

High Plasma Retinol Binding Protein-4 and Low Plasma Adiponectin Concentrations Are Associated with Severity of Glucose Intolerance in Women with Previous Gestational Diabetes Mellitus

Sung Hee Choi,* Soo Heon Kwak,* Byung-Soo Youn, Soo Lim, Young Joo Park, Hyewon Lee, Namseok Lee, Young Min Cho, Hong Kyu Lee, Young-Bum Kim, Kyong Soo Park, and Hak C. Jang

Division of Endocrinology and Metabolism (S.H.C., S.L., Y.J.P., H.C.J.), Department of Internal Medicine, Seoul National University Bundang Hospital, Sunnam City, Gyeonggi-Do 463-707, South Korea; Seoul National University College of Medicine (S.H.C., Y.M.C., H.K.L., Y.J.P., H.C.J., K.S.P.), Seoul 110-799, Korea; Genome Research Center for Diabetes and Endocrine Disease (S.H.K., Y.M.C., H.K.L., K.S.P.), Clinical Research Institute, Seoul National University Hospital, Seoul 110-799, Korea; AdipoGen, Inc. (B.-S.Y., H.L., N.L.), College of Life Science and Biotechnology, Korea University, Seoul 130-701, Korea; Immunomodulation Research Center (B.-S.Y.), University of Ulsan, Ulsan 680-749, Korea; and Division of Endocrinology, Diabetes, and Metabolism (Y.-B.K.), Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts 02215

Context: Women with previous gestational diabetes mellitus (pGDM) are at high risk of developing type 2 diabetes mellitus in the future. The role of adipokines in women with pGDM has not been established.

Objective: We investigated whether circulating adipokine concentration is associated with abnormal glucose homeostasis in women with pGDM.

Design, Setting, Patients, and Main Outcome Measures: We measured the plasma concentrations of retinol-binding protein-4 (RBP4), transthyretin (TTR), and adiponectin and metabolic parameters in four groups of women who exhibited normal glucose tolerance (NGT) during a previous pregnancy (NP, n = 17), NGT after GDM (GDM-NGT, n = 72), impaired glucose tolerance after GDM (GDM-IGT, n = 60), and type 2 diabetes after GDM (GDM-DM, n = 8).

Results: Plasma RBP4 concentration was significantly higher in women with GDM-DM, GDM-IGT, and GDM-NGT than in those with NP. RBP4 concentration correlated positively with TTR concentration; fasting plasma glucose, insulin, and triglyceride concentrations; blood pressure; abdominal fat area; and homeostasis model assessment of insulin resistance. Plasma TTR concentration was elevated in women with GDM-DM compared with other groups. In contrast, adiponectin concentration was lowest in the GDM-DM group and correlated inversely with parameters of insulin resistance. Resistin concentration was higher only in the GDM-NGT and GDM-IGT groups, whereas leptin did not differ between groups. Plasma RBP4 and adiponectin concentrations were inversely correlated.

Conclusions: The severity of glucose intolerance in women with pGDM is associated with high RBP4 and low adiponectin concentrations. (*J Clin Endocrinol Metab* 93: 3142–3148, 2008)

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy (1). Women with GDM have prominent insulin resistance regardless of compensatory insulin

secretion and are at high risk for developing type 2 diabetes (2). Women with GDM have a 17–63% increased risk of type 2 diabetes within 5–16 yr postpartum (3, 4). In Korean women with GDM, the conversion rate to type 2 diabetes is as high as

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* S.H.C. and S.H.K. contributed equally to this work.

Abbreviations: BMI, Body mass index; CT, computed tomography; CV, coefficient of variation; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; HOMA-B, homeostasis model assessment for β -cell function; HOMA-IR, homeostasis model assessment for insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low-density lipoprotein; NGT, normal glucose tolerance; NP, NGT during previous pregnancy; OGTT, oral glucose tolerance test; pGDM, previous GDM; RBP4, retinol binding protein-4; TTR, transthyretin.

