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Adiponectin Level in Non-Pregnant Women, Pregnant Women without Diabetes and Pregnant Women with Diabetes

Yoon-Kyung Jo[1] and Jee-Aee Im[2,†]

[1]Department of Clinical Laboratory Science, Dongnam Health College, Suwon, 440-714, Korea.
[2]Sport and Medicine Research Center, INTOTO Inc., Seoul, Korea

Gestational diabetes mellitus (GDM) is a common complication during pregnancy and one of the main causes of adverse fetal-maternal outcomes. However, the pathogenesis of GDM has not been clearly stated. Adiponectin, an adipose tissue-derived plasma protein, is involved in regulation of insulin resistance and glucose hemostasis, and thus is a key modulator of insulin action and glucose metabolism. In this study, we investigated to compare serum adiponectin levels in pregnant women with diabetes, pregnant women who are without diabetes, and non-pregnant women, and to evaluate relationship between serum adiponetin levels and metabolic parameters. Forty-one pregnant women with diabetes, fifty-nine pregnant women without diabetes and forty non-pregnancy women were recruited. Adiponectin levels were significantly lower in pregnant women with diabetes when compared to non-pregnant women and pregnant women without diabetes. Pregnant women without diabetes at second trimester had lower adiponectin levels compared to non-pregnant women. Adiponectin was negatively correlated with BMI, fasting insulin, HOMA-IR, total cholesterol, and triglyceride. In conclusion, this study confirmed that the decreased level of adiponectin precedes the onset of abnormal glucose level during pregnancy and also normal pregnant women had lower adiponectin levels compared to non-pregnant women. This knowledge may help to identify strategies for lowering the occurrence of GDM in women who are at high risk of developing the disorder.

Key Words: Gestational diabetes mellitus, Adiponectin

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common complication during pregnancy and one of the main causes of adverse fetal-maternal outcomes (Sun and Yang, 2007). The most common theory is that GDM is caused by reduced insulin sensitivity combined with the anti-insulin hormones, which is increasingly secreted by the placenta during pregnancy, such as human placental lactogen, prolactin, glucocorticoid, and progesterone (Hod et al., 2003; Cunningham et al., 2005). GDM affects roughly 4~8% of pregnancies (Hadden, 1985; Beischer et al., 1996; Buchanan and Kjos, 1999). Women with a history of GDM have risk of developing type 2 diabetes mellitus (T2DM) (Henry and Beischer, 1991). Therefore, GDM can be a model of the early events in the natural history of T2DM (Kjos and Buchanan, 1991).

Recent studies have suggested the broad role of adipokines in the control of glucose metabolism during pregnancy. Adiponectin, an adipose tissue-derived plasma protein, is involved in regulation of insulin resistance and glucose hemostasis, and thus is a key modulator of insulin action and glucose metabolism (Mazaki-Tovi et al., 2005). It is found to be related with diabetes, obesity, coronary heart disease, obstructive sleep syndrome apnea (Zhang et al., 2007) and breast cancer (Hou et al., 2007). Previous studies have shown hypoadiponectinemia in pregnancies complicated by GDM, as compared to normal pregnancies (Worda et al., 2004; Cortelazzi et al., 2007). Pregnancy is a unique situation in which there is a physiological increase in

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†Corresponding author: Jee-Aee Im, Sport and Medicine Research Center, INTOTO Inc., 1304, ACE High-end Tower 2, 222-14, Guro 3-dong, Guro-gu, Seoul, Korea.
Tel: 82-2-6340-5533, Fax: 82-2-6340-5905
e-mail: jeaeim@hanmail.net

insulin resistance, because of several factors: the progressive increase in postprandial glucose and insulin response in late gestation, a 50% decrease in insulin-mediated glucose disposal, and a 200~250% increase in insulin secretion to maintain euglycemia in the mother (Malek et al., 2001; Ramos et al., 2003). As an increase in maternal adipose tissue is a common feature of normal gestation, detailed understanding of gestational changes in adiponectin is required to elucidate both physiologic role related to insulin action in the pregnant state. However, little has been reported about adiponectin expression in normal pregnant women.

