Decreased Insulin Secretion in Women with Previous Gestational Diabetes Mellitus

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Introduction

Patients with type 2 diabetes mellitus (DM) typically display both defective insulin secretion and insulin resistance. Whether insulin secretory defect precedes insulin resistance or insulin resistance precedes the insulin secretory defect at the evolution of type 2 DM is unknown [1,2]. Assessment of the insulin secretory capacity and insulin sensitivity in high risk groups before the development of glucose intolerance may suggest the pathophysiology of type 2 DM [3]. Gestational diabetes (GDM) is defined as an abnormal glucose tolerance diagnosed for the first time in pregnancy [4], and previous studies have shown the prevalence of type 2 DM after GDM generally in the range of about 30%–50% [5]. Women with a history of GDM have a sevenfold increased risk of developing type 2 DM [5], even with their glucose values restored to normal after delivery. It has been reported that 33% to 70% of physiologic decrease in insulin sensitivity occurs in all women during the second half...
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of pregnancy by euglycemic hyperinsulinemic clamp test or frequently sampled intravenous glucose tolerance test (FSIGT) as a result of increased blood levels of several hormones [6] during gestation. Some researchers suggest the possibility that GDM and type 2 DM as two of the same entity [7], as they share a similar pathophysiology [8] and also genetic features [7]. The American Diabetes Association (ADA) now recommends to screen women with a history of GDM, and to perform life-long regular follow-up [9]. Assessment of insulin secretion and insulin sensitivity in women with a history of GDM may elucidate the underlying defects and ultimately prevent the development of type 2 DM. We performed this study to determine whether there are defects of insulin secretory capacity and sensitivity in women with previous GDM even after delivery.

Methods

1. Subjects

Thirty-six women with previous GDM participated in this study. All subjects were tested with 75 g oral glucose tolerance test (OGTT) at pregnancy 24 to 28 weeks and were diagnosed as GDM, and tested 75 g OGTT again at postpartum 8–10 weeks. We also studied 19 age-matched and body weight-matched non-pregnant subjects as control, who had no family history of diabetes and normal glucose tolerance (NGT) confirmed by 75 g OGTT.

2. Methods

Blood samples were collected after a 10-hour overnight fast for the measurement of serum glucose, insulin, and lipid profile. A 75 g OGTT was performed in all subjects 8–10 weeks after delivery to confirm glucose tolerance status by World Health Organization (WHO) criteria [10]. Plasma glucose concentrations were determined by glucose oxidase method (Beckman Model Glucose Analyzer 2, Beckman Coulter, Brea, CA, USA). Fasting total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined using auto-analyzer technique (Hitachi 7150 autochemistry analyzer, Hitachi, Tokyo, Japan) by enzymatic assay, and low-density lipoprotein (LDL) cholesterol was calculated by Friedewald equation [11]. Serum insulin levels were measured by radioimmunoassay (Diagnostic Products Co., Southport, North Carolina, USA).

Height and body weight were measured, and body mass index (BMI) was calculated. Waist circumference was measured at the site of shortest circumference between the last subcostal area and umbilicus, and hip circumference was measured at the longest circumference of the hip protrusion area. Waist to hip ratio (WHR) was used as a marker for central obesity.

Women with previous GDM and control were performed FSIGT at postpartum 10–14 weeks. FSIGT was performed while the subject was supine after 10 hours of fasting. An intravenous line was inserted in each antecubital fossa to sample the blood and to inject dextrose fluid. Baseline sample was drawn for glucose and insulin, 5 minutes before injection of dextrose. At 0 time, 0.3 g/kg of 20% dextrose fluid was injected intravenously over 1 minute. Fourteen blood samples were drawn for insulin and glucose determinations at 2, 3, 4, 5, 6, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes after intravenous glucose administration. Insulin at a 0.025 U/kg was given intravenously 20 minutes after the glucose injection. All samples were centrifuged immediately and measured glucose concentration. Thereafter samples were stored at −70°C for measurement of insulin.

Insulin sensitivity index (SI) and glucose effectiveness (SG) were calculated from insulin and glucose results of FSIGT using a minimal model analysis program (MINMOD ver. 2.0) provided by Bergman et al. [12]. Acute insulin response to glucose (AIRg) was assessed as the incremental area under the insulin curve during the first 10 minutes after the glucose injection. The relationship between acute insulin responses to intravenous glucose and insulin sensitivity has been shown to be hyperbolic in cross-sectional studies [13], allowing the use of the insulin sensitivity–secretion product (disposition index) to assess β-cell compensation for insulin resistance.

