Visceral Fatness and Insulin Sensitivity in Women With a Previous History of Gestational Diabetes Mellitus

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OBJECTIVE — The purpose of this study was to investigate the insulin sensitivity and visceral fatness in women with previous gestational diabetes mellitus (GDM), who are prone to develop type 2 diabetes.

RESEARCH DESIGN AND METHODS — A 75-g oral glucose tolerance test (OGTT) performed 1 year postpartum identified 21 GAD$^-$ women with previous GDM and impaired glucose tolerance (GDM-IGT). Sixty age- and BMI-matched women with normal glucose tolerance (GDM-NGT) were selected by 1:3 matching to the GDM-IGT group. Another 18 women with normal glucose metabolism during a previous pregnancy and no family history of diabetes were recruited as the normal control group. Age and BMI matching was performed using a range of ±1.0 years and ±1.0 kg/m^2, respectively. Total body fat was measured by tetrapolar bioelectrical impedance, and visceral fat was determined using a single cut of a computed tomography scan. Insulin sensitivity was determined by the minimal model technique using the frequently sampled intravenous glucose tolerance test.

RESULTS — One year postpartum, visceral fat was greater in the GDM-IGT group than in the age- and BMI-matched GDM-NGT or normal control groups. The insulin sensitivity index was lower in the GDM-IGT group than in the GDM-NGT or normal control groups. β-Cell function, as measured by the acute insulin response to glucose, was also lower in GDM-IGT.

CONCLUSIONS — High body fat content, especially visceral fat content, and a low insulin response to glucose seem to contribute simultaneously to the development of impaired glucose metabolism in Korean women with previous GDM.

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Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity first recognized in pregnancy (1). GDM may complicate as many as 5–8% of all pregnancies in North America (2). Recent reports have shown that the prevalence of GDM has been increasing in multiethnic populations (3,4). Although the reported prevalence of GDM seems to be slightly lower in Asian countries (5,6), adverse outcomes are similar in these two regions. Women with GDM have an increased risk of later development of type 2 diabetes (7). Studies in Western populations have found conversion rates of 3–38% within the 1st year postpartum (8–10). Although a limited number of studies have been performed in Asian countries, the prevalences of impaired glucose metabolism in the early postpartum period have been reported to be 20% in Hong Kong and 38.3% in Korea (11,12).

Several reports have identified clinical factors at antepartum testing or during pregnancy that predict the development of future diabetes in women with GDM. However, few reports have focused on postpartum metabolic characteristics as a risk factor for future diabetes. More than two decades ago, Ward et al. (13) showed that women with previous GDM had insulin-secretion defects and that only obese women with GDM had a lower insulin sensitivity index (S_I) and higher waist-to-hip ratio than their obese counterparts when tested postpartum. Since then, several studies have revealed that women with previous GDM have greater insulin resistance and lower insulin responses than women with no history of GDM (14–17).

Buchanan et al. tested >30 clinical parameters to discriminate between women with previous GDM who have a high and low risk for type 2 diabetes, and they found that the postpartum oral glucose tolerance test (OGTT) provides the best discrimination (18). Women who develop diabetes have a lower acute insulin response to glucose and lower disposition index than women who remain free of diabetes (19).

To our knowledge, few reseachers have investigated both insulin sensitivity and body composition, especially the amount of visceral fat at the postpartum evaluation, as contributors to the development of impaired glucose metabolism after GDM. Many studies showed that Asians have a higher percentage of body fat compared with Caucasians with the same BMI (20,21). The prevalence of obesity is lower in Asian women than in their Western counterparts, but the GDM prevalence is not lower in Asian women than in Western women (11,22). We have reported previously that most women in Korea who develop GDM are not obese before pregnancy according to the usual body weight criteria for obesity (11). Increased visceral fat deposition plays an

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Abbreviations: AIRg, acute insulin response to glucose; CT, computed tomography; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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important role in the development of type 2 diabetes in Japanese Americans (23). This finding suggests that a high amount of visceral fat could have an important role in the development of diabetes in Asian women with GDM even though they are not obese by the usual BMI criteria. Body fatness can now be evaluated by more technologically advanced methods such as bioelectrical impedance or computed tomography (CT) (24,25), but these methods remain largely untested in women with a history of GDM. Postpartum insulin sensitivity and body composition, especially visceral fat amount, have not been assessed systematically to determine their combined role in the development of impaired glucose metabolism in women with a history of GDM.