In this study, we compared serum concentrations of adiponectin in normal pregnant women to those in non-pregnant women, also, compared serum adiponectin levels between pregnant women with diabetes and pregnant women without diabetes, and investigated the relationship between serum adiponetin levels and metabolic parameters.

MATERIALS AND METHODS

1. Subjects

Forty-one women with GDM were diagnosed by the American Diabetes Association criteria (American Diabetes Association, 2003). Diagnostic criteria for abnormal glucose metabolism during pregnancy are as follows: for all women with 50 g glucose challenge test ≥130 mg/dl, 75 g OGTT was performed and the cut-off value of fasting, 1, 2, and 3 hours glucose level after glucose intake were 95, 180, 155 and 140 mg/dl, respectively. GDM was diagnosed in those women who had two abnormal values out of the four results. Forty non-pregnancy women and fifty-nine non-GDM women were also recruited. Subjects with pre-existing diabetes and hypertension, pre-eclampsia, polycystic ovarian syndrome, chronic systemic or inflammatory diseases, or current use of corticosteroids were not included in this study. All subjects with GDM were not treated with insulin or any medications. All pregnancies were singletons and estimation of gestational age was based on routine ultrasonographic screening.

2. Anthropometric evaluation and Biochemical analyses

Body weight was measured to the nearest 0.1 kg on an electronic scale. Patients were weighed in light clothing without shoes. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Serum levels of fasting glucose, total cholesterol, HDL-cholesterol, and triglyceride levels were assayed using an ADVIA 1650 Chemistry system (Siemens, Tarrytown, NY, USA). LDL-cholesterol was calculated by Friedewald's formula, if serum triglyceride levels were below 400 mg/dL. Fasting insulin was measured by electrochemiluminescence immunoassay (Roche, Indianapolis, IN, USA). Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) index [(Insulin (μIU/ml) × Fasting blood glucose (mg/dl)/18) / 22.5]. Adiponectin (AdipoGen, Seoul, Korea) levels were measured by enzyme-linked immunosorbent assay.

3. Statistical analyses.

Data are expressed as mean ± SD. Variables such as fasting insulin, HOMA-IR, triglyceride and adiponectin levels were logarithmically transformed prior to statistical analysis to approximate a normal distribution. Baseline characteristics and adiponectin levels among three groups were compared using an analysis of variance (ANOVA). Pearson correlation coefficients were calculated to evaluate a relationship between adiponectin levels and study variables such as age, BMI, blood pressure, glucose tolerance indices, and lipid profiles. Significance was defined at the 0.05 level of confidence. All calculations were performed using the Statistical Package for Social Sciences software, version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The clinical characteristics of study subjects are shown in Table 1. Pregnant women with diabetes had significantly higher levels of BMI. However, there was no significant difference in age and blood pressure among the study

Table 1. Clinical characteristics of study subjects

Group	Age (years)	BMI[a] (Kg/m^2)	Weight gain (kg)	Systolic BP	Diastolic BP
Non-pregnant women (N=40)	30.5±5.4	20.5±2.2		111.4±11.3	67.2±10.6
Non-GDM [b] (N=59)	31.8±3.2	21.7±3.2	7.8±3.3	111.0±11.4	65.0±10.1
GDM (N=41)	30.9±3.5	23.0±3.7	6.7±4.0	117.8±14.3	71.0±12.3
P-value	0.27	<0.01	0.14	0.07	0.23

P-values are calculated by ANOVA. [a]Body mass index, [b]Gestational diabetes mellitus.