20% at the postpartum follow-up examination (5–8). The mechanism responsible for the development of diabetes is unclear, but obesity-related factors are strongly implicated (6–9).

Adipocyte-derived cytokines (adipokines) provide an important link between obesity-related disorders and insulin resistance (10–12). Retinol-binding protein-4 (RBP4) is an adipokine that may play a role in regulating glucose metabolism and insulin sensitivity (13, 14). Overexpression of RBP4 induces systemic insulin resistance in normal mice, whereas genetic disruption of RBP4 increases insulin sensitivity (14). Several studies have demonstrated that circulating RBP4 concentration is elevated in humans with insulin resistance (15–18). In contrast, other studies have shown normal serum RBP4 concentration in obese menopausal women and low concentration in individuals with type 2 diabetes mellitus and that RBP4 concentration is unrelated to insulin sensitivity in calorie-restricted obese individuals (19–21).

RBP4 binds to retinol and transthyretin (TTR) homotetramer to form a tertiary protein complex that reduces renal clearance of RBP4 (22). It is of interest to measure the circulating concentrations of RBP4 and TTR in individuals with insulin resistance or at high risk of diabetes.

Adiponectin is one of the most abundant adipokines (23). Plasma adiponectin concentration is low in obese individuals and in those with type 2 diabetes and the metabolic syndrome (23, 24). In addition, circulating adiponectin concentration is low in women with previous GDM (pGDM) (25), but there are few data on women with pGDM.

We investigated whether circulating concentrations of adipokines, particularly RBP4 and adiponectin, are associated with the severity of glucose intolerance in women with pGDM. We also evaluated whether the concentrations of these adipokines correlate with metabolic parameters associated with insulin resistance and obesity.

Subjects and Methods

Study subjects

Between January 1999 and December 2002, we identified 551 women with GDM, of whom 510 undertook a 75-g oral glucose tolerance test (OGTT) at 2 months postpartum. Our protocol for diagnosis of GDM and postpartum examination has been described in detail previously (8, 26). The diagnosis of GDM was made using the criteria of the Third International Workshop-Conference on GDM (27). The threshold values were as follows: fasting, 5.8 mmol/liter or higher; 1 h, 10.6 mmol/liter or higher; 2 h, 9.2 mmol/liter or higher; and 3 h, 8.1 mmol/liter or higher. The reclassification of postpartum glucose tolerance status was made using the revised American Diabetes Association criteria (28). After excluding women with type 2 diabetes 2 months after delivery and those not willing to participate in the study, we recruited 193 women with pGDM and performed the first baseline examination for evaluating glycemic status from November 2001 to December 2004.

All participants were examined the morning after a 14-h overnight fast. Height, weight, waist and hip circumferences, and blood pressure were measured. Fasting blood samples were drawn for measurements of adipokines, glucose, insulin, total cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol concentrations. A 75-g OGTT and a bioimpedance test and fat computed tomography (CT) were performed the day after an OGTT test. The mean duration between delivery and the

first baseline examination was 1.57 yr (575 ± 184 d). After baseline examination, we excluded four women who were currently taking oral contraceptives or who were positive for glutamic acid decarboxylase antibody. Of the remaining 189 women, 110 women had normal glucose tolerance (NGT), 5 women had impaired fasting glucose (IFG), 53 women had impaired glucose tolerance (IGT), seven women had IFG and IGT, and 14 women had diabetes. To compare the adipokine levels between age- and body mass index (BMI)-matched groups, we selected finally eight women with diabetes, 60 women with IGT or IFG (GDM-IGT), and 72 women with NGT (GDM-NGT) by matching within a range of ± 2.0 yr and ± 1.0 kg/m², respectively. At the same time, we recruited another 17 subjects with NGT during and after pregnancy and no family history of diabetes for the normal control group (NP) in this follow-up study. This control group was selected from women who, in a 50-g OGTT, had 1-h plasma glucose concentration less than 7.2 mmol/liter at 24–28 wk gestation and NGT in a 75-g OGTT at the first baseline examination (Table 1). The modified National Cholesterol Education Program, Adult Treatment Panel III criteria (waist circumference for women ≥ 80 cm) were used to diagnose the metabolic syndrome (29). The Institutional Review Board of the Clinical Research Institute in Seoul National University Hospital approved the study protocol, and written informed consent was obtained from each subject.

