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THE IMPORTANCE OF SERUM ADIPONECTIN CONCENTRATIONS DURING PREGNANCY AND POSTPARTUM PERIOD IN WOMEN WITH GESTATIONAL DIABETES MELLITUS

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Abstract

Background. The prevalence of gestational diabetes mellitus (GDM) continues to increase worldwide and women with a history of GDM are at high risk for type 2 diabetes. The role of adiponectin in GDM has not been clearly defined.

Objective. Our objective was to investigate the relationship between adiponectin levels in women with GDM, and insulin resistance and glucose and lipid metabolism.

Methods. Twenty-four women with GDM were compared with 20 women with normal glucose tolerance (NGT). Serum adiponectin level, the homeostasis model assessment of insulin resistance (HOMA-IR), and metabolic variables related to glucose and lipid metabolism were measured in the third trimester of pregnancy and 3 months after delivery.

Results. Adiponectin level was significantly lower in pregnant women with GDM than in those with NGT during pregnancy [6.5 (1-24) vs. 12.5 (5-18) μg/mL; $p < 0.001$] and at 3 months postpartum [7.0 (1-21) vs. 12.5 (4-19) μg/mL; $p < 0.001$]. HOMA-IR was higher in women with GDM during pregnancy ($p = 0.001$) and postpartum ($p = 0.012$).

Insulin resistance, pre-pregnancy BMI (pr BMI), age, HDL-cholesterol during pregnancy, 2-h postprandial glucose level, insulin resistance, age and postpartum BMI during postpartum period were independently correlated with adiponectin level. Adiponectin level during pregnancy and postpartum was negatively correlated with pr BMI.

Conclusion. Gestational diabetes is associated with hypoadiponectinemia during pregnancy and postpartum.

Hypoadiponectinemia during pregnancy may contribute to the pathogenesis of GDM

Key words: adiponectin, gestational diabetes mellitus.

INTRODUCTION

Pregnancy is associated with an increase in insulin resistance that

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becomes more marked as pregnancy progresses (1). Insulin sensitivity decreases by about 50% during a normal pregnancy (1,2). The onset of glucose intolerance of any level during pregnancy is defined as gestational diabetes mellitus (GDM) (3-5) and is observed in about 7% of all pregnancies (6).

Biochemically and epidemiologically, it resembles type 2 diabetes in non-pregnant adult females (7,8). Women with GDM are at high risk for developing type 2 diabetes later in life (8-10). The prevalence of GDM continues to increase worldwide, and thus its follow-up is important.

Adiponectin is a 29-kD protein secreted by adipose tissue. It is an adipocytokine with strong insulin-sensitizing, anti-inflammatory, and anti-atherogenic effects (11-14). It may decrease the risk for type 2 diabetes by suppressing hepatic gluconeogenesis and by stimulating fatty acid oxidation in liver and skeletal muscle, glucose uptake in skeletal muscle, and insulin secretion (15). Adiponectin is the only adipocyte-derived hormone known to be downregulated under conditions of insulin resistance (16). It is an important potential mediator of insulin resistance, which is a common feature among obesity, type 2 diabetes, and atherosclerotic cardiovascular diseases (17).

Hypoadiponectinemia has been shown to occur during pregnancy (16), and it accompanies insulin resistance, diabetes and obesity (11,16). Adiponectin concentrations are closely linked to insulin sensitivity and glucose metabolism, rather than adiposity or changes in lipid metabolism (16).

In addition to the adipose tissue, the placenta also produces adiponectin during pregnancy (18,19). Although it has been shown that adiponectin levels decrease during pregnancy (16,19), it has not been clearly documented whether hypoadiponectinemia accompanies GDM or what its exact role is. Furthermore, there have been conflicting reports regarding postpartum adiponectin concentrations (2,14,20,21). Some investigators have reported lower postpartum adiponectin levels in women with a history of GDM (14,20,21), whereas one study reported no change in the postpartum adiponectin concentration (2). There is controversy in the literature about association of pre-pregnancy BMI (pr BMI) with adiponectin level (3,7,14,22) and BMI with adiponectin level during pregnancy (8,11,13,23). Furthermore, there is a lack of information about the association between adiponectin and glucose levels during the follow-up of GDM (9,24,25) and the postpartum period (19,21,26). Despite many studies and stated opinions concerning the role of adiponectin in gestational diabetes and during the postpartum period, the mechanisms involved have not been clarified.

