

Original Article



Adiponectin Concentration in Gestational Diabetic Women: a Case-Control Study

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Conflict of Interest

The authors declare that they have no competing interests.

ABSTRACT

Gestational diabetes mellitus (GDM) is an impaired fasting glucose condition during pregnancy. Adiponectin is a polypeptide hormone that is extensively released by adipocytes which regulates energy homeostasis and carbohydrate and lipid metabolism. In addition, adiponectin has antidiabetic and anti-inflammatory properties. The aim of our research was to study about the relationship of adiponectin levels to GDM and glucose intolerance. We selected 25 GDM women and 35 healthy pregnant subjects (18–46 years) who were screened between 24 and 28 weeks of gestation based on the result of oral glucose tolerance test (OGTT). We designed a case-control study and measured the concentrations of serum adiponectin and compared the concentrations between the groups. Serum adiponectin concentration was measured using enzyme-linked immunosorbent assay (ELISA). Sociodemographic data were collected by personal interview. Serum adiponectin concentrations were significantly lower in the subjects with GDM (5.10 ± 2.15 ng/mL vs. 7.86 ± 3.52 ng/mL, $p = 0.001$) than in healthy pregnant subjects. The mean concentration of fasting blood glucose was considerably lower in control subjects (86.9 ± 9.0 mg/dL vs. 175.9 ± 20.1 mg/dL, $p < 0.001$) in comparison to GDM subjects. Our findings showed that serum concentrations of adiponectin were significantly lower in gestational diabetic women and this may help to predict the risk of GDM.

Keywords: Adiponectin; Gestational diabetes; Glucose intolerance

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common pathologic situations in pregnancy which is characterized as glucose intolerance with onset during pregnancy and affects approximately 1%–14% of pregnant women [1]. GDM is associated with an increased risk of short- and long-term ill-health for both mother and offspring [2]. Moreover, Women with GDM are likely to develop type 2 diabetes up to 7 times more than women with normal glucose tolerance in pregnancy [3]. According to the prevalence of GDM, some earlier studies have recommended that the diagnosis and treatment of GDM can decline the future complications and be cost-effective [4,5]. Also, several factors can contribute to the incidence of GDM including, high maternal age, obesity, family history of GDM, high parity, and previous delivery of a macrosomic infant [6]. The incidence of this metabolic

dysfunction is increasing [7]. The International Association of Diabetes in Pregnancy Study Groups (IADPSG) has reported that the prevalence of GDM is as high as 17.8% [8]. The prevalence of GDM in Iran is about 4%–8% [9]. The failure of the β cell to release insulin is accounted for the insulin resistance during pregnancy and development GDM [10]. In addition, maternal adiposity may have an influence on insulin resistance that leads to GDM. Adiponectin is an adipocyte-derived protein and may have activities against atherosclerosis and insulin resistance [11].

Low concentration of adiponectin has been reported in GDM subjects during pregnancy [12]. Rentankaran et al. [12] have displayed a reduction of adiponectin concentration associated with insulin resistance during pregnancy, which would support that adiponectin contributes to the pathogenesis of insulin resistance. Adiponectin is physiologically active polypeptide hormone of which its positive effects appear by increasing adenosine monophosphate-activated protein kinase (AMPK) activity in the liver and skeletal muscles and decreasing glucose concentration by the inhibition of the gluconeogenic enzyme and stimulation of fatty acid β oxidation [13]. The adiponectin gene has been located chromosome 3q27 which is involved in diabetes development [14]. In addition, some studies have reported an inverse association between low adiponectin levels and insulin resistance, obesity and metabolic dysfunction [15]. Many studies reported that risk of GDM is 5–6 times higher in women with low adiponectin levels than women with high levels [16].

The concentration of adiponectin has been reduced in normal pregnancy possibly due to the decline of insulin sensitivity [17]. Therefore, the main purpose of our study was to observe changes in maternal adiponectin concentration during 24–28 weeks of gestation in both healthy pregnant women and women with GDM and to investigate the association of serum adiponectin levels with risk of GDM.

MATERIALS AND METHODS

This case-control study was conducted between April and December in 2016 among pregnant women who admitted in Shahid Beheshti Obstetrics and Gynecology Clinic. All participants were permanent residents of Isfahan. Case-control subjects were matched for maternal age, gestational age, and pre-pregnancy body mass index (BMI). The protocol of research was supported by the Institutional Review Board of Isfahan University of Medical Sciences (IRB No. 1394.3.964). The aims of this study were instructed to all participants and they signed informed consent letter.