Data were analyzed using SPSS ver. 11.0 (SPSS Inc., Chicago, IL, USA). Because fasting insulin, SI, and AIR×SI were slightly skewed distributions, analyses were performed using log-transformed data. Although mean values are shown for untransformed data, all P values are based on log-transformed data. One way analysis of variance was used to compare the metabolic variables among three groups. Multiple regression analysis was used to determine the associating factors with AIR×SI. All P values were two-tailed, and statistical significance was defined as P<0.05.
Results

Women with previous GDM showed similar age (31±4 years vs. 32±4 years) and BMI (23.4±2.3 kg/m² vs. 22.2±3.0 kg/m²) compared to controls. According to 75 g OGTT, the women with previous GDM were classified into NGT (n=19) and impaired glucose tolerance (IGT; n=17). The WHR, Visceral fat area, Superficial fat area, blood pressure, total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol did not differ among control, postpartum-NGT, and postpartum-IGT groups. Fasting plasma glucose was significantly higher in postpartum-IGT group compared to control (P<0.05).

Postchallenge 2-hour plasma glucose was significantly higher in both postpartum-IGT and NGT group compared to control group (P<0.05). Fasting insulin was significantly lower in both postpartum-IGT and NGT group compared to control group (P<0.05). The frequency of parental history of diabetes was significantly greater in postpartum-IGT group compared to postpartum-NGT group (76.4% vs. 15.8%; P<0.05) (Table 1).

AIRg was significantly lower in postpartum-NGT (190.9±81.1 pmol/L) and postpartum-IGT (151.4±96.9 pmol/L) compared to control group (330.1±184.4 pmol/L; P<0.05). AIRg×SI was significantly lower in postpartum-IGT group (70.8±34.7) compared to control group (231.1±153.9; P<0.05).

Table 1. Clinical and biochemical characteristics in women with history of gestational diabetes mellitus and control group

| Variable                  | Postpartum-IGT (n=17) | Postpartum-NGT (n=19) | Control (n=19) |
|---------------------------|------------------------|------------------------|----------------|
| Age (yr)                  | 31±4                   | 32±4                   | 32±4           |
| Body mass index (kg/m²)   | 23.7±3.2               | 23.0±3.7               | 22.2±3.0       |
| Waist to hip ratio        | 0.81±0.03              | 0.79±0.07              | 0.77±0.05      |
| Systolic blood pressure (mmHg) | 111.4±8.9            | 110.0±8.9              | 108.9±9.6      |
| Diastolic blood pressure (mmHg) | 70.0±8.6             | 68.2±6.0               | 70.0±5.0       |
| FPG (mmol/L)              | 5.2±0.5*               | 4.8±0.4*               | 4.6±0.5        |
| PPG (mmol/L)              | 8.6±0.8*               | 6.5±0.9*               | 5.1±2.4        |
| Total cholesterol (mmol/L) | 4.4±0.9                | 4.7±0.7                | 4.3±0.7        |
| Triglycerides (mmol/L)    | 1.6±1.6                | 1.3±1.2                | 1.7±0.9        |
| Low density lipoprotein cholesterol (mmol/L) | 2.4±0.7                | 2.9±0.7                | 2.5±0.7        |
| High density lipoprotein cholesterol (mmol/L) | 1.4±0.9                | 1.3±0.3                | 1.2±0.2        |
| Parental history of type 2 diabetes mellitus (%) | 13 (76.4)*           | 3 (15.8)               | -              |

Values are presented as mean±SD.

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; FPG, fasting plasma glucose at postpartum; PPG, post-challenge plasma glucose at postpartum.

Table 2. Indices of insulin secretion, insulin sensitivity and glucose effectiveness in women with a history of gestational diabetes mellitus and control group

| Variable                  | Postpartum-IGT | Postpartum-NGT | Control |
|---------------------------|----------------|----------------|---------|
| AIRg×SI                  | 70.8±34.7*     | 137.2±119.5    | 231.1±153.9 |
| AIRg (pmol/L)             | 151.4±96.9*    | 190.9±81.4*    | 330.1±184.4 |
| SI (x10⁻⁴ min/µU/mL)      | 4.6±2.3        | 5.4±2.8        | 5.7±3.6  |
| SG (x10⁻²/min)            | 2.2±0.4        | 2.2±0.7        | 2.0±0.7  |

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; AIRg, acute insulin response to glucose; SI, insulin sensitivity index; AIRg×SI, β-cell disposition index; SG, glucose effectiveness.

*P<0.05 vs. control.
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In the postpartum-NGT group, AIRg×SI (137.2±119.5) was lower than control, but there was no statistical significance. SG tended to be higher in postpartum-IGT and postpartum-NGT group compared to control (2.2±0.4×10^-2/minute vs. 2.2±0.7×10^-2/minute vs. 2.0±0.7×10^-2/minute; P=0.08) without statistical significance. Although SI was lower in postpartum-NGT and IGT group (5.4±2.8×10^-4/min/μU/mL and 4.6±2.3×10^-4/min/μU/mL) compared to control group (5.7±3.6×10^-4/min/μU/mL), it was not statistically significant (Table 2).