We investigated factors that might be associated with altered glucose metabolism in women with previous GDM at 1 year postpartum. In particular, we proposed that we would find a relationship between insulin sensitivity and visceral fatness measured by CT. To accomplish these aims, we studied an age- and BMI-matched sample of Korean women with previous GDM, whose insulin sensitivity was determined by the minimal model technique.

RESEARCH DESIGN AND METHODS

The study subjects were recruited at Seoul National University hospitals in Seoul, Korea. Between 1999 and 2000, GDM was diagnosed in 236 women in the Seoul National University Hospital. Our protocol for screening and diagnosis of GDM has been described previously (5,11). The diagnosis of GDM was made using the criteria of the Third International Workshop-Conference on GDM (1). To evaluate their glucose metabolism, 173 women were given the standard 75-g OGTT at 2 months postpartum, and 28 were excluded because of a diagnosis of diabetes. At 1 year postpartum, 132 of 145 women completed the 75-g OGTT, and 11 were excluded because they were taking an oral contraceptive or were positive for GAD antibody. Of the 121 remaining women at 1 year postpartum, diabetes was diagnosed in 5, 28 had impaired glucose tolerance (IGT), and 88 had normal glucose tolerance (NGT). Of the 116 women with IGT and NGT, 21 who agreed to have a frequently sampled intravenous glucose tolerance test and a CT scan to measure fat content were selected for the GDM-IGT group. Sixty age- and BMI-matched women were assigned to the GDM-NGT group by 1:3 matching to the GDM-IGT group. At the same time, we also recruited another 18 subjects with normal glucose metabolism during pregnancy and no family history of diabetes as a normal control group in the follow-up study. This control group was selected from women who had a 50-g glucose challenge test at 24–28 weeks of gestation, and their 1-h plasma glucose concentration after the glucose challenge was <7.2 mmol/l. Subjects were matched for age and BMI using ranges of ±1.0 years and ±1.0 kg/m^2, respectively. All subjects provided informed consent, and the study protocol was approved by the ethical committee of the institutional review board of Seoul National University Hospital.

OGTT

All participating women completed a standard 75-g OGTT at 1 year postpartum. A 2-h postload plasma glucose concentration >11.1 mmol/l was used as the diagnosis of diabetes, and a 2-h postload glucose concentration of 7.8–11.1 mmol/l was used as the criterion for IGT.

Anthropometric assessments and blood pressure measurement

Height and body weight were measured to the nearest 0.1 cm and 0.1 kg with the patient barefoot in light clothing, respectively. BMI was calculated as body weight in kilograms divided by the square of height in meters. Blood pressure was measured after the subject had remained seated for 10 min. Measurements were made twice with a 5-min rest period between measurements. If a difference >5 mmHg was found between these two measures, blood pressure was measured one more time, and the average of two measures that showed the least difference among the three was used.

Laboratory assessments

After a 12-h overnight fast, venous blood samples were drawn from an antecubital vein at 0800–0900 h. Plasma was separated immediately by centrifugation (2,000 rpm, 20 min, 4°C). Serum insulin concentration was measured using insulin-specific radioimmunoassay kits (Linco Research, St. Louis, MO). Total cholesterol and triglyceride concentrations were determined by enzymatic procedures using a Beckman analyzer (Beckman Instruments, Brea, CA). HDL cholesterol concentration was determined using the Sigma direct EZ-HDL assay. Antibody levels to GAD were measured using a radioimmunoassay method (RSR, Cardiff, U.K.). Plasma glucose concentration was measured using a glucose oxidase method (YSI 2300-STAT; Yellow Springs Instrument, Yellow Springs, OH) immediately after blood was drawn. The oral and intravenous glucose tolerance tests were scheduled during the follicular phase of the menstrual cycle.

Body composition measurement

Body fat was measured by tetrapolar bioelectrical impedance analysis (Inbody 3.0; Biospace, Seoul, Korea). Bioelectrical impedance measures two parameters, fat and lean tissue, using empirically derived formulas that have been validated by earlier studies and that correlate well with values obtained using underwater weighing (25). For the accuracy of the body composition measurement, the interobserver variation (<0.1%) was confirmed by testing of the same subjects by different observers. Intraobserver variation was also confirmed by testing of the same subjects on different days by the same observer (<1.0%).

