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Associations between serum levels of adiponectin and resistin and metabolic parameters in pregnant women with gestational diabetes mellitus

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Summary

Introduction: Gestational diabetes mellitus (GDM) is defined as a glucose intolerance firstly diagnosed during pregnancy. In this study, the authors aimed to investigate the association between serum adiponectin, and resistin levels with insulin resistance and metabolic parameters in patients with GDM. *Material and Methods:* A total of 80 patients: 40 healthy pregnant women (control group) and 40 pregnant women diagnosed with GDM (study group) were included in this study. Serum adiponectin, resistin, glucose, insulin, HbA1c levels, and lipid parameters were measured. Insulin resistance index HOMA-IR values were calculated. *Results:* Serum adiponectin levels were detected to be significantly lower ($p < 0.001$), whereas serum resistin levels were found to be significantly higher ($p = 0.004$) in GDM group compared with the control group. Levels of HDL-C, LDL-C, VLDL-C, and triglycerides were similar in both groups, but the total cholesterol level was significantly higher in the GDM group ($p = 0.013$). In the GDM group, adiponectin levels were negatively correlated with HbA1c levels ($r = -0.368$; $p = 0.010$) but were not correlated with any other parameter. A significant positive correlation was evident between resistin levels and both total cholesterol ($r = 0.476$, $p = 0.001$), and LDL-cholesterol ($r = 0.293$; $p = 0.033$). *Conclusion:* The results of this study demonstrated that serum resistin levels were significantly higher and serum adiponectin levels were significantly lower in pregnant women with GDM patients compared with normoglycemic pregnants. Also, it was detected that there was no correlation between serum adiponectin and resistin levels and insulin resistance in GDM patients.

Key words: Adiponectin; Gestational diabetes mellitus; Insulin resistance; Resistin.

Introduction

Gestational diabetes mellitus (GDM) is a form of impaired glucose tolerance characterized by severe hyperglycemia that commences during gestation (and thus is first recognized during pregnancy) [1]. GDM complicates approximately 7% of all pregnancies; the rate varies from 1–28% depending on the population studied and the tests performed [2]. GDM increases the risk for hypertensive disease in pregnancy, obesity, polyhydramnios, operative delivery, and cesarean delivery in mothers, and macrosomia, birth trauma, and death in fetuses particularly in the last trimester [3]. Thus, screening for GDM is recommended between 24–28 weeks of gestation when diabetogenic effects of pregnancy are evident [4].

In pregnancy, anabolism predominates during the first trimester, characterized by increased gluconeogenesis and glycogen, protein, and fat storage. Catabolism commences in the second trimester; the levels of glycerol, free fatty acids, and ketone bodies increase as a result of lipolysis triggered by human placental lactogen (HPL) secreted by syncytiotrophoblasts [5]. Prolactin, cortisol, and progesterone also modulate pregnancy-associated glucose and lipid metabolism. These hormones antagonize the effects of insulin in the second and third trimesters of pregnancy, creating a form of insulin resistance. However, increasing evidence suggests that adipocytokines secreted by adipose tissue may also trigger insulin resistance during pregnancy. Of the various adipocytokines, resistin and adiponectin have attracted particular attention because of their close associations with obesity and insulin resistance [6]. Resistin is a dimeric 12.5 kDa protein of 108 amino acids; the chains are linked by a cys-26 disulfide bridge. This adipocytokine plays important roles in adipogenesis, inflammation, and cardiovascular disease, and is synthesized principally by adipocytes and peripheral mononuclear cells of the pancreas, lung, and placenta [7]. Adiponectin is synthesized primarily in adipocytes but also in bone marrow, fetal tissues, monocytes, and salivary glands [8, 9]. Adiponectin exhibits cardioprotective, antineoplastic, anti-inflammatory, anti-atherogenic, and anti-apoptotic properties, and may play a role in obesity-related disorders (the serum levels are lower in obese patients) [10]. Hypoadiponectinemia