Measurement of plasma RBP4, TTR, and adiponectin concentrations

Plasma RBP4 concentration was measured by an ELISA as described previously (16). The ELISA system had an intraassay coefficient of variation (CV) of 4–8% and an interassay CV of 5–10% (16). For immunoblotting analysis of RBP4 and TTR ($n = 5$ for each group), plasma was diluted 50–100 times in a standard detergent-containing buffer, and the proteins were resolved by 15–18% SDS-PAGE and transferred to nitrocellulose membranes. The membranes were incubated with a polyclonal RBP4 antibody (AdipoGen, Inc., Seoul, Korea) or a polyclonal TTR antibody (DakoCytomation, Hamburg, Germany). The bands were visualized with enhanced chemiluminescence (Amersham, Uppsala, Sweden) and quantified by densitometry. The interassay CV was 5–10%. All determinations were performed in triplicate.

Adiponectin concentration was measured using an ELISA kit according to the manufacturer's instructions (AdipoGen; intraassay CV, 3.48%, and interassay CV, 4.36%). Leptin and resistin concentrations were measured using a RIA kit (Linco Research, St. Charles, MO).

Measurement of concentrations of glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein (LDL)-cholesterol, and HDL-cholesterol

Plasma glucose concentration was measured by the glucose oxidase method using a YSI 2300 STAT (Yellow Springs Instrument Co., Yellow Springs, OH). The concentration of insulin was measured using a human-specific RIA kit (Linco). Total cholesterol, triglyceride, and HDL-cholesterol concentrations were measured enzymatically using an auto-analyzer (Hitachi 747; Hitachi, Ltd., Tokyo, Japan). LDL-cholesterol concentration was calculated according to the following formula: total cholesterol – HDL-cholesterol – triglyceride/5 (30).

Homeostasis model assessment

The degree of insulin resistance and β -cell function were estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) as described by Matthews *et al.* (31). HOMA-IR was calculated by the following formula: fasting plasma glucose (mmol/liter) \times fasting plasma insulin (mU/liter)/22.5. HOMA-B, a measure of β -cell function, was calculated as $20 \times$ fasting plasma insulin divided by (fasting plasma glucose – 3.5).

Measurement of body fat

Body fat was measured by tetrapolar bioelectrical impedance analysis (Inbody 3.0; Biospace, Seoul, Korea). Bioelectrical impedance