Visceral fat measurement

The abdominal adipose tissue areas were quantified by a single scout view of a CT scan (Somatom Sensation 16; Siemens, Munich, Germany). Subjects were examined in the supine position with arms outstretched overhead to decrease beam hardening or streak artifact. Scanning was performed at a 90-kV exposure. The exposure time was 0.1 s, and the scanning time was 0.5 s. A 10-mm CT slice scan was acquired at the L3–L4 level to measure the total abdominal and visceral fat areas. Adipose tissue attenuation was determined by measuring the mean value of all pixels within the range of −190 to −30 Hounsfield units. The images were converted into files compatible with a commercial software program (Rapidia; 3DMED, Seoul, Korea). To assess visceral adipose tissue volume, each abdominal image was edited by erasing the image exterior to the innermost abdominal wall muscles with a mouse-driven cursor, and the resulting images were saved in separate files.

The frequently sampled intravenous glucose tolerance test and the minimal model

In the morning between 0700 and 0900 h, after an overnight fast of 12 h or more, an intravenous catheter was placed

Table 1—*Anthropometric characteristics and biochemical parameters 1 year postpartum in study subjects*

	Control	GDM-NGT	GDM-IGT	*P* value*
n	17	60	21	
Age (years)	33.6 ± 4.4	33.6 ± 4.2	34.4 ± 3.0	NS
Height (cm)	158.6 ± 6.3	158.1 ± 5.6	157.7 ± 5.5	NS
Weight (kg)	54.9 ± 7.0	56.3 ± 8.1	57.9 ± 9.3	NS
BMI (kg/m^2)	21.8 ± 2.4	22.5 ± 2.8	23.3 ± 3.3	NS
Systolic blood pressure (mmHg)	108.4 ± 7.7	114.8 ± 10.3	114.4 ± 8.6	NS
Diastolic blood pressure (mmHg)	67.6 ± 6.2	70.7 ± 7.2	70.1 ± 8.2	NS
A1C (%)	4.6 ± 0.4	4.9 ± 0.3	5.4 ± 1.4	B,C
Total cholesterol (mmol/l)	5.0 ± 0.8	4.7 ± 0.7	4.9 ± 0.7	NS
Triglyceride (mmol/l)	0.9 ± 0.4	1.2 ± 0.6	1.7 ± 1.1	B,C
HDL cholesterol (mmol/l)	1.5 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	NS
LDL cholesterol (mmol/l)	3.0 ± 0.7	2.8 ± 0.6	2.8 ± 0.9	NS
75-g OGTT				
Glucose, 0 min (mmol/l)	5.0 ± 0.4	5.3 ± 0.6	5.4 ± 0.7	B
Glucose, 30 min (mmol/l)	7.3 ± 0.9	9.1 ± 1.3	10.6 ± 3.0	B,C
Glucose, 60 min (mmol/l)	5.9 ± 1.8	8.8 ± 1.8	12.5 ± 3.9	B,C
Glucose, 90 min (mmol/l)	5.8 ± 1.0	7.4 ± 1.5	11.6 ± 4.4	B,C
Glucose, 120 min (mmol/l)	5.8 ± 1.0	6.5 ± 0.9	9.4 ± 1.2	B,C
Insulin, 0 min (pmol/l)	56.2 ± 11.4	77.2 ± 35.5	91.5 ± 61.0	B
Insulin, 30 min (pmol/l)	369.8 ± 183.7	355.9 ± 158.2	416.6 ± 324.0	NS
Insulin, 60 min (pmol/l)	230.9 ± 162.3	496.6 ± 270.4	642.0 ± 498.3	B
Insulin, 90 min (pmol/l)	225.5 ± 128.3	459.3 ± 283.5	694.1 ± 656.8	B,C
Insulin, 120 min (pmol/l)	195.8 ± 150.7	377.8 ± 194.0	745.6 ± 591.3	B,C

Data are means ± SD. *ANOVA with post hoc test was used (A, B, and C indicate significant difference between two groups: A = control vs. GDM-NGT, B = control vs. GDM-IGT, C = GDM-NGT vs. GDM-IGT; $P < 0.05$ in all cases).