We propose that maternal adiponectin concentrations change during the third trimester in women with GDM, a condition of advanced insulin resistance, and during the postpartum period, in which insulin resistance is thought to be relieved. Given that gestational diabetes is accompanied by an increase in body mass index (BMI) and a decrease in insulin sensitivity, it is of interest to assess adiponectin levels in GDM patients. Therefore, we investigated the

relationship between the adiponectin level and glucose tolerance during pregnancy and the postpartum period. The main objective of this study was to compare adiponectin levels during the third trimester of pregnancy and the postpartum period between women with normal glucose tolerance (NGT) and those with GDM. The potential relationships of the adiponectin level with insulin resistance, the fasting blood glucose (FBG) level, the postprandial blood glucose (PPBG) level, and lipid parameters were also investigated.

MATERIALS AND METHODS

Twenty-four pregnant women with GDM who were between 28 and 31 weeks of gestation (mean age 34 years; age range 20-41 years; BMI 32.6 ± 3.8 kg/m^2) and 20 pregnant women with NGT (mean age 30 years; age range 19-33 years; BMI, 28.1 ± 3.1 kg/m^2) were recruited. All subjects were evaluated within the third trimester of pregnancy and at 3 months after delivery. The BMI was recorded at recruitment and 3 months after delivery. pr BMI values were obtained from the subjects' medical records in the Gynecology and Obstetrics Clinic. All subjects underwent a 50-g oral glucose challenge test (GCT), and women with blood glucose levels exceeding 140 mg/dL in this test were given a 100-g 3-h oral glucose tolerance test (OGTT). According to the diagnostic criteria of the American Diabetes Association, GDM was diagnosed in subjects who had two or more abnormal readings (normal values: fasting <95, 1 h <180, 2 h <155, and 3 h <140 mg/dL) in OGTTs performed between weeks 24 and 28 (6). Those with fasting blood glucose levels below 95 mg/dL and 1-h postprandial glucose levels below 140 mg/dL were confirmed as exhibiting NGT. The following exclusion criteria were applied: systemic disease known to affect inflammation markers; infection of new onset; high blood pressure and associated diseases (preeclampsia and eclampsia); pregnancy assisted by reproduction techniques; chronic drug use (excluding vitamins and iron); history of GDM, polycystic ovary syndrome and thyroid dysfunction; prior diagnosis of diabetes; and multiple pregnancies.

None of the pregnant women had reported to have an abortion. Gestational age was estimated based on routine ultrasonographic screening and the date of last menstrual bleeding. Informed consent was obtained from all participants, and the local ethics committee approved the study.

Blood samples were collected following fasting for at least 8 h. Lipid parameters and the levels of adiponectin, FBG, PPBG, and fasting insulin were measured in all subjects during pregnancy (between weeks 28 and 31) and 3 months following delivery. A postpartum re-evaluation, in this study, was performed at three months postpartum. We checked furthermore, on the women with a history of GDM, the fasting blood glucose (<126mg/dL) and 2-h postprandial blood glucose (<200 mg/dL) for diabetes screening immediately and at

6 weeks postpartum. We obtained results similar to the results achieved in 3 months postpartum. Later on together with the measurements of adiponectin level, we performed OGTT at 3 months postpartum.

For adiponectin measurements, sera were isolated immediately and stored until analysis at −80°C.