Our study included 25 GDM women and 35 non-GDM subjects who were screened for GDM diagnosis at 24 and 28 weeks of gestation [18]. Diagnosis of GDM was confirmed if 2 or more of the values of glucose levels met the American Diabetes Association (ADA) standard by gynecologist: fasting ≥ 95 mg/dL, 1-hour ≥ 180 mg/dL, 2 hours ≥ 155 mg/dL, 3 hours ≥ 140 mg/dL [19]. The subjects of pre-pregnancy with BMI > 30 , aged less than 18 and more than 46, smokers, and having diagnosed with hypertension, preeclampsia, retinopathy, and nephropathy [18,20] were excluded.

All blood samples were collected from all pregnant women after at least 8 hours of fasting and allowed the serum to clot in a serum separator tube at room temperature. Then blood samples were centrifuged at nearly $1,000 \times g$ for 15 minutes and stored at -20°C . The

concentration of serum adiponectin was examined by an enzyme-linked immunosorbent assay (ELISA) Kit: Human adiponectin ELISA catalog NO. EX 0595T (8 × 12 divisible strips) from Boster Biological Technology (Pleasanton, CA, USA) was applied. The sensitivity of detection was less than 60 pg/mL.

Demographic data

From systematized questionnaire and medical records, we gained sociodemographic data of the subjects. The questionnaire completed carefully. Also, we noted the confounders factor for designing this questionnaire.

Sociodemographic data of the subjects including maternal age, parity, smoking status, family history of diabetes, family medical history, socioeconomic status, education level, and job were gathered by interview.

Anthropometric measurement

Height, weight, BMI, and blood pressure (BP) were measured when they admitted in the Gynecology and Obstetrics Center. Height, weight, and BP were evaluated at the antenatal visit. Height was measured by using standard wall-mounted tape and in standing position weight was measured by using a digital scale and the scale made by Seca GmbH (Hamburg, Germany) and the maximum capacity of weighting is 150 kg. BP was measured by a manual sphygmomanometer in sitting position and the arm laid at the level of the heart and the same arm was used for measurement at all antenatal visits. All mothers rested for 5 minutes before measurement. Pre-pregnancy BMI was calculated by dividing weight/height (kg/m²). All measurements carried out by an expert dietitian.

Statistical analysis

Statistical data were analyzed by SPSS version 20 (SPSS Inc., Chicago, IL, USA). All results were shown as a mean ± standard deviation. One-way analysis of variance (ANOVA) was applied for numerical variables and χ^2 test was performed to compare categorized variables. Student's t-test was utilized to compare the means when data were in a normal distribution, and Mann-Whitney U test was used for quantitative variables that were not normally distributed. Association between continuous variables was calculated with Pearson correlation coefficient. If p values were < 0.05, the results were considered significant. Mann-Whitney U test showed that the parity and family size were not normally distributed.

RESULTS

A total of 60 pregnant women were registered in this study. Twenty-five of the subjects were GDM (41.6%) and 35 of them were healthy pregnant subjects (58.3%). The demographic and anthropometric characteristics of case and control subjects are presented in **Table 1**. Our findings did not show any significant differences in the weight before pregnancy, height, parity, the educational level, socioeconomic level, and the number of family member between 2 groups. The data showed that 2.4% of cases had the previous history of GDM.

We also showed the distribution of socioeconomic characteristics like educational level, job and housing situation among GDM and healthy pregnant subjects. Mann-Whitney test (educational level) and χ^2 test (job and housing situation) did not show any considerable difference between GDM and healthy pregnant subjects **Table 2**.

Table 1. Demographic and anthropometric characteristics of GDM and healthy pregnant subjects

Variable	GDM	Healthy	p value
Age, yr	26.16 ± 3.00	26.40 ± 2.60	0.784
Pre-pregnancy BMI, kg/m ²	22.98 ± 1.60	22.81 ± 3.60	0.882
Weight before pregnancy, kg	61.00 ± 62.00	60.00 ± 89.00	0.887
Gestational age, wk	27.64 ± 2.10	27.54 ± 1.90	0.858
Parity	1.76 ± 0.52	1.85 ± 0.69	0.557
Education level	2.28 ± 0.97	2.65 ± 1.05	0.165
Family size	3.00 ± 0.54	3.00 ± 0.69	0.412

Values are presented as mean ± standard deviation.
 GDM: gestational diabetes mellitus.

Table 2. Distribution of socioeconomic characteristics among GDM and healthy pregnant subjects

Variable	GDM	Non-GDM	p value
Education level	Bachelor degree	11.4	0.153
	Associate degree	42.9	
	Diploma degree	14.3	
	Primary school	31.4	
Job	Employee	71.4	0.220
	Housewife	28.6	
Housing situation	Occupant	51.4	0.386
	Householder	48.6	

Values are presented as percentage.
 GDM: gestational diabetes mellitus.

Table 3. Serum concentration of adiponectin and fasting blood glucose between GDM subjects and healthy pregnant subjects

Serum	GDM	Healthy	p value*
Adiponectin, ng/mL	5.1 ± 2.2	7.9 ± 3.5	0.001
Fasting blood glucose, mg/dL	175.9 ± 20.1	86.9 ± 9.0	< 0.001

Values are presented as mean ± standard deviation.
 GDM, gestational diabetes mellitus.