in the subject's forearms: one catheter for bolus injections of glucose and the other for rapid, repeated blood sampling to measure glucose and insulin concentrations. After baseline samples (−30, −15, and −1 min), a bolus of glucose (0.3 g/kg body wt) was injected over a 60-s period. Human regular insulin (0.03 units/kg) was injected 20 min later over a 30-s interval. Blood was sampled 29 times over the next 180 min at an initial frequency of one sample per minute for the first 10 min and then at longer intervals as follows: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 160, and 180 min. Bergman's minimal model was used to determine the S_I, which measures the quantitative influence of insulin that enhances the fractional rate of glucose disappearance. A nonlinear least-squares method was used to fit the time course of plasma glucose disappearance with the plasma insulin concentration as a known input to the system (26). The acute insulin response to glucose (AIRg), the mean insulin increment in the plasma insulin concentration above the basal level in the first 10 min after the administration of glucose, was also calculated. The disposition index, a measure of acute pancreatic β-cell compensation for insulin resistance, was calculated by multiplying S_I by AIRg (27).

Statistical analysis

Statistical analyses were conducted using SPSS for Windows, version 11.0 (Chicago, IL). Data are expressed as means ± SD. Significant differences between groups were evaluated using Student's *t* test and ANOVA with post hoc tests to locate the difference. Correlations between variables were analyzed by Spearman correlation because of the relatively small numbers of women in each subgroup. $P < 0.05$ was considered significant.

RESULTS — Table 1 shows the anthropometric characteristics, biochemical parameters, and results of the 75-g OGTT at the 1 year postpartum evaluation in the three groups: GDM-IGT, age- and BMI-matched GDM-NGT, and normal control subjects. Height, body weight, systolic and diastolic blood pressure, and the concentrations of total cholesterol, HDL cholesterol, and LDL cholesterol did not differ among the three groups. The concentrations of A1C and triglycerides were higher in the GDM-IGT group than in the GDM-NGT and normal control groups. As expected, fasting and postload glucose concentrations and plasma insulin concentration were highest in the GDM-IGT group, intermediate in the GDM-NGT group, and lowest in the control group. The increment of insulin at 30 min during the OGTT was divided by the increment of glucose for the same time using the equation:

$$[\Delta I_{30}/\Delta G_{30} = \text{insulin (30 min} - \text{0 min)}/\text{glucose (30 min} - \text{0 min)}].$$

$\Delta I_{30}/\Delta G_{30}$ was significantly higher in the control group (147.6 ± 93.4) than in the GDM-NGT group (83.7 ± 48.6, $P < 0.01$) and GDM-IGT group (71.0 ± 58.0, $P < 0.01$).

Table 2 shows the mean body composition measured by bioelectrical impedance in the three groups. Total body fat and lean body mass did not differ among the groups. However, in the fat amounts measured by CT, visceral fat and the visceral-to-subcutaneous fat ratio were significantly higher in the GDM-IGT group than in the GDM-NGT or normal control groups. Interestingly, total, visceral, and thigh fat were similar in the normal control and the GDM-NGT groups.

Table 2—*Body composition by bioimpedance method, body fat by CT, and S_I, AIRg, and disposition index by minimal model*

	Control (n = 18)	GDM-NGT (n = 60)	GDM-IGT (n = 21)	P value*
n	18	60	21	
Bioimpedance				
Total body fat (%)	28.7 ± 4.3	28.7 ± 5.2	29.7 ± 4.2	NS
Lean body mass (kg)	36.7 ± 3.4	38.0 ± 4.3	38.5 ± 4.7	NS
Fat CT				
Total fat amount (cm^2)	306.3 ± 95.0	309.7 ± 108.7	350.1 ± 117.3	NS
Visceral fat amount (cm^2)	86.9 ± 38.3	85.9 ± 30.8	113.9 ± 42.4	B,C
Subcutaneous fat amount (cm^2)	223.4 ± 63.9	224.6 ± 80.9	240.1 ± 93.8	NS
Visceral-to-subcutaneous fat ratio	0.38 ± 0.13	0.40 ± 0.12	0.51 ± 0.22	B,C
Thigh fat amount (cm^2)	108.9 ± 31.8	101.1 ± 29.8	95.2 ± 33.2	NS
Minimal model				
S_I (10^{-4} min^{-1} per μU/ml)	5.6 ± 2.3	4.9 ± 2.1	3.6 ± 1.9	B,C
AIRg (μU/ml)	450.7 ± 240.4	265.5 ± 193.0	170.3 ± 118.3	B
Disposition index	2,420.3 ± 1,345.8	1,194.4 ± 840.0	581.2 ± 421.7	A,B