Plasma adiponectin levels were determined using a commercial sandwich immunoassay kit (Human Adiponectin / Acrp30 Immunoassay; R&D Systems Inc., Minneapolis, MN, USA). Intra-assay and inter-assay coefficients of variation were less than 4.7% and 6.9%, respectively. The minimum detectable adiponectin concentration was 0.25 ng/mL. Glucose levels were measured by standard enzymatic methods (Roche Diagnostic GmbH, Manheim, Germany). Serum insulin levels were measured by immunoradiometric assay (sandwich-type assay) using an insulin IRMA kit (Immunotech, Prague, Czech Republic). Intra-assay and inter-assay coefficients of variation were 4.3% and 3.4%, respectively, and the minimum detectable insulin concentration was 0.5 μIU/mL. Insulin resistance was determined using the homeostasis model assessment-insulin resistance (HOMA-IR) index, calculated as:

HOMA-IR = [serum glucose level (mg/dL) x insulin (μIU/mL)]/405.

Serum concentrations of total cholesterol (TC), HDL cholesterol (HDL-C), and triglycerides (TG) were measured by enzymatic calorimetric methods using commercially available kits (Roche Diagnostic GmbH). LDL cholesterol (LDL-C) levels were calculated using the Friedewald equation.

Statistical analysis

Data analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as means ± standard deviation (SD) or median (minimum-maximum). Differences between group means and group medians were tested for significance using Student's *t*-test and the Mann-Whitney *U* test, respectively. Within-group comparisons were assessed using a paired Student's *t*-test, or the Wilcoxon signed-rank test when necessary. Kendall tau-b correlation test was used to assess the relationships between maternal adiponectin levels and the associated variables. Receiver operating characteristic (ROC) curve analysis was used to test whether adiponectin was an important marker in distinguishing between GDM and NGT. Stepwise linear regression analysis was used to identify the factors that were most strongly associated with adiponectin levels during both pregnancy and the postpartum period. A p value <0.05 was considered to indicate statistical significance.

RESULTS

Women with GDM were significantly older than those with NGT (p<0.001). Mean BMI was significantly higher in women with GDM than in women with NGT prior to pregnancy (p <0.001), during pregnancy (p<0.001), and 3 months postpartum (p<0.001) (Table 1). Therefore, subsequent statistical analyses incorporated adjustments for age and BMI.

Table 1. The characteristics of pregnant women with GDM and NGT in the third trimester of pregnancy and three months after delivery

	Pregnancy			After delivery					
Variables	GDM	NGT	p	GDM	NGT	p*	p†	p‡	p§
n	24	20							
Age (year)	34 (20-41)	30 (19-33)	<0.001a						
prBMI (kg/m^2)	27.4±2.5	24.7±2.0	<0.001						
BMI (kg/m^2)	32.6±3.8	28.1±3.1	<0.001	30.4±3.9	25.0±2.8	<0.001	<0.001[b]	<0.001[b]	0.637
HOMA-IR	3.3 (2.0-11.1)	2.0 (0.8-8.6)	0.001[a]	2.4 (1.3-5.6)	1.3 (0.4-6.6)	0.012[a]	<0.001[b]	0.005[b]	0.120
FBG (mg/dL)	89.5 (69-132)	75.5 (58-84)	<0.001	97 (84-156)	84 (57-97)	<0.001	0.02[b]	0.003b	0.480
PPBG (mg/dL)	139 (121-204)	94 (74-141)	<0.001[a]	126 (88-169)	99 (75-126)	<0.001[a]	0.07	0.197	0.017
Fasting insulin (mIU/mL)	10.1 (4.5-18)	4.3 (2.2-22)	<0.001[a]	7.8 (3.1-24)	3.9 (1.5-20)	0.002[a]	0.001[b]	0.011[b]	0.253
TC (mg/dL)	240.3±18.8	227.3±30.1	0.090	206.8±22.8	204.3±22.4	0.863	<0.001[b]	<0.001[b]	0.224
LDL-C (mg/dL)	133.5 (95-203)	126.5 (87-177)	0.120[a]	103.5 (78-165)	110.5 (70-148)	0.777[a]	<0.001[b]	0.001[b]	0.057
HDL-C (mg/dL)	55.9±13.7	62.2±10.4	0.090	69.1±12.3	68.5±16.3	0.890	<0.001[b]	<0.001[b]	0.055
TG (mg/dL)	248.2±38.9	227.3±41.4	0.094	195.7±52.1	172.8±34.2	0.088	<0.001[b]	<0.001[b]	0.871
Adiponectin (μg/mL)	6.5 (1-24)	12.5 (5-18)	<0.001[a]	7.0 (1-21)	12.5 (4-19)	<0.001[a]	0.52[b]	0.25[b]	0.741