TABLE 1. Clinical characteristics of the subjects

	NP (n = 17)	GDM-NGT (n = 72)	GDM-IGT (n = 60)	GDM-DM (n = 8)	P
Age (yr)	33 ± 5	35 ± 4	35 ± 4	32 ± 3	0.06
Systolic blood pressure (mm Hg)	109 ± 7	108 ± 11	110 ± 11	110 ± 11	0.51
Diastolic blood pressure (mm Hg)	67 ± 6	71 ± 8	73 ± 9	71 ± 8	0.14
BMI (kg/m ²)	21.8 ± 2.4	22.5 ± 2.7	23.1 ± 3.2	22.1 ± 3.5	0.32
Waist circumference (cm)	77 ± 9	76 ± 7	79 ± 7	75 ± 9	0.10
Interval from delivery to blood sampling (d)	550, 349–681	574, 302–796	560, 348–788	489, 319–832	0.51
Fasting plasma glucose (mmol/liter)	5.0 ± 0.4	4.9 ± 0.4	5.5 ± 0.6	6.7 ± 1.1	<0.01
2 h post-OGTT glucose (mmol/liter)	5.8 ± 1.0	6.3 ± 0.9	8.3 ± 1.2	11.5 ± 2.2	<0.01
Fasting plasma insulin (pmol/liter)	56, 31–83	63, 23–125	67, 14–229	79, 47–111	0.11
Triglycerides (mmol/liter)	0.80, 0.50–1.68	0.99, 0.41–3.49	1.15, 0.42–6.69	1.27, 0.61–2.16	0.03
Total cholesterol (mmol/liter)	4.97 ± 0.80	4.53 ± 0.72	4.74 ± 0.69	4.47 ± 0.55	0.14
LDL-cholesterol (mmol/liter)	3.06 ± 0.65	2.74 ± 0.56	2.76 ± 0.84	2.62 ± 0.41	0.56
HDL-cholesterol (mmol/liter)	1.30, 1.17–2.05	1.22, 0.80–2.12	1.17, 0.75–5.18	1.19, 0.75–5.18	0.32
% body fat	28.7 ± 4.4	28.9 ± 4.7	29.8 ± 4.6	21.9 ± 5.6	0.89
Total abdominal fat area (cm ²)	201 ± 69	246 ± 89	276 ± 85	216 ± 128	0.01
sc fat area (cm ²)	143 ± 47	174 ± 63	195 ± 67	165 ± 72	0.03
Visceral fat area (cm ²)	58 ± 26	69 ± 32	81 ± 31	51 ± 57	0.04
HOMA-IR	1.9, 0.9–2.8	1.9, 0.8–4.3	2.5, 0.4–9.8	4.0, 1.9–6.0	0.01
HOMA-B	95, 64–256	129, 34–1447	110, 34–253	56, 47–64	0.05
Metabolic syndrome, n (%)	0 (0%)	7 (9.7%)	18 (30.0%)	2 (25.0%)	<0.01
Leptin (ng/ml)	4.10, 1.62–17.52	4.84, 1.38–41.48	5.49, 1.46–26.50	4.43, 1.57–7.38	0.23
Resistin (ng/ml)	0.95, 0.22–5.48	2.87, 0.09–12.20	2.65, 0.15–12.72	1.80, 0.72–4.40	<0.01

Except for the metabolic syndrome, the data are expressed as mean ± SD when normally distributed, otherwise as median, range. The *P* values are from ANOVA.

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 (32). The abdominal fat areas were quantified by a single scout of a CT scan (Somatom Sensation 16; Siemens, Erlangen, Germany). A 5-mm CT slice scan was acquired at the umbilical level to measure the total abdominal and visceral fat areas. Fat attenuation was determined by measuring the mean value of all pixels within the range of –190 to –30 Hounsfield units. The percentage of the visceral to sc fat was calculated as follows: (visceral fat area)/(total fat area – visceral fat area) × 100 (%).

Statistical analysis

All continuous variables with normal distribution are expressed as means ± SD, and variables with a skewed distribution are expressed as the median and range. Variables with skewed distribution were log-transformed for statistical analysis. Baseline clinical characteristics were compared between groups using ANOVA. To evaluate the differences in the concentrations of RBP4, TTR, and adiponectin in various states of glucose tolerance after GDM, ANOVA with Scheffé's *post hoc* analysis and a test for linearity were applied. The data for RBP4, TTR, and adiponectin satisfied Levene's test of homogeneity of variances. Pearson's correlation analysis identified significant correlations between RBP4 and adiponectin concentrations with various metabolic parameters. Stepwise linear regression analysis was used to identify independent predictors of RBP4 and adiponectin concentrations. Student's *t* test was used to compare adipokine concentration between subjects with or without the metabolic syndrome. Statistical analyses were performed using SPSS 15.0 software for Windows (SPSS Inc., Chicago, IL). A *P* value <0.05 was considered significant.

