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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 (IS_{OGTT}), 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. $AUC_{ins/glu} \times IS_{OGTT}$). 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

PANCREATIC BETA CELLS compensate for changes in whole body insulin sensitivity through an increase in insulin secretion. The relationship between insulin sensitivity and insulin secretion is characterized by a rectangular hyperbolic function, such that the product of the two variables, termed as the disposition index, should yield a constant for a given degree of glucose tolerance [1-2]. Although beta cell dysfunction and insulin resistance may occur independently, the disposition index typically decreases through the progression from normal glucose toler-

ance to diabetes. Reduced disposition index reflects deterioration in beta cell compensation for insulin sensitivity [1-2].

During pregnancy, beta cells normally increase their insulin secretion to compensate for a decrease in insulin sensitivity [3-4]. Therefore, a potential etiology for gestational diabetes mellitus (GDM) is a limitation in beta cell reserves [1-3, 5]. Available evidence with regard to beta cell dysfunction in GDM is based on studies conducted in Caucasian and Hispanic women. Asian subjects are classified as a genetically highly susceptible to glucose intolerance (i.e. GDM, type 2 diabetes, and impaired glucose tolerance) [6-9]. Since Asians are less obese than Caucasians, its metabolic features might be different from those found in Caucasians [10-11]. To the best of our knowledge, however, little evidence is available with regard to beta cell function in Asian pregnant women. In addi-

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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 (IS_{OGTT}) as proposed by Matsuda and DeFronzo [15-16]. The IS_{OGTT} is calculated by the following formula: $10,000 / \text{square root} \{Glu_0 \times Ins_0 \times (Glu_0 + Glu_{60} \times 2 + Glu_{120}) / 2 \times (Ins_0 + Ins_{60} \times 2 + Ins_{120}) / 2\}$, where Glu_y and Ins_y represent plasma glucose (mg/dL) and insulin values ($\mu\text{U/mL}$), respectively, at time y min during

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

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

NGT: normal glucose tolerance; GDM: gestational diabetes mellitus. *: $p < 0.0001$, 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.

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

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 GDM. †: $p < 0.001$, ‡: $p < 0.0001$ 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 ($AUC_{\text{ins/glu}}$) 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 $AUC_{\text{ins/glu}}$ multiplied by IS_{OGTT} .

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 χ^2 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 μ U/mL, $p < 0.0001$).

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

The relationships between IS_{OGTT} 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 IS_{OGTT} 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 IS_{OGTT} 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 IS_{OGTT} 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 ± 1.0 , $p < 0.0001$) (Fig. 2C). Likewise, obese women with GDM showed lower disposition index compared to those with NGT (1.3 ± 0.4 vs. 2.2 ± 0.5 , $p < 0.01$). The disposition indices were comparable between non-obese and obese women with NGT ($p = 0.07$).

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

Fig. 1 Insulin sensitivity-secretion relationship in women with NGT or GDM. (A) Scatterplots of insulin sensitivity determined by IS_{OGTT} vs insulin secretion determined by AUC_{ins/glu} in women with NGT (white circle) and GDM (closed triangle). (B) The hyperbolic correlation between IS_{OGTT} and AUC_{ins/glu} in the NGT ($r = 0.82$, $p < 0.0001$) and GDM groups ($r = 0.82$, $p < 0.0001$). The hyperbolic curve in women with GDM was shifted down and to the left compared to that in those with NGT. NGT: normal glucose tolerance, GDM: gestational diabetes mellitus.

Fig. 2 Insulin sensitivity and beta cell function in women with NGT or GDM. Insulin sensitivity was determined by IS_{OGTT} (A), insulin secretion determined by AUC_{ins/glu} (B), and beta cell function quantified as AUC_{ins/glu} × IS_{OGTT} (i.e. disposition index) (C) in women stratified by glucose tolerance status and the presence of obesity. Insulin secretion did not increase to compensate for decreased insulin sensitivity in women with GDM compared to NGT in both non-obese and obese individuals. Disposition index in women with GDM was significantly lower than that in those with NGT in both non-obese and obese individuals. *: $p < 0.05$ vs. non-obese NGT, #: $p < 0.05$ vs. non-obese GDM, +: $p < 0.05$ vs. obese NGT. NGT: open bar, GDM: closed bar.

index was not significantly correlated with coefficient of variation (CV) of daily capillary glucose levels ($r = 0.15$, $p = 0.3$) (Fig. 3F). Of 57 women with GDM, 43 women (non-obese, $n=27$; obese, $n=16$) needed insulin therapy to achieve the glycemic goal (total insulin dosage: 25 ± 20 units daily; regular insulin: 19 ± 13 units daily, NPH insulin: 5 ± 10 units daily). The disposition index was inversely correlated with the total dosage of insulin needed to attain the defined glycemic target ($r = -0.42$, $p = 0.006$, Fig. 4A). This correlation persisted

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 ($AUC_{ins/glu} \times IS_{OGTT}$) 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 ($AUC_{ins/glu} \times IS_{OGTT}$) 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.

secretion in Japanese pregnant women. The product of insulin sensitivity and insulin secretion (i.e. disposition index), a measure of beta cell function in relation to insulin sensitivity, was low in women with GDM compared with those with NGT both in obese and non-obese subgroups. Moreover, beta cell dysfunction in women with GDM was associated with fasting and the mean daily capillary glucose levels and insulin dosage needed to achieve good glycemic control. To the best of our knowledge, this is the first report to demonstrate beta cell dysfunction and its clinical significance in Asian women with GDM.

The $AUC_{\text{ins/glu}}$ and IS_{OGTT} obtained from OGTT have been widely used and well validated [16, 18]. Similar to previous data in Caucasian subjects, we found that the hyperbolic curve in women with GDM lay down and to the left compared with the women with NGT. Consistent with this observation, the disposition index (i.e. $AUC_{\text{ins/glu}} \times IS_{\text{OGTT}}$) in women with GDM was significantly lower than that in those with NGT. Therefore, our results indicate beta cell dysfunction in Japanese women with GDM irrespective of presence or absence of obesity.

Despite less obesity, the incidence of type 2 diabetes in Japanese subjects is similar to that in the United States, suggesting Japanese have less beta cell functional capacity compared to Caucasians [10]. Additionally, Japanese seem to be more susceptible to obesity-induced glucose intolerance than Caucasians [17]. To date, most studies on beta cell function in GDM were performed in a cohort of obese Caucasian and Hispanic subjects. Therefore, Japanese subjects are useful to investigate the presence of beta cell dysfunction in non-obese as well as obese subjects with GDM.

Since the women with NGT in this study had an abnormal GCT value, the ~40% decrease in the disposition index in women with GDM may be underestimated.

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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