Data are expressed as means±SD, a with Mann Whitney U test, b with Wilcoxon Sign Rank test. prBMI: prepregnancy BMI; BMI: body mass index, HOMA-IR: homeostasis model assessment- insulin resistance; FBG: fasting blood glucose; PPBG: post-prandial blood glucose; TC: total cholesterol; LDL-C: LDL cholesterol; HDL-C:HDL cholesterol; TG: triglycerides.p, demonstrates difference between subjects with GDM and NGT in pregnancy, p*,demonstrates difference between subjects with GDM and NGT after delivery, p†,demonstrates difference in intra-group comparison of subjects with GDM in pregnancy and after delivery, p‡,demonstrates difference in intra-group comparison of subjects with NGT in pregnancy and after delivery, p§, demonstrates difference in interaction of group - time. If the distribution is normal, variance analysis was used in repeated measures. Group-effect (p, p*), time-effect (p†,p‡) and group - time effect (p§) were evaluated. If the distribution is not normal, the comparison was made between the groups using Mann Whitney U test with bonferroni-correction (p, p*). In the comparison between the times was used Wilcoxon Sign Rank test with bonferroni correction (p†, p‡). To test the interaction of group-time, per cent variations were calculated and they were compared by Mann Whitney U test.

The clinical and biochemical characteristics of the study subjects are presented in Table 1. During pregnancy, the values for all tested parameters, excepting the lipid parameters, were significantly higher and adiponectin levels were significantly lower in women with GDM than in women with NGT. During the postpartum period, BMI, the HOMA-IR value, and the FBG, PPBG, and fasting insulin levels were significantly higher and adiponectin levels were significantly lower in women with GDM than in women with NGT. Compared with the prepartum values, the postpartum FBG and HDL-C levels were significantly higher; BMI, the HOMA-IR value, and the levels of fasting insulin, TG, TC, and LDL-C were significantly lower; and the PPBG and adiponectin levels were not significantly different.

Serum adiponectin levels of women with GDM and NGT during pregnancy and the postpartum period are shown in Fig. 1. The plasma adiponectin level was significantly lower in pregnant women with GDM than in those with NGT during pregnancy ($p < 0.001$) and at 3 months postpartum ($p < 0.001$). There was no significant difference between the prepartum and postpartum adiponectin levels within the GDM ($p = 0.52$) or NGT group ($p = 0.25$) (Table 1).

The HOMA-IR value was significantly higher in women with GDM than in those with NGT in the third trimester ($p = 0.001$) and at 3 months postpartum ($p = 0.012$). The postpartum HOMA-IR value was significantly lower than the prepartum value in the GDM and NGT groups ($p < 0.001$ and $p = 0.005$, respectively). There was a negative correlation between adiponectin and HOMA-IR levels of all the pregnant women in the third trimester of pregnancy ($r = -0.47$; $p < 0.001$) and this correlation was maintained in 3 months postpartum ($r = -0.35$; $p = 0.001$).

The FBG and PPBG levels were significantly higher in women with GDM than in women with NGT during

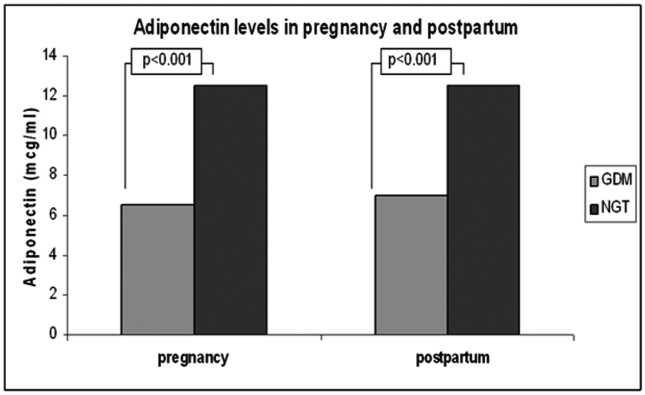

Figure 1. Serum adiponectin levels before and after delivery in women with gestational diabetes mellitus (GDM) and normal glucose tolerance (controls). A significant decrease was found in both periods for women with GDM.