Results

Clinical and metabolic characteristics of the subjects

The mean age, systolic and diastolic blood pressure, BMI, waist circumference, and body fat percentage were not different

between the four groups (Table 1). The fasting plasma glucose concentration, 2-h post-OGTT glucose concentration, triglyceride concentration, and HOMA-IR were highest in the GDM-DM group. Abdominal total fat area, sc fat area, and visceral fat area as determined by CT were highest in the GDM-IGT group. The prevalence of the metabolic syndrome was also highest in the GDM-IGT group (Table 1).

Plasma RBP4, TTR, and adiponectin concentrations in subjects with GDM

The plasma RBP4 concentration was significantly higher in the GDM-NGT, GDM-IGT, and GDM-DM groups than in the NP group (*P* < 0.05; Fig. 1A). Although plasma RBP4 concentration did not differ significantly between GDM groups, there was a trend toward increasing RBP4 concentration according to the severity of glucose intolerance (*P* for linearity = 0.006).

Plasma TTR concentration was higher in the GDM-DM group than in the NP and GDM-NGT groups (Fig. 2A). TTR and RBP4 concentrations were significantly correlated in the GDM group (*r* = 0.76; *P* < 0.001; Fig. 2B).

Plasma adiponectin concentration was significantly lower in the GDM-DM group than in the GDM-NGT and NP groups (Fig. 1B). There was a trend toward a reduction in plasma adiponectin concentration from the NP group to the GDM-DM group (*P* for linearity = 0.006).

Plasma resistin concentration was higher in the GDM-NGT group (*P* = 0.001) and GDM-IGT group (*P* = 0.002) than in the NP group, but resistin concentration did not differ between the GDM-DM and NP groups. Plasma leptin concentration did not differ between groups (Table 1).

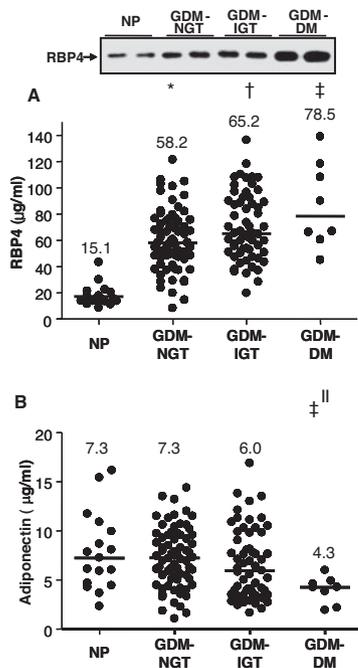


FIG. 1. Plasma RBP4 and adiponectin concentrations measured at the first baseline examination in the NP, GDM-NGT, GDM-IGT, and GDM-DM groups. A, Representative autoradiogram of RBP4 immunoblotting and plasma RBP4 concentrations measured by ELISA. The scatter graph shows the individual values of RBP4 concentration for each subject. B, Plasma adiponectin concentration was measured by ELISA. The scatter graph shows the individual values of adiponectin concentration for each subject. The *hatched line* represents the median value of each group. *, $P < 0.05$ vs. NP; †, $P < 0.05$ vs. NP; ‡, $P < 0.05$ vs. NP; †‡, $P < 0.05$ vs. GDM-NGT.

Correlations between plasma RBP4 and adiponectin concentrations and metabolic parameters

Plasma RBP4 concentration correlated positively with systolic and diastolic blood pressure, fasting plasma glucose concentration, 2-h post-OGTT glucose concentration, fasting concentrations of insulin and triglycerides, abdominal total fat area, sc fat area, visceral fat area, and HOMA-IR in all subjects (Table 2). Stepwise linear regression analysis revealed that only fasting plasma glucose and triglyceride concentrations were independent predictors of plasma RBP4 concentration (Table 3). Plasma adiponectin concentration correlated inversely with waist circumference, systolic blood pressure, fasting and 2-h post-OGTT glucose concentration, fasting insulin and triglyceride concentrations, abdominal total fat area, sc fat area, visceral fat area, and HOMA-IR (Table 2). In the stepwise regression analysis with adiponectin as a dependent variable, only abdominal total fat area remained as an independent determinant of plasma adiponectin concentration (Table 3).