Data are means ± SD. *ANOVA with post hoc test was used (A, B, and C indicate significant difference between two groups: A = control vs. GDM-NGT, B = control vs. GDM-IGT, C = GDM-NGT vs. GDM-IGT; $P < 0.05$ in all cases). S_I, minimal model insulin sensitivity index; AIRg, incremental area under plasma insulin curve during the first 10 min after glucose injection; disposition index = $S_I \times$ AIRg, β-cell compensation for insulin resistance.

Minimal model parameters calculated for the frequently sampled intravenous glucose tolerance test are also summarized in Table 2. At 1 year postpartum, S_I and AIRg were highest in the normal control group and lowest in the GDM-IGT group. β-Cell function, as measured by AIRg, was highest in the normal control group and lowest in the GDM-IGT group. The disposition index differed significantly between the control and GDM-NGT and GDM-IGT groups. Glucose effectiveness was significantly lower in the GDM-IGT group than in the GDM-NGT or control groups (data not shown).

The associations between visceral fat and insulin sensitivity, insulin secretion, and disposition index (β-cell compensation for insulin sensitivity) were examined. The S_I by the minimal model was significantly negatively correlated with the visceral fat amount by CT when the three groups were combined ($r = -0.421$, $P < 0.01$, Spearman correlation). Compared by subgroup, S_I was significantly negatively correlated in the GDM-NGT group ($r = -0.352$, $P = 0.012$) and GDM-IGT group ($r = -0.644$, $P = 0.003$) but not in the normal control group ($r = -0.259$, NS) (Fig. 1). After excluding two outliers with visceral fat >175 cm^2, the Spearman correlation between S_I and visceral fat decreased slightly to −0.535 in the GDM-IGT group but remained significant ($P = 0.033$). The absolute value of the correlation coefficient was higher in the GDM-IGT group than in the GDM-NGT group, although the slopes of the regression lines did not differ significantly.

Body weight varied substantially in all groups. Mean body weight was 3 kg greater in the GDM-IGT subgroup than in the control subjects, although this difference was not significant. We included body weight in the regression model as a covariate to investigate the association between S_I and visceral fat. S_I remained significantly associated with visceral fat after adjusting for body weight ($P = 0.013$). Insulin secretion (AIRg) and visceral fat amount were significantly negatively correlated in the normal control group ($r = -0.520$, $P = 0.033$), although these variables did not differ when all groups were combined or in GDM subgroups. The disposition index and visceral fat amount were significantly negatively correlated when all groups were combined ($r = -0.242$, $P = 0.025$) and in the control group ($r = -0.517$, $P = 0.034$), although these variables did not differ between the GDM subgroups.

CONCLUSIONS — We previously demonstrated in Korean women that impaired β-cell function during pregnancy is associated with early postpartum glucose intolerance (11). Buchanan and colleagues (28,29) showed that the plasma insulin concentration in the 75-g OGTT is lower during pregnancy in women with GDM who were proved to have diabetes or IGT than in normal control subjects.

In ths age- and BMI-matched study, the visceral fat content was greater 1 year postpartum in the women with previous GDM and IGT (GDM-IGT group) than in those who had previous GDM and NGT (GDM-NGT group) or in those who had normal glucose metabolism during pregnancy (normal control group). This finding agrees with previous data in Japanese Americans by Fujimoto et al. (23). Insulin sensitivity measured by the minimal model (S_I) was lower in the GDM-IGT group than in the GDM-NGT or normal control groups and was significantly correlated with visceral fat content, with or without adjustments for body weight or BMI.