Table 2. Kendall tau-b correlation coefficients of adiponectin levels with selected variables in pregnant women with GDM and NGT

	Pregnancy						After delivery					
Variables	All subjects		GDM		NGT		All subjects		GDM		NGT	
	r	p	r	p	r	p	r	p	r	p	r	p
Age (year)	-0.13	0.23	-0.16	0.29	-0.1	0.55	-0.17	0.13	-0.07	0.632	-0.11	0.5
pBMI (kg/m^2)	-0.42	<0.001	-0.40	0.008	-0.01	0.97	-0.41	<0.001	-0.4	0.008	-0.02	0.92
BMI (kg/m^2)	-0.45	<0.001	-0.40	0.008	-0.12	0.47	-0.39	<0.001	-0.26	0.08	-0.06	0.72
HOMA-IR	-0.47	<0.001	-0.41	0.006	-0.31	0.061	-0.35	0.001	-0.28	0.06	-0.14	0.41
FBG (mg/dL)	-0.46	<0.001	-0.45	0.003	-0.06	0.72	-0.27	0.013	-0.02	0.9	-0.08	0.65
PPBG (mg/dL)	-0.42	<0.001	-0.31	0.041	-0.04	0.82	-0.33	0.002	-0.07	0.62	-0.17	0.31
Fasting insulin mIU/mL)	-0.49	<0.001	-0.33	0.026	-0.35	0.035	-0.32	0.003	-0.01	0.94	-0.18	0.28
TC (mg/dL)	-0.27	0.013	-0.29	0.052	-0.13	0.43	-0.04	0.7	-0.04	0.8	-0.05	0.74
LDL-C (mg/dL)	-0.33	0.002	-0.36	0.017	-0.27	0.1	-0.14	0.2	-0.17	0.26	-0.27	0.11
HDL-C (mg/dL)	0.39	<0.001	0.33	0.026	0.29	0.08	0.14	0.19	0.03	0.84	0.33	0.046
TG (mg/dL)	-0.32	0.003	-0.56	<0.001	-0.17	0.3	-0.1	0.3	-0.08	0.6	-0.13	0.43

prBMI: pre-pregnancy BMI; BMI: body mass index; HOMA-IR: homeostasis model assessment-insulin resistance; FBG: fasting blood glucose; PPBG: post prandial blood glucose; HDL-C: HDL cholesterol; TG: triglycerides

pregnancy and postpartum ($p < 0.001$ for all). Similarly, fasting insulin levels during pregnancy and postpartum were higher in women with GDM ($p < 0.001$ and $p = 0.002$, respectively).

The results for Kendall tau-b correlation analysis of the plasma adiponectin level and selected variables are shown in Table 2. In the analysis of the prepartum data for all subjects, the plasma adiponectin level was negatively correlated with pr BMI, third-trimester BMI, the HOMA-IR value, and the FBG, PPBG, fasting insulin, TG, TC, and LDL-C levels, and positively correlated with the HDL-C level. When the groups were analyzed separately, the same correlations were found for women with GDM in the third trimester of pregnancy (except TC level),

whereas only the fasting insulin level was negatively correlated with the adiponectin level in women with NGT during pregnancy. The analysis of the postpartum data for all subjects revealed negative correlations between the adiponectin level and pr BMI, postpartum BMI, the HOMA-IR value, and the FBG, PPBG, and fasting insulin levels (Table 2). When the postpartum data for each group were analyzed separately, the adiponectin level was negatively correlated with pr BMI in women with GDM and positively correlated with the HDL-C level in women with NGT. Thus, the adiponectin level and pr BMI were negatively correlated during pregnancy ($r = -0.40$; $p < 0.01$) and the postpartum period ($r = -0.40$; $p < 0.01$). Significant negative correlations were also identified between the adiponectin level during pregnancy and the postpartum HOMA-IR value ($r = -0.36$; $p = 0.001$) and postpartum FBG level ($r = -0.26$; $p < 0.05$).