Plasma RBP4 and adiponectin concentrations were negatively correlated ($r = -0.29$; $P < 0.01$; Fig. 3).

Plasma resistin concentration correlated with BMI, fat amount, percentage of body fat, plasma insulin and triglyceride concentrations, abdominal total fat area, and HOMA-B. The presence of the metabolic syndrome or diabetes was not significantly associated with plasma resistin concentration (data not shown).

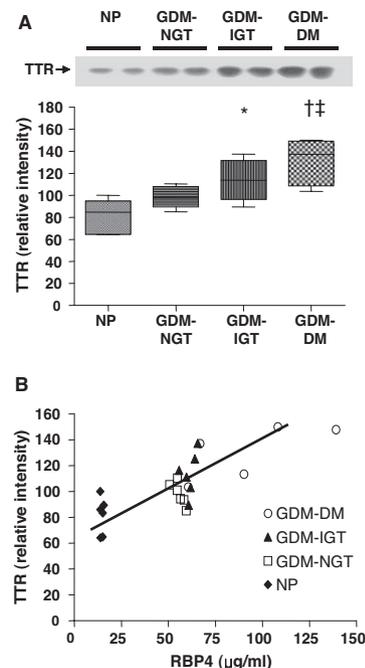


FIG. 2. Plasma TTR concentration in the NP, GDM-NGT, GDM-IGT, and GDM-DM groups after delivery and the correlation with plasma RBP4 concentration. A, Proteins in plasma (1:100 dilution) were separated by SDS-PAGE on 18% gels and transferred to nitrocellulose membranes. TTR was visualized by immunoblotting. Representative autoradiograms of plasma TTR concentration are indicated for each group (n = 5 from each group). *, $P < 0.05$ vs. NP; ‡, $P < 0.05$ vs. GDM-NGT. B, Correlation between plasma TTR and RBP4 concentrations. Pearson’s correlation coefficient = 0.76; $P < 0.001$ in the GDM group only.

Plasma RBP4 and adiponectin concentrations in women with and without the metabolic syndrome

Plasma RBP4 concentration was significantly higher in women with the metabolic syndrome than in those without it

TABLE 2. Correlations between plasma RBP4 and adiponectin concentrations and various metabolic parameters

	RBP4		Adiponectin	
	Pearson’s coefficient	P	Pearson’s coefficient	P
Age	0.05	0.53	-0.01	0.99
BMI	0.05	0.55	-0.13	0.12
Waist circumference	0.04	0.66	-0.18	0.03
Systolic blood pressure	0.18	0.03	-0.18	0.03
Diastolic blood pressure	0.22	0.01	-0.08	0.33
Fat amount	0.04	0.66	-0.10	0.23
% body fat	0.01	0.91	-0.09	0.24
Fasting plasma glucose	0.30	<0.01	-0.22	<0.01
2-h post-OGTT	0.34	<0.01	-0.24	<0.01
Fasting plasma insulin	0.18	0.04	-0.21	0.01
Triglyceride ^a	0.32	<0.01	-0.19	0.08
Total cholesterol	0.12	0.15	-0.07	0.39
LDL-cholesterol	0.09	0.27	-0.08	0.33
HDL-cholesterol ^a	-0.16	0.05	0.15	0.07
Total abdominal fat area	0.28	<0.01	-0.24	<0.01
sc fat area	0.26	<0.01	-0.22	0.01
Visceral fat area	0.23	0.01	-0.21	0.01
HOMA-IR ^a	0.23	0.01	-0.23	0.01
HOMA-B ^a	-0.03	0.73	-0.06	0.48

^a These variables were log-transformed before analysis.