Parental history of diabetes and WHR were significantly related to AIRg×SI in multiple regression analysis after adjustment for age, BMI, blood pressure, and visceral adiposity in women with previous GDM (P<0.05) (Table 3).

### Discussion

In this study, AIRg was significantly lower in women with previous GDM compared to control group, but SI did not differ significantly. These results were similar to several previous studies [13,14] as Sakamaki et al. [14] reported that non-obese normal glucose tolerant Japanese women with previous GDM had reduced early phase insulin secretion and β-cell function assessed by FSIGT. Turner et al. [15] also reported that normal glucose tolerant women with a history of GDM had decreased acute insulin response. These findings suggest that impaired insulin secretion may be a major pathophysiologic risk factor for the development of type 2 DM in subjects with previous GDM. However, in Caucasian women with former GDM, both insulin secretion and sensitivity were decreased before the development of hyperglycemia [16–18]. It has been suggested that insulin resistance is the primary defect in type 2 DM, while impairment of insulin secretion is a secondary defect in Caucasians or Pima Indians [19–21]. Although we cannot explain these discrepancies, the differences in subjects or methods of insulin secretion/sensitivity measurement, as well as racial difference may cause this discrepancy. In Korean population, it is characteristic that non-obese type 2 DM is more prevalent than western countries, and natural weight loss in disease progression and failure of glycemic control with oral hypoglycemic agent are more common, suggesting insulin secretory dysfunction may be predominant instead of insulin resistance [22].

In recent literature, approximately 41% of Korean women with the history of GDM developed type 2 DM over 5 years [23]. The prevalence of diabetic complication is also higher in women with previous GDM than those without GDM [7]. Hence, it seems important to perform intensive screening on individuals with a history of GDM. ADA now recommends screening women with a history of GDM at 6–12 week postpartum using the 2 hours 75 g OGTT, with non-pregnancy criteria. Also, ADA advises to have them on lifelong screening for the development of type 2 DM or prediabetes at least every 3 years, by using HbA1c, fasting plasma glucose, or 2 hours 75 g OGTT. However, the attendance rate at the 6-week follow-up remains low [24,25]. This might be the consequence of unawareness of women with GDM, or healthcare professional, or both. Still there is more consensus to be made about details in screening, but the results from recent studies emphasizes that adequate monitoring should be done.

As GDM and type 2 DM shares impaired insulin secretion, insulin resistance as pathophysiology, investigators tried to identify their genetic relationship. Several previously proven type 2 DM risk alleles were more frequent among women with a history of GDM [7,26]. Also, variants for melatonin receptor 1B (MTNR1B) was found to be associated with increased risk for GDM in Korean women [27]. Interestingly, this variant in the MTNR1B is associated with impairment of early insulin response [28], which may provide some explanation for our result.

In this study, 47% of women with previous GDM developed impaired glucose tolerance by OGTT after delivery. Pancreatic β-cell dysfunction was the independent factor for the development of postpartum glucose intolerance, and parental history of diabetes was also significantly associated with future glucose intolerance. Gestational age at GDM diagnosis and method of glucose control are also risk factor for the subsequent development of type 2 DM [29]. Previous study identified waist cir-

### Table 3. Multiple regression analysis for AIRg×SI in women with previous gestational diabetes mellitus

| Variable                        | β      | P value |
|--------------------------------|--------|---------|
| Age                            | 0.215  | 0.105   |
| Parental history of diabetes mellitus | 0.391  | 0.008   |
| Body mass index                | 0.194  | 0.182   |
| Waist to hip ratio             | -0.711 | <0.05   |

AIRg×SI, β-cell disposition index; AIRg, acute insulin response to glucose; SI, insulin sensitivity index.
cumference as a key risk factor for development of type 2 DM in Korean women with a history of GDM, with 3.86 of odds ratio [23].

Parental history of diabetes and WHR were significantly associated to ARxS. These results suggest that decreased early insulin secretion may be the main factor for the future development for the type 2 DM, and defects in early insulin secretion are possibly genetically determined.

In conclusion, women with previous GDM showed impaired insulin secretion even though their glucose tolerance states were restored to normal after delivery. It suggests that impaired early insulin secretion may be a major pathophysiologic factor for the development of type 2 DM in Korean women with previous GDM and this defect is possibly genetically determined. Further investigation on insulin secretion capacity and insulin sensitivity in women with a history of GDM may elucidate the underlying defects of type 2 DM, and this may allow to delay the disease progression, and ultimately to prevent the development of type 2 DM.

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