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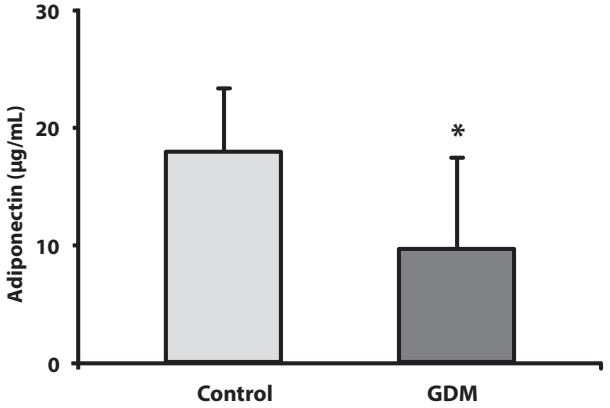

Figure 1. — Serum adiponectin levels of normoglycemic and GDM group (*$p < 0.001$).

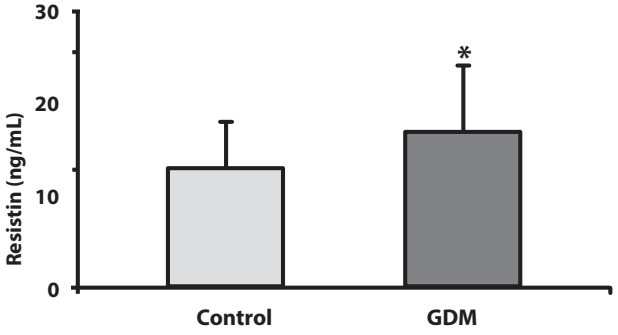

Figure 2. — Serum resistin levels of normoglycemic and GDM group (*$p = 0.004$).

triggers vascular smooth muscle cell proliferation and endothelial dysfunction, increasing the expression of adhesion molecules and the level of the superoxide anion in endothelial cells [11]. Adiponectin also enhances insulin sensitivity. Amelioration of insulin resistance by adiponectin is thought to involve activation of AMP-activating protein kinase (AMPK) (enzyme phosphorylation) in both skeletal muscle and the liver [12].

In the present study, the authors aimed to compare serum levels of adiponectin and resistin in patients with and without GDM and investigate the relationships between adipocytokine levels and insulin resistance and dyslipidemia in women with pregnancies complicated by GDM.

Materials and Methods

This was a prospective case-control study of 80 participants [40 pregnant women with GDM (study group) and 40 healthy age-matched pregnant women (control group)] recruited from the Department of Obstetrics and Gynecology of the Firat University Faculty of Medicine between January 2015 and January 2016. The Ethics Committee for Clinical Investigations of the Faculty of Medicine of Firat University approved the study and all participants were fully informed of the purpose of the work, in accordance with the principles of the Declaration of Helsinki (ethics committee approval no: 2014/A183).

The inclusion criteria were maternal age 18–39 years, viable singleton pregnancy, being at 24–28 weeks of gestation, body mass index < 35 kg/m^2, and no adverse medical or obstetric history. The exclusion criteria were the presence of any congenital fatal or chromosomal abnormality, maternal polycystic ovary syndrome, pregestational diabetes, hypertensive disease in pregnancy, obstetric cholestasis, chronic maternal disease (dyslipidemia, chronic hypertension, chronic renal failure, a malignancy, asthma, pulmonary or cardiac disease), and the use of any antihypertensive, antidiabetic, or antidepressive medication or tobacco or alcohol.