TABLE 3. Stepwise linear regression of independent predictors of plasma RBP4 and adiponectin concentration

Variables	Unstandardized coefficients		P
	β	SE	
RBP4			
Fasting plasma glucose	0.004	0.002	0.012
Triglyceride ^a	0.348	0.097	<0.001
Adiponectin			
Abdominal total fat area	-0.000005	0.000002	0.026

Independent variables included for RBP4 were systolic blood pressure, abdominal total fat area, and fasting plasma concentrations of glucose, insulin, and triglycerides. Independent variables included for adiponectin were systolic blood pressure, waist circumference, abdominal total fat area, and fasting plasma concentrations of glucose, insulin, and triglycerides. Criteria were as follows: probability of F to enter ≤ 0.05 and probability of F to remove ≥ 0.10 . Dependent variables were plasma RBP4 and adiponectin concentrations, respectively.

^a This variable was log-transformed before analysis.

($P < 0.02$; Table 4). We excluded women with GDM-DM ($n = 8$) and analyzed adipokine concentration in women with or without the metabolic syndrome. Plasma RBP4 concentration correlated significantly with biochemical components of the metabolic syndrome in women who had the syndrome (data not shown). In contrast, plasma adiponectin concentration tended to be lower in women with the metabolic syndrome compared with those without the syndrome (Table 4).

Discussion

It is now evident that adipose tissue is an endocrine organ and that adipokines play critical roles in the regulation of glucose homeostasis and insulin sensitivity in rodents and humans (10, 13–15, 22–24). We investigated whether circulating RBP4 and adiponectin concentrations are associated with glycemic status in women with pGDM. We found a tendency toward high plasma RBP4 concentration and decreased plasma adiponectin concentration according to the severity of glucose intolerance in women with pGDM. The GDM-DM group showed significantly higher plasma RBP4 concentration and lower plasma adiponectin concentration than the NP group. The concentrations of these adipokines correlated inversely with a number of variables related to insulin resistance and the metabolic syndrome.

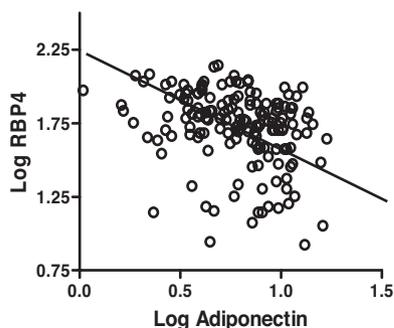


FIG. 3. Correlation between plasma RBP4 and adiponectin concentrations. Pearson's correlation coefficient = -0.29 ; $P < 0.01$.

We found that plasma RBP4 concentration was significantly higher in all women with pGDM than in women with normal glucose tolerance without GDM (the NP group). Although the mechanism underlying this increase is unclear, we suspect that RBP4 concentration is influenced by the altered metabolic milieu during pregnancy in women with GDM and pronounced insulin-resistant features (6, 33). Changes in many hormonal factors such as the amounts of estrogen, progesterone, cortisol, human placenta lactogen, glucagon, and leptin are presumed to be related to metabolic disturbance in GDM (2). The finding that RBP4 concentration is significantly higher during GDM pregnancy than in normal pregnancy (34) is consistent with this notion.

Because RBP4 is bound to TTR in a 1:1 molar complex under normal conditions *in vivo* (35), we also measured plasma TTR concentration. As expected, circulating TTR concentration was higher in glucose-intolerant women with pGDM. Our result is consistent with a previous report that TTR concentration is higher in individuals with IGT or type 2 diabetes mellitus (36). Evidence suggests that TTR stabilizes RBP4 concentration in the circulation by inhibiting its renal excretion and that the formation of an RBP4-TTR complex in plasma is critical for maintaining RBP4 levels (22, 35). Therefore, it is likely that an increase in plasma TTR concentration results in increased RBP4-TTR binding. On the other hand, the increase in the amount of RBP4-TTR complex could lower RBP4 clearance in the kidney, which may also contribute to the higher RBP4 concentration in women with GDM-DM in our study.

