>
<td>80.6 ± 33.7</td>
<td>108.1 ± 45.5§#</td>
</tr>
<tr>
<td>120 min</td>
<td>53.5 ± 31.6</td>
<td>83.9 ± 49.0</td>
<td>71.2 ± 46.2</td>
<td>121.2 ± 48.7§#‡†</td>
</tr>
</tbody>
</table>

NGT: normal glucose tolerance; GDM: gestational diabetes mellitus. *: p <0.001, §: p <0.0001 vs. non-obese women with NGT. £: p <0.05, ¶: p <0.01, †: p <0.0001 vs. non-obese women with NGT. ‡: p <0.01, ††: p <0.0001 vs. non-obese women with GDM. ‡: p <0.01, ‡‡: p <0.0001 vs. obese women with NGT.

The OGTT. Insulin secretion was assessed by the ratio of the total area under the insulin curve to the total area under the glucose curve (AUC ins/glu) during the OGTT. Beta cell function was assessed by the product of insulin sensitivity and insulin secretion (i.e. the disposition index), as follows: the AUC ins/glu multiplied by ISOGTT.

To investigate the metabolic characteristics (i.e. insulin sensitivity, insulin secretion, and beta cell function) in subjects stratified by glucose tolerance status and anthropometric parameters, subjects were divided into the four subgroups: (i) non-obese women with NGT, (ii) non-obese women with GDM, (iii) obese women with NGT, (iv) obese women with GDM. Since Japanese women tend to be leaner than their Caucasian counterparts, obesity was defined as body mass index (BMI) ≥25 based on weight and height before pregnancy, as proposed by Japan Society for the Study of Obesity [17].

Statistical analysis

Data are presented as mean ± SD in text and tables, and illustrated as mean ± SEM in figures. In Tables 1 and 2, and Fig. 2, continuous variables were tested for normality of distribution and were compared among four subgroups using the one-way analysis of variance or the Kruskal-Wallis test, followed by Scheffe’s post hoc analysis. In Table 1, categorical variables are presented as proportions and were assessed with the χ² test or Fisher’s exact test. Simple or multiple regres-
sion analysis was used to test the correlation between the disposition index and the glycemic profiles or total insulin dosage (Fig. 3 and 4). Statistical analysis was performed using StatView (SAS Institute, Cary, NC, USA). Hyperbolic curves were drawn by GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) (Fig. 1). $P < 0.05$ was considered as statistically significant.

Results

Maternal demographic characteristics and 75 g OGTT profiles

Demographic characteristics of the subjects stratified by glucose tolerance status and the presence of obesity are shown in Table 1. There were no significant differences between groups with respect to maternal age, gestational weeks at the diagnostic OGTT, parity, and the prevalence of a family history of diabetes and a history of previous GDM. Pregravid BMI in non-obese women with NGT was similar to those with GDM (20.4 ± 2.0 and 19.9 ± 2.2, respectively). Likewise, there was no significant difference in pregravid BMI between obese women with NGT and GDM (27.6 ± 2.4 and 27.6 ± 1.9, respectively). Since changes in body weight during pregnancy were similar among the groups, neither non-obese nor obese women showed significant differences in body weight at the OGTT between those with NGT and GDM (Table 1).

The 75 g OGTT profiles in each study group are summarized in Table 2. Women with GDM showed significantly higher plasma glucose concentrations at all time points during the OGTT compared to those with NGT in either non-obese or obese subjects ($p < 0.001$). Obese women with GDM showed significantly higher fasting glucose concentration than non-obese women with GDM (93 ± 11 vs. 83 ± 8 mg/dL, $p < 0.0001$), while plasma glucose levels at 30, 60, and 120 min were comparable between the two groups.

There were no significant differences between non-obese women with GDM and NGT regarding plasma insulin levels throughout the OGTT. In contrast, obese women with GDM showed significantly higher plasma insulin concentration at 0 and 120 min, compared with obese women with NGT. Similarly, obese NGT women showed higher fasting plasma insulin concentration than non-obese NGT women (9.4 ± 3.7 vs. 6.0 ± 2.9 µU/mL, $p < 0.0001$).