To determine whether adiponectin is an important marker for differentiating between GDM patients and controls, ROC analysis was performed and the area under the curve was calculated. In screening for GDM, the serum adiponectin cut-off concentration was 8.5 µg/ml, with a sensitivity of 62.5% and specificity of 95.0% (area under the curve = 0.815, SE = 0.065, 95 % CI = 0.686-0.943; $p = 0.001$).

Regression analysis of factors affecting the adiponectin level during pregnancy revealed that age, pr BMI, the HOMA-IR value, and the HDL-C level collectively accounted for 68% of the change in the adiponectin level ($R^2 = 0.683$; Table 3, A). In a regression analysis of factors during the postpartum period, PPBG, the HOMA-IR level, age, and postpartum BMI collectively accounted for 53% of the change in the adiponectin level ($R^2 = 0.537$; Table 3, B).

All women in both groups were breastfeeding when reevaluation was performed at 3 months postpartum and there was no difference between groups for prolactin levels.

DISCUSSION

This study shows that the plasma

Table 3. Regression analyses

A

	B	SE	t	p
Constant	24.27	7.47	3.25	0.00
age	-0.31	0.10	-2.98	0.00
pr BMI	-0.85	0.21	-4.06	0.00
HOMA-IR	-0.88	0.25	-3.51	0.00
HDL-C	0.16	0.04	3.60	0.00

Dependent variable: Adiponectin (R2=0.683)

B

	B	SE	t	p
Constant	30.57	4.90	6.24	0.00
age	-0.40	0.14	-2.81	0.01
BMI	-0.44	0.18	-2.47	0.02
2-h PPBG	-0.10	0.03	-3.29	0.00
HOMA-IR	-1.20	0.47	-2.57	0.01

Dependent variable: Adiponectin (R2=0.537)

Stepwise linear regression analysis of affecting factors on adiponectin in GDM (A) and postpartum (B).

adiponectin concentration is markedly lower in women with GDM than in those with NGT, both in the third trimester of pregnancy and 3 months postpartum. The HOMA-IR value was higher in the women with GDM than in those with NGT during pregnancy. The postpartum HOMA-IR value remained higher in women with GDM. During pregnancy and postpartum, the adiponectin level was negatively correlated with pr BMI in women with GDM. Furthermore, the adiponectin level during pregnancy was negatively correlated with the postpartum HOMA-IR value and postpartum FBG level.

Adiponectin levels are low in GDM (8,13,18,22,27), because adipocyte-derived adiponectin is downregulated under conditions of insulin resistance (16,28). Consistent with previous studies (4,8,18,19,23,25-27,29), we also found lower adiponectin levels in pregnant women with GDM than in those with NGT. On the contrary, McLachlan *et al.* (2) found no difference in the adiponectin level between pregnant women with and without GDM.

Pr BMI is reported to be the primary factor in determining BMI during pregnancy, with high pr BMI being a risk factor for GDM (4,30). In addition, high pr BMI is an independent risk factor for postpartum glucose intolerance (10,31). Soheilykhah *et al.* (22) identified a negative correlation between the adiponectin level and pr BMI in women with GDM.