Increased plasma RBP4 concentration correlated independently with fasting glucose and triglyceride concentrations in our subjects. This independent correlation between triglyceride and RBP4 concentrations is consistent with recent Asian data on Chinese people with the metabolic syndrome (37) and Japanese patients with type 2 diabetes (38). In our data, RBP4 concentration was significantly higher when in the presence of the metabolic syndrome, of which elevated triglyceride concentration is a key marker. Moreover, RBP4 is involved in retinol metabolism and in 13-*cis*-retinoic acid-related hypertriglyceridemia and insulin resistance in humans (39, 40). From these data, we assume that RBP4 is linked directly or indirectly to triglyceride or lipid metabolism in humans.

RBP4 concentration was positively correlated with systolic blood pressure, fasting insulin concentration, abdominal fat, and HOMA-IR, which are markers of insulin resistance. However, no independent correlations were observed after multiple regression analysis. Previous studies have shown that RBP4 concentration does not correlate with insulin resistance in individuals with NGT, under calorie-restricted diets, or with type 2 diabetes mellitus (20, 41). More evidence is needed to explain the correlation between elevated RBP4 concentration and insulin resistance in humans under different clinical conditions.

Given that adipose tissue is the most important source of RBP4 in rodents and humans (11–16), it would be interesting to know whether the amount of visceral fat is associated with increased plasma RBP4 concentration. We found no correlation between plasma RBP4 concentration and visceral fat area, although RBP4 concentration correlated with the total abdominal

TABLE 4. Plasma RBP4 and adiponectin concentrations in women with or without the metabolic syndrome

	Without the metabolic syndrome (n = 122)	With the metabolic syndrome (n = 27)	P
Plasma RBP4 ($\mu\text{g/ml}$)	58.2, 8.3–139.1 ^a	66.3, 28.4–136.1	0.02
Plasma adiponectin ($\mu\text{g/ml}$)	6.5, 1.1–16.9	4.8, 1.9–11.3	0.17

Data are expressed as median, range. Plasma RBP4 and adiponectin concentrations were log-transformed before analysis.

^a Women with GDM-DM (n = 8) were excluded from this analysis.

fatness including both visceral and sc fat. However, the relationship between visceral fatness and elevated RBP4 concentration is debated (18, 36, 42). The differences between studies may relate to the different methodology to measure fat or the genetic background of the subjects, and further investigation is needed to clarify this point.

In contrast to RBP4, plasma adiponectin concentration is lower in obese humans and those with type 2 diabetes and is inversely related to cardiovascular risk factors accompanying insulin resistance (22–24). Our data also demonstrated that plasma adiponectin concentration was markedly lower in DM converters with pGDM (GDM-DM). Consistent with previous findings (23, 24), our data also showed an inverse relationship between plasma adiponectin concentration and components of insulin resistance and that total abdominal fat area was an independent predictor of adiponectin concentration. Collectively, these data suggest that a low adiponectin concentration is associated with impaired glucose metabolism in women with pGDM.

In conclusion, our data provide evidence that plasma RBP4 and TTR concentrations are elevated in women with pGDM and that elevated concentrations of these adipokines are related to the severity of glucose intolerance. Fasting plasma glucose and triglyceride concentrations are independent determinants of plasma RBP4 concentration. Plasma adiponectin concentration is low in women with GDM-DM, and the amount of abdominal fat is an independent determinant of plasma adiponectin concentration. These data suggest that high RBP4 and low adiponectin concentrations are associated with abnormal glucose metabolism in women with pGDM.

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Address all correspondence and requests for reprints to: Hak C. Jang, M.D., Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 300 Gumi-Dong, Bundang-Ku, Sungnam City, Gyeonggi-Do 463-707, South Korea. E-mail: janghak@snu.ac.kr.

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