All women attending the outpatient clinic of the Obstetrics and Gynecology Department were screened for GDM between gestational weeks 24 and 28 using the 50-gram glucose test, which was performed within five minutes of oral administration of 50 grams of anhydrous glucose dissolved in 300 mL of water. Venous blood samples were taken one hour later, and plasma glucose levels were measured. The oral glucose tolerance test (OGTT) (100 grams of glucose) was conducted on those with blood glucose levels ≥ 140 mg/L. Blood (5 mL) was collected between 08:00 and 09:00 after 10 hours of overnight fasting. Then each subject ingested 100 grams of anhydrous glucose in 300 mL water within five minutes. Blood samples (2 mL) were collected one, two, and three hours later. All samples were centrifuged at 3,500 rpm for five minutes to separate sera. Fasting and postprandial plasma glucose levels, and the fasting serum level of insulin, were used to evaluate pancreatic β-cell function; the authors also measured serum levels of lipids [total cholesterol; high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density (VLDL) lipoprotein cholesterol, and triglycerides). Glucose, lipid, and HbA1c levels were measured on an autoanalyzer. The homeostatic model assessment-insulin resistance (HOMA-IR) formula of Matthews *et al*. [13] (fasting insulin level [µU/mL] × fasting glucose level [mmol/L]/22.5) was used to measure insulin resistance. Body mass index (BMI) was calculated as kg/height (m)^2. GDM was diagnosed when at least two of the thresholds suggested by the National Diabetes Data Group were either met or exceeded (fasting blood glucose level: 105 mg/dl, one-hour level: 190 mg/dl; two-hour level: 165 mg/dl; three-hour level: 145 mg/dl) [14].

Serum levels of resistin were determined using an enzyme-linked immunosorbent assay (ELISA). Absorbances at 450 nm were recorded using a model ELISA reader. The authors also used an automated model washer. The dilution levels were corrected and the final levels were expressed as ng/mL (range: 78–5,000 pg/mL). Serum levels of adiponectin were assayed using a human adiponectin ELISA kit. The dilution levels were corrected and the final levels are expressed as µg/mL (range: 0.781–50 ng/mL).

Power analysis suggested that at least 39 individuals should be included in each group if the greatest between-group difference in adiponectin level was 2.46 µg/mL, the standard deviation 2.7 µg/mL, the type I error 0.05, and the type II error 0.10 [15]. The authors recorded the age, BMI, and obstetric and medical histories of both the patient and control groups. SPSS version 22.0 software was used for all statistical analyses. Student's *t*-test was employed to compare biochemical parameters between the control and study groups. Pearson's correlation test was used to define relationships between these parameters. The authors present means ± standard deviations; a p value < 0.05 was considered to reflect statistical significance.

Table 1. — *Demographic and biochemical characteristics of subjects.*

	GDM (n=40)	Control (n=40)	*p* value
Age (years)	30.97±5.32	29.22±5.86	0.431
BMI (kg/m^2)	29.33±3.76	28.96±3.69	0.662
Glucose (mg/dL)	103.32±33.40	91.15±14.59	0.038
HbA1c (%)	5.71±1.10	5.02±0.53	<0.001
Insulin (µIU/mL)	28.11±24.04	16.93±12.27	0.011
Total cholesterol (mg/dL)	229.47±41.65	206.48±38.97	0.013
HDL cholesterol (mg/dL)	62.30±12.40	59.23±12.02	0.264
LDL cholesterol (mg/dL)	123.97±31.59	125.34±26.83	0.835
VLDL cholesterol (mg/dL)	45.20±15.19	40.49±13.09	0.142
Triglyceride (mg/dL)	226.02±75.98	202.47±65.49	0.142
HOMA-IR	7.81±6.05	4.01±3.43	0.008
Adiponectin (µg/mL)	9.70±7.76	17.78±5.57	<0.001
Resistin (ng/mL)	16.78±6.83	12.79±5.02	0.004

BMI: body mass index, HbA1c: hemoglobin A1C, HDL: high density lipoprotein, LDL: low density lipoprotein, VLDL: very low density lipoprotein, HOMA-IR: homeostatic model of assessment-Insulin resistance.