Table 2. Glucose and lipid parameters of study subjects

Group	Fasting glucose (mg/dl)	Fasting insulin[a] (μIU/ml)	HOMA-IR[a,b]	Total cholesterol (mg/dl)	Triglyceride[a] (mg/dl)	HDL-cholesterol[c] (mg/dl)	LDL-cholesterol[d] (mg/dl)
Non-pregnant women (N=40)	80.5±4.8	3.7±1.7	0.8±0.4	161.4±26.1	69.5±28.7	59.5±16.3	88.0±21.0
Non-GDM [e] (N=59)	76.0±9.3	6.3±3.1	1.2±0.7	225.2±34.3	177.4±58.6	69.5±14.1	120.3±28.7
GDM (N=41)	83.4±13.7	8.1±4.6	1.7±1.1	231.1±42.2	232.0±154.2	68.2±13.2	116.5± 30.2
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

P-values are calculated by ANOVA.
[a]Values have been analyzed after log-transformation, [b]Homeostasis model assessment insulin resistance, [c]High density lipoprotein cholesterol, [d]Low density lipoprotein cholesterol, [e]Gestational diabetes mellitus.

Table 3. Serum adiponectin levels in study subjects

Group	Adiponectin (mg/dl)
Non-pregnant women (N=40)	8.7±3.9
Non-GDM (N=59)	3.8±1.8[a]
GDM (N=41)	3.1±1.4[b,c]
P-value	<0.01

P-values are calculated by ANOVA.
[a]Non-pregnant women versus Non-GDM $P<0.01$, [b]Non-GDM versus GDM $P<0.05$, [c]Non-pregnant women versus GDM $P<0.01$

Table 4. Correlations between adiponectin[a] levels and various parameters

Variables	Adiponectin[a]	
	r	*P*
Age	-0.13	0.12
BMI[b]	-0.31	<0.01
Systolic BP	-0.04	0.67
Diastolic BP	-0.05	0.66
Fasting glucose	0.03	0.74
Fasting insulin[a]	-0.37	<0.01
HOMA-IR[a,c]	-0.33	<0.01
Total cholesterol	-0.23	0.01
Triglyceride[a]	-0.52	<0.01
HDL-cholesterol[d]	0.10	0.24
LDL-cholesterol[e]	-0.13	0.12

Coefficients (*r*) and *P*-values were calculated by the Pearson correlation model.
[a]Values have been analysed after log-transformation, [b]Body mass index, [c]Homeostasis model assessment insulin resistance, [d]High density lipoprotein cholesterol, [e]Low density lipoprotein cholesterol.

subjects. Weight gain at second trimester was not different between pregnant women with diabetes and pregnant women without diabetes, Pregnant women with diabetes had significantly higher levels of fasting glucose, fasting insulin, HOMA-IR, total cholesterol, and triglyceride than non-pregnant women or pregnant women without diabetes ($P<0.01$, respectively) (Table 2). Adiponectin levels were significantly lower in pregnant women with diabetes when compared to non-pregnant women and pregnant women without diabetes ($P<0.01$). Furthermore, the pregnant women without diabetes had lower adiponectin levels than non-pregnant women (Table 3). Adiponectin was negatively correlated with BMI ($r=-0.31$, $P<0.01$), fasting insulin ($r=-0.37$, $P<0.01$), HOMA-IR ($r=-0.33$, $P<0.01$), total cholesterol ($r=-0.23$, $P=0.01$), and triglyceride ($r=-0.52$, $P<0.01$). Whereas, age, SBP, DBP, fasting glucose, HDL-cholesterol and LDL-cholesterol were not correlated with adiponectin (Table 4).