Like the patterns of visceral fatness and insulin sensitivity, β-cell function, as measured by the AIRg, was lower in the GDM-IGT group. Similarly, $\Delta I_{30}/\Delta G_{30}$, which reflects β-cell function compensation for insulin resistance and is calculated as the increment of insulin relative to the increment of glucose in the first 30 min during the OGTT, was lower in the two GDM groups than in the control group. The disposition index, the index of β-cell compensation for insulin resistance, was also lower in both GDM subgroups. Interestingly, the disposition index and $\Delta I_{30}/\Delta G_{30}$ were lower in the GDM-NGT group than in the control group. β-Cell function, expressed by AIRg, was lower in the GDM-NGT group than in the control group. Thus, the decreases in insulin sensitivity and the insulin secretory response to glucose along with the increase in visceral fat content are associated with the presence of IGT in Korean women with a history of GDM; this suggests that these factors play a role in the development of IGT, which may account for the similar prevalence of GDM and postpartum diabetes in Korean women and women in Western countries despite the lower BMI in Korean women than in Caucasian women (11).

Prepregnancy obesity is an independent risk factor for postpartum glucose intolerance (11,29,30). We focused on visceral fatness by matching BMI, because BMI is an important risk factor for the development of insulin resistance or dia-

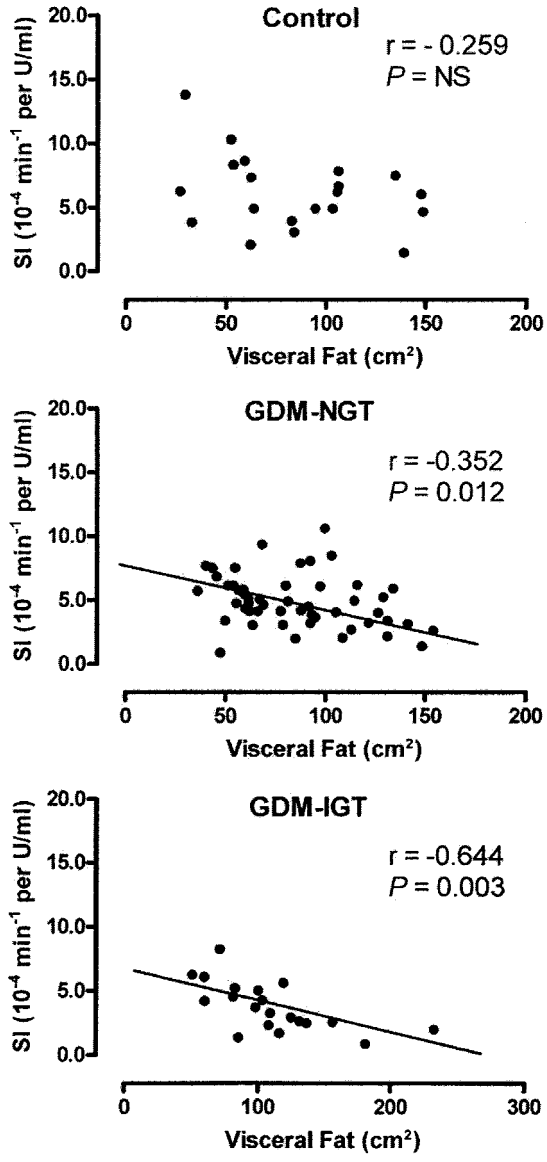

Figure 1—*Correlation between S_I by the minimal model and visceral fat amount by CT according to three groups: control, GDM-NGT, and GDM-IGT.*

betes (31). We found that the visceral fat content was higher in the GDM-IGT group than in the GDM-NGT group after matching for age and BMI, suggesting that visceral obesity is one possible pathophysiological mechanism responsible for the development of impaired glucose metabolism in women with previous GDM. It has been suggested that enlarged fat cells in the fat depot are more responsive to the lipolytic effects of catecholamines and less sensitive to the antilipolytic action of insulin than are smaller fat cells from the gluteal-femoral region and that this difference in responsiveness may underlie the detrimental effects of visceral fat (32,33). These actions are believed to promote the release of fatty acids into the portal circulation and liver, leading to an increase in hepatic glucose output and induction of elevated insulin resistance (34). Taken together, these data suggest that, in Korean women with previous GDM, development of IGT is related to both insulin resistance (the insulin secretory response to glucose) and an increase in body fat content, especially the visceral fat content.

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