Relationship between insulin sensitivity and insulin secretion in women with NGT or GDM

The relationships between ISOGTT and AUC_ins/glu were non-linear and best described by a hyperbolic function: NGT ($r = 0.82$, $p < 0.0001$) and GDM ($r = 0.82$, $p < 0.0001$) (Fig. 1). In addition, the hyperbolic curve of the women with GDM lay down and to the left from those with NGT.

Insulin sensitivity and beta cell function in women with NGT or GDM

The ISOGTT was highest in non-obese NGT, followed in turn by non-obese GDM, obese NGT, and obese GDM women ($p < 0.0001$) (Fig. 2A). Non-obese women with GDM exhibited lower ISOGTT values than non-obese women with NGT (5.3 ± 2.2 vs. 7.7 ± 4.0, $p < 0.01$). Although the difference did not reach statistical significance, the ISOGTT was lower in obese women with GDM than in obese women with NGT (2.6 ± 0.8 vs. 4.8 ± 1.7, $p = 0.3$).

With regard to insulin secretion, there were no significant differences in the AUC_ins/glu between non-obese women with GDM and NGT (0.40 ± 0.18 vs. 0.38 ± 0.19, $p = 0.6$) (Fig. 2B). Likewise, the AUC_ins/glu was similar in obese women with GDM and NGT (0.55 ± 0.20 vs. 0.51 ± 0.20, $p = 0.9$). The AUC_ins/glu in obese women with GDM and NGT were significantly higher than that in non-obese women, respectively (both $p < 0.05$). The disposition index in non-obese women with GDM was significantly lower than in non-obese women with NGT (1.7 ± 0.4 vs. 2.6 ± 0.8, $p = 0.07$).

Daily glycemic profiles, insulin therapy, and beta cell dysfunction in women with GDM

When the relationship between the disposition index and glycemic profiles was examined, a significant inverse correlation was noted between the disposition index and levels of HbA1c ($r = -0.49$, $p = 0.0002$), fasting ($r = -0.45$, $p = 0.0006$), mean daily and preprandial capillary glucose levels ($r = -0.38$ and -0.31; $p < 0.005$ and 0.02, respectively) (Fig. 3, A-D). However, the disposition index was not significantly correlated with the mean postprandial capillary glucose levels ($r = -0.12$, $p = 0.4$) (Fig. 3E). Moreover, the disposition
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after adjustment for body weight ($r = -0.40, p = 0.008$, Fig. 4B). Furthermore, multiple regression analysis revealed that the disposition index was independently correlated with insulin dose after adjustment for BMI ($r = -0.36, p = 0.02$).

Discussion

The current study demonstrates a hyperbolic relationship exists between insulin sensitivity and insulin
Fig. 3  Relationship between disposition index (AUC_{ins/glu} × IS_{OGTT}) and blood glucose levels in women with GDM. Note that the disposition index was significantly correlated with levels of fasting and the mean daily and preprandial capillary glucose, and HbA1c. Non-obese GDM: open circle, Obese GDM: closed circle.

Fig. 4  Relationship between disposition index (AUC_{ins/glu} × IS_{OGTT}) and total insulin dosage needed in women with GDM (A: U/day, B: U/kg/day, n = 43). The disposition index was significantly correlated with total insulin dosage to achieve glycemic control. Non-obese GDM: open circle, Obese GDM: closed circle.
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Bed. Consistent with previous studies, we also found decreased insulin sensitivity in women with GDM compared to BMI-matched women with NGT [3-5]. However, it remains unknown whether it is due to a primary defect or is secondary to hyperglycemia.

In women with GDM, the lower the disposition index, the higher the fasting and mean preprandial plasma glucose and HbA1c. Likewise, the disposition index was inversely correlated with total insulin dosage to achieve good glycemic control irrespective of obesity. These results suggest that the severity of the glucose intolerance in women with GDM reflects the degree of their beta cell dysfunction. Of interest, the disposition index was not associated with postprandial and CV and the standard deviation of daily capillary glucose levels in our study (data on the standard deviation of daily capillary glucose levels not shown). These findings might be because these plasma glucose levels were measured after meal ingestion, but not glucose ingestion.

In conclusion, women with GDM have beta cell dysfunction irrespective of presence or absence of obesity. In women with GDM, beta cell dysfunction was associated with increased fasting and mean daily capillary glucose levels and total insulin dosage needed to achieve good glycemic control. These findings underpin the clinical significance of beta cell dysfunction in GDM.

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