DISCUSSION

In this study, we confirmed that serum adiponectin levels are significantly lower in pregnant women with diabetes

compared to the non-pregnant women and pregnant women without diabetes. The results of the present study are line with the findings of previous studies (Ranheim et al., 2004; Williams et al., 2004; Worda et al., 2004). Thus, it seems that GDM is associated with low production of adiponectin, an insulin sensitivity-related adipocytokine. Recent studies reporting that pregnancies with GDM are associated with low adiponectin levels during the 2nd trimester (Kinalski et al., 2005; Ategbo et al., 2006; Retnakaran et al., 2007). The variation of adiponectin level during pregnancy is just contrary to the levels of TNF-α and leptin, and the level of adiponectin is lower in GDM women than in controls, showing a decreasing trend with the progress of pregnancy. This suggests that the low level of adiponectin may induce severe insulin resistance before the onset of GDM and that adiponectin may be related to the pathogenesis of abnormal glucose metabolism during pregnancy. Earlier reports found in 968 pregnant women the same result that the adiponectin level was <6.4 mg/ml in 73% of GDM women and 33% of the controls (Williams et al., 2004). The risk of GDM in women with an adiponectin level of <6.4 mg/ml was 4.6 times as that in those with the level of >6.4 mg/ml. This finding was consistent with the fact that low level of adiponectin is the risk factor for T2DM. However, more studies are required to postulate this theory for GDM.

Furthermore, in the present study, pregnant women without diabetes at second trimester had lower adiponectin levels compared to non-pregnant women. Human pregnancy is characterized by metabolic changes that promote adipose tissue accretion in early gestation, followed by insulin resistance and facilitated lipolysis in late pregnancy (Ramos et al., 2003). Also, recent findings show that adiponectin secretion and adiponectin mRNA levels in white adipose tissue decline as gestation progresses, even in lean women, suggesting that there are pregnancy-associated factors that reduce adiponectin levels (Catalano et al., 2006). Differences in circulating adiponectin between pregnant and nonpregnant women have not been a focus of previous investigation, although some reports have considered other aspects of plasma adipenectin during pregnancy (Cseh et al., 2004; Williams et al., 2004). Williams's study (2004) found that lower plasma concentrations of adiponectin in early pregnancy were associated with increased risk of GDM; defining subjects with prepregnancy BMI >25 as overweight, they noted that GDM occurred significantly more often in overweight subjects. However, other studies show no significant change of maternal serum adiponectin during all trimesters of normal pregnancy (Mazaki-Tovi et al., 2007; Mastorakos et al., 2007) while others show progressive decrease (Catalano et al., 2006; Fuglsang et al., 2006). In the present investigation, adiponectin was inversely correlated with insulin, HOMA-IR, total cholesterol and triglyceride. All of these results are in good agreement with previous reports. Adiponectin, the most abundant of adipose-specific proteins, is known to modulate the action of insulin via activation of AMP-activated protein kinase in the muscle and the liver (Yamauchi et al., 2002). Serum adiponectin levels were found to correlate directly with whole-body insulin sensitivity in patients with obesity and T2DM (Weyer et al., 2001). The adiponectin level is also known to correlate with the level of insulin resistance, as well as HOMA-IR, in the various races (Weyer et al., 2001; Inoue et al., 2005). Adiponectin is negatively correlated to 2h plasma glucose and insulin concentrations of the oral glucose tolerance test in pregnancies with and without GDM (Tsai et al., 2005) and positively to insulin secretion sensitivity index only in pregnancies with GDM (Retnakaran et al., 2005). Im et al (2006) and Park et al (2004) confirmed that plasma adiponectin levels were inversely correlated with levels of BMI, fasting glucose, fasting insulin, HOMA-IR, triglyceride, and LDL-cholesterol, but positively correlated with HDL-cholesterol in normal population. These data are in line with the prediction of insulin sensitivity for both glucose and lipid metabolism by plasma adiponectin levels.

We recognize that the cross-sectional nature of this study precludes comment on causality in the levels of adiponectin in pregnant women with or without diabetes. Clearly, further study is warranted to elucidate the potential role of adiponectin in regulating insulin resistance and development of GDM.

In conclusion, this study confirmed that the decreased level of adiponectin precedes the onset of abnormal glucose level during pregnancy and also pregnant women had lower adiponectin levels compared to non-pregnant women. This

knowledge may help to identify strategies for lowering the occurrence of GDM in women who are at high risk of developing the disorder.

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