There is a controversy in the literature about the association of the adiponectin levels with pr BMI (3,7,14,22,26,27,29) and BMI (8,11,13,23,24) during pregnancy. We found an inverse correlation between adiponectin levels and pre BMI and BMI during pregnancy. Our findings are similar to the results of three other studies (3,7,27). Our findings are consistent with other studies reporting an inverse association between the values of pr BMI and adiponectin levels in GDM (3,7,22,26,27,29). This association is not confirmed by the study of Weerakiet *et al* (14). Also, we found a negative association between BMI during pregnancy and adiponectin levels. This finding is also inconsistent with other studies (8,11,13,24) whereas it is consistent with the study of Cseh *et al* (23). Furthermore, although some other studies have indicated that the values of pr BMI in women with GDM were higher than those with NGT, no association with the adiponectin level has been demonstrated (11,14). The reason for these controversies is unclear but the wide range of pr BMI and BMI of women with GDM in the reported studies might be one of the reasons for the conflicting results.

This negative correlation between pr BMI and the adiponectin levels during pregnancy suggests that a decrease in adiponectin occurs during the early part of pregnancy, before the development of GDM, and is linked to insulin resistance, which is itself related to high BMI. The change in the adiponectin level in GDM precedes the onset of insulin resistance and abnormal glucose levels (32). The decreased adiponectin level, together with insulin resistance and increased BMI, persists to the third trimester. Our study also shows that the persistence of the negative correlation between the adiponectin level and pr BMI into the postpartum period suggests that the same mechanism contributes to impaired

glucose metabolism both before and after delivery.

The decreased adiponectin level in GDM is accompanied by an increased HOMA-IR value (13,18). McLachlan *et al.* (2) found no such a relationship and suggested that the decrease in insulin sensitivity in women with GDM occurs prior to pregnancy. However, in our study, the HOMA-IR value was higher in women with GDM than in those with NGT during the third trimester of pregnancy as well as in the postpartum period. Furthermore, there was a negative correlation between the adiponectin level and HOMA-IR value in GDM patients during pregnancy.

Kautzky-Willer *et al*. (33) reported that lean women with GDM released more insulin and had greater insulin resistance. In our study, the insulin level was significantly higher in women with GDM than in those with NGT during pregnancy. Vitoratos *et al.* (18) showed that women with GDM had lower adiponectin levels and higher HOMA-IR values than pregnant women with NGT on postpartum day three. The postpartum data in the present study are partially consistent with those of Vitoratos *et al.* (18), who reported a postpartum reduction in the adiponectin level of subjects with GDM, but no reduction in subjects with NGT. Homko *et al.* (9) reported that postpartum insulin sensitivity improved approximately two-fold in women with GDM and those with NGT, but that insulin resistance remained approximately 40% higher in the women with GDM.

Impaired glucose tolerance (IGT) postpartum in women with GDM has been investigated previously, and prevalences of 17-23% have been reported in the majority of the studies (34). Heitritter *et al.* (21) reported a prevalence of 43% for IGT during the first postpartum year. In addition, a 17-63% risk for type 2 diabetes over the subsequent 5-16 years has been reported (5,21). Likewise, in our study, the IGT rate in women with a history of GDM was 25% (6 of 24 patients) at the postpartum follow-up.

Williams *et al.* (7) reported lower adiponectin levels in women with GDM compared with controls. Women with adiponectin concentrations below 6.4 µg/mL increase the risk for developing GDM by 4.6-fold compared with the risk at higher concentrations. According to Weerakiet *et al.* (14), when an adiponectin level of 10 µg/mL is used as the cut-off value for screening pregnant women for GDM, 27% of women can be spared an OGTT (sensitivity 91%, specificity 31%). Vitoratos *et al.* (13) excluded GDM using a serum adiponectin cut-off value of 5.253 µg/mL, with a sensitivity of 86.4% and specificity of 59.1%. In the present study, an adiponectin cut-off value of 8.5 µg/mL afforded a sensitivity of 62.5% and specificity of 95.0%.

It is reported that the adiponectin levels, as compared with controls, were lower in the first postpartum year in women with a history of GDM (20,21). McLachlan *et al.* (2) reported that adiponectin levels did not differ between the two groups either during pregnancy or in the fourth postpartum month. In our study, there was no difference between the pregnancy and postpartum adiponectin levels in subjects with GDM and those with NGT, although both adiponectin levels were lower in women with GDM than in those with NGT.