Table 2. — *Correlations between adiponectin and resistin levels, and other variables, in the control group at 24–28 weeks of pregnancy*

n=40	*Serum adiponectin level*		*Serum resistin level*	
	r	*p*	*r*	*p*
Age	0.122	0.226	0.024	0.441
BMI at week 24–28 of pregnancy	0.099	0.271	0.169	0.148
Fasting glucose level	0.005	0.488	0.216	0.090
HbA1C level	-0.286	0.037*	0.201	0.107
Insulin level	-0.322	0.021*	0.136	0.201
HOMA-IR score	-0.291	0.034*	0.145	0.186
Triglyceride level	0.040	0.402	0.027	0.434
Total cholesterol level	0.317	0.023*	0.088	0.295
HDL-cholesterol level	0.169	0.149	0.115	0.140
LDL-cholesterol level	0.065	0.344	0.220	0.086
VLDL-cholesterol level	0.040	0.402	0.027	0.434

** p < 0.05, indicating significance.*

Results

The authors included 80 pregnant women in the study. Neither age nor BMI differed between the GDM and control groups. As expected, blood glucose, HbA1c, and insulin levels, as well as HOMA-IR values were significantly higher in women with GDM than in controls ($p = 0.038$, $p = 0.001$, $p = 0.011$, and $p = 0.008$, respectively).

Levels of HDL-C, LDL-C, VLDL-C, and triglycerides were similar in both groups, but the total cholesterol level was significantly higher in the GDM group ($p = 0.013$). Adiponectin levels were significantly lower in the GDM group ($p < 0.001$) (Figure 1), whereas resistin levels were significantly higher in that group ($p = 0.004$) (Figure 2).

Table 3. — *Correlations between adiponectin and resistin levels and other variables in the GDM group between weeks 24–28 weeks of pregnancy*

n=40	*Serum adiponectin level at week 24–28*		*Serum resistin level at week 24–28*	
	r	p	r	p
Age	0.041	0.402	0.149	0.180
BMI at week 24–28	0.159	0.164	0.140	0.194
Fasting glucose level	0.121	0.229	0.134	0.205
HbA1C level	-0.368	0.010*	0.038	0.408
Insulin level	0.061	0.355	0.149	0.179
HOMA-IR score	0.077	0.319	0.054	0.371
Triglyceride level	0.077	0.318	0.121	0.229
Total cholesterol level	0.024	0.442	0.476	0.001*
HDL-cholesterol level	0.209	0.097	-0.360	0.011*
LDL-cholesterol level	0.017	0.459	0.293	0.033*
VLDL-cholesterol level	0.077	0.318	0.121	0.229

**p < 0.05, indicating significance.*

The demographic and biochemical characteristics of both groups are summarized in Table 1.

In the control group, significant negative correlations were evident between adiponectin level and HbA1c levels ($r = -0.286$; $p = 0.037$), insulin levels ($r = -0.322$; $p = 0.021$), and HOMA-IR values ($r = -0.291$; $p = 0.034$). However, a significant positive correlation was apparent between adiponectin and total cholesterol ($r = 0.317$; $p = 0.023$). In the GDM group, adiponectin levels were negatively correlated with HbA1c levels ($r = -0.368$; $p = 0.010$), but were not correlated with any other parameter. A significant positive correlation was evident between resistin levels and both total cholesterol ($r = 0.476$, $p = 0.001$) and LDL-cholesterol ($r = 0.293$; $p = 0.033$). A negative correlation was apparent between resistin and HDL-cholesterol levels ($r = -0.360$, $p = 0.011$). These correlations are summarized in Tables 2 and 3.

Discussion

Peripheral insulin resistance that develops in parallel with rises in maternal hormone levels during pregnancy is counteracted by changes in pancreatic Langerhans islets. Therefore, insulin synthesis increases, glucose-stimulated insulin secretion rises, and the beta cell mass grows [16]. The absence of such adaptations triggers the development of gestational diabetes [17]. In the present study, significantly elevated HOMA-IR levels, indicative of insulin resistance, and increased blood glucose, HbA1c, and insulin levels were evident in the GDM group (compared to the control group), supporting the idea that insulin resistance is involved in GDM development. Similarly, Gorkem *et al*. found higher insulin and HOMA-IR levels in pregnant women with GDM, and suggested that adipokine levels and insulin resistance were positively correlated [18].

Although the causes of maternal and fetal complications

attributable to GDM remain unclear, maternal hyperglycemia caused by reduced insulin sensitivity may represent the underlying mechanism [19]. However, hyperinsulinemia, hyperleptinemia, inflammation, oxidative stress, and hyperglycemia may play roles in the development of GDM-associated complications, even in patients in whom glycemic control is improved [20]. In the present study, total cholesterol levels were significantly higher in GDM patients but there were no significant between-group differences in HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, or triglyceride levels. Daghash *et al*. found that diabetics had high total cholesterol and triglyceride levels and low HDL-cholesterol levels [21]. Khan *et al*. found that cholesterol and triglyceride levels were significantly elevated in GDM patients, and speculated that it could play an important role in GDM pathophysiology [22]. In a meta-analysis, total and LDL-cholesterol levels were similar, whereas triglyceride levels were significantly higher in pregnancies complicated by GDM in all three trimesters [23]. The present results suggest that hypercholesterolemia, rather than hypertriglyceridemia, may explain the development of insulin resistance; endothelial dysfunction caused by increased cholesterol levels may trigger maternal and fetal complications of GDM.

Studies on the levels of small peptide hormones (such as resistin and adiponectin) expressed by fatty tissue or macrophages have yielded conflicting results. Resistin levels are associated with both obesity and insulin resistance in patients with type II DM. Several studies have reported higher resistin levels in pregnant women with GDM but others have reported similar or lower levels in GDM patients compared to normoglycemic pregnant women [24-26]. The present authors found that the resistin level was significantly higher in GDM patients than in controls. However, resistin levels were not correlated with the extent of insulin resistance, similar to a previous study that found no correlations between resistin or insulin levels and the HOMA-IR value in patients with GDM [27]. Vitoratos *et al*. reported a positive correlation between resistin levels and the HOMA-IR value, with resistin levels of GDM patients being notably higher at week 38 of gestation [28]. These differences in study results may be attributable to the use of different criteria to diagnose GDM, variation in serum storage protocols and assessment methods, and/or differences in the gestational week during which assessments were performed.

The present authors found a significant association between resistin levels and levels of triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol in GDM patients. Similarly, Takhshid *et al*. found significant positive correlations between resistin levels and atherogenic markers including triglycerides and each class of cholesterol; however, they did not find a significant relationship between resistin levels and the extent of insulin resistance [29]. The correlations between resistin levels and triglycerides and cholesterol levels suggest that resistin plays an important role in the regulation of lipid metabolism, and its presence may explain the dyslipidemia evident in GDM-associated pregnancies.

The present authors also found that adiponectin levels were significantly lower in GDM than normoglycemic patients, but were not significantly correlated with the extent of insulin resistance. Although several studies have reported that adiponectin levels are lower in pregnant women with GDM, others have reported that the levels are no different compared to controls [30, 31]. The present findings are in line with Pala *et al*., who reported that adiponectin levels were significantly lower in women with GDM-complicated than normoglycemic pregnancies, and were not correlated with insulin resistance [32]. Noureldeen *et al*. found that adiponectin levels in GDM women were similar in the second trimester but significantly lower in the third trimester, compared to controls [33]. Chen *et al*. reported that adiponectin gene expression was lower in the placentas of women with GDM; Williams *et al*. showed that sequential 1 ng/mL reductions in adiponectin levels were associated with a 20% increase in GDM risk, and an adiponectin level < 6.4 ng/mL at 13 weeks of gestation was associated with a four-fold increased risk of later GDM development [34, 35].

Conclusion

This study showed that serum levels of resistin were significantly higher and serum levels of adiponectin were significantly lower in pregnant women with GDM, compared to normoglycemic pregnant women. Also it was observed that the levels of neither marker correlated with the extent of insulin resistance, which is a key feature of GDM pathophysiology. The present results suggest that adipocytokine levels may predict GDM development during the second trimester. Further studies are required to confirm the roles played by adipocytokines in the pathophysiology of GDM-related complications.

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