Choi *et al.* (5) reported a correlation between hypoadiponectinemia and the severity of glucose intolerance in women with a history of GDM and found a lower level of adiponectin after GDM in the diabetes group than in the IGT or control group. Delivery of the fetus and placenta removes the effect of pregnancy on maternal BMI and partially normalizes maternal body weight, but postpartum adiponectin levels and insulin resistance do not rapidly return to normal, suggesting a complex regulatory mechanism.

The previous studies reveal that higher fasting glucose, 2-h postprandial glucose, and 2-h postprandial insulin levels and lower adiponectin levels in women with a history of GDM compared with normal controls (21,25). The results of the present study agree with the results of said reports.

Changes in adiponectin levels are related to decreased insulin sensitivity and glucose disposal, rather than altered lipid metabolism (16). Plasma adiponectin levels are reported to be negatively correlated with triglyceride levels and positively correlated with HDL-C levels (16,27,35). Furthermore, it has been suggested that these relationships are independent of systemic insulin resistance and are affected by central obesity (visceral fat) (36). The level of hepatic HDL-C synthesis is an indicator of insulin sensitivity, particularly in the liver, and adiponectin has been shown to improve hepatic insulin sensitivity (37). In the present study, the adiponectin level was negatively correlated with the TG level and positively correlated with the HDL-C level.

Retnakaran *et al.* (26) recently proposed that low levels of adiponectin in patients with GDM may predict postpartum insulin resistance, fasting hyperglycemia, and β-cell dysfunction. In view of their regression findings, we believe that the negative correlations we identified between the adiponectin level during pregnancy and the postpartum HOMA-IR value and postpartum FBG level may indicate that low levels of a adiponectin during pregnancy contribute to insulin resistance and changes in glucose metabolism following delivery. Our regression analysis showed that the HOMA-IR value affects adiponectin levels, both during pregnancy and in the period following delivery. We are of the opinion that the adiponectin level declines during the early pregnancy period and continues to fall as insulin resistance increases and that the adiponectin level is linked to postpartum insulin resistance and changes in glucose metabolism.

Recent studies have shown that adiponectin is a promising target for reducing the risk for type 2 diabetes (15). In women with a history of GDM, the improvement of chronic postpartum hypoadiponectinemia may be a treatment goal. Several studies demonstrated that adiponectin concentrations can be increased by lifestyle modifications and pharmaceutical interventions such as thiazolidinediones, statins, ACE inhibitors and angiotensin receptor blockers in order to reduce the risk for type 2 diabetes in women with a history of GDM (15,26,38-44). The results of the tested treatments in these individuals are promising, but none of these medications is currently approved by the FDA for use in preventing diabetes.

This study has some limitations. First, the number of patients recruited

was small, which might have prevented the detection of significant correlations and/or differences between the two subject groups. Second, as in the great majority of the previous studies, the adiponectin level was measured only once during each period. Longitudinal studies involving serial measurements (e.g., weekly measurements) of plasma adiponectin concentrations and insulin sensitivity markers, during both pregnancy and the postpartum period, are required to obtain more precise and reliable results and to clarify the mechanisms of hypoadiponectinemia and its pathophysiological consequences. Third, although it is a less specific method for measuring insulin sensitivity than the clamp method, we used the HOMA-IR index, because it was used in most of the studies cited above.

This study reports that decreased adiponectin levels during pregnancy is also maintained in the postpartum period in women with a history of GDM. Adiponectin level during pregnancy and in the postpartum period is negatively correlated with pr BMI. Our study shows that low adiponectin levels have an association with GDM and postpartum insulin resistance.

Pregnant women with low adiponectin levels should be monitored for insulin resistance. Accordingly, for overweight or obese women who intend to be pregnant, and with a history of GDM, the lifestyle modifications (low calorie diet, physical activity, weight loss) should be offered.

In conclusion, gestational diabetes is accompanied by hypoadiponectinemia both during pregnancy and in the postpartum period. It is possible that hypoadiponectinemia during pregnancy plays a role in the pathogenesis of GDM

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