*p < 0.05 considered significant by t-test.

Table 4. The association between serum adiponectin (ng/mL) and BMI in case and control subjects

BMI, kg/m ²	Adiponectin, ng/mL		p value
	GDM	Healthy	
< 25	5.57 ± 2.03	8.11 ± 3.50	0.005 [†]
≥ 25	2.65 ± 0.19	7.25 ± 3.69	0.003 [†]
p value	0.01 [†]	0.50 [†]	0.002*

BMI, body mass index; GDM, gestational diabetes mellitus; ANOVA, analysis of variance.

*p < 0.05 considered significant by ANOVA test; [†]p value obtained by t-test.

The mean concentration of serum adiponectin was significantly lower among GDM (5.10 ± 2.15 ng/mL) groups compared to healthy subjects (7.86 ± 3.52 ng/mL) (p = 0.001). Also, the concentration of fasting plasma glucose was significantly lower in healthy pregnant women (86.9 ± 9.0 mg/dL vs. 175.9 ± 20.1 mg/dL, p < 0.001) than GDM subjects. The biochemical data in both groups are shown in **Table 3**.

We classified pre-pregnancy BMI into 2 categories: BMI ≥ 25 and BMI < 25, and analyzed the association between adiponectin levels and pre-BMI for cases and control subjects. One-way ANOVA showed that the mean concentration of adiponectin between 4 groups was statistically significant (p = 0.002, **Table 4**)

We applied logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate logistic regression analysis showed that adiponectin levels were significantly related to the risk of GDM. Each unit increase in adiponectin level reduced the odds of GDM by 32% (OR, 0.68; 95% CI, 0.52–0.89; p = 0.004).

DISCUSSION

In our study, the levels of serum adiponectin were obviously lower in GDM subjects than healthy pregnant women and related adversely to blood glucose level. Saini et al. [21] showed that adiponectin concentration was lower in pregnant women with GDM and found an inverse relationship between adiponectin level and fasting blood sugar. Also, we examined the effects of adiponectin concentration and Pre-pregnancy BMI and found that the risk of GDM was an independent factor of BMI. Hedderson et al. [22]. revealed that the risk of GDM increased in subjects who had BMI < 25 and having low levels of adiponectin. Results of the study by Pala et al. [23] were similar to ours; adiponectin levels were significantly lower than the control group. Williams et al. [24] showed that each μg per mL decline in maternal adiponectin concentration increased the risk of GDM about 20%. It was demonstrated that maternal adiponectin was higher in normal pregnant women [25,26]. Consistent with our results; Tsai et al. [27] reported that the concentration of serum adiponectin was extremely lower in GDM group. In addition, they showed a negative relationship between serum adiponectin levels and development of GDM. Williams et al. [24] revealed that the reduction in maternal adiponectin levels was an indicator of 4.6 times increased chance of GDM. Meller et al. [28] showed that the concentration of adiponectin was reduced in GDM subjects. A study on 180 pregnant women revealed that hypoadiponectinemia correlated with GDM [12]. A systematic review and meta-analysis have demonstrated a significant decline in adiponectin levels in GDM group vs. control group [29]. Ranheim et al. [30] also proposed that pregnant women with GDM had lower levels of adiponectin. This result is compatible with our findings. Lain et al. [31] showed that cases with the lowest quartile of adiponectin were at higher risk of GDM.

The evaluation of adiponectin concentration on 445 pregnant women was done in the first trimester then exhibited a decline in adiponectin levels and positive relationship with GDM in the mid-pregnancy, suggesting this hormone may use as an indicator of GDM [32].

Adiponectin is a polypeptide cytokine which secreted by adipose tissue and it seems to have a critical role in whole body metabolism and also has cardioprotective properties [33-35]. Even though the mechanisms by which adiponectin may have positive effects on tissues are not completely clear but it seems when adiponectin binds to receptors and protein kinase cascade was activated, which leads to enhance fatty acid oxidation and also prevent gluconeogenesis [36,37]. It is suggested that adiponectin affects carbohydrate and fat metabolism, its concentration at 24–28 weeks of gestation is affected by GDM which is related to hormonal changes during pregnancy. This may be that adiponectin's secretion can be induced by developing insulin resistance in the course of pregnancy [38,39].

Some studies have shown an association between adiponectin and lower levels of fasting glucose, triacylglycerol, low-density lipoprotein (LDL) cholesterol, and higher high-density lipoprotein (HDL) concentration [40,41]. The rate of coronary vascular disease was doubled in male subjects with hypoadiponectinemia, possibly showing anti-atherogenic properties of adiponectin [42].

The multifactorial role of adiponectin in obesity, metabolic syndrome, GDM and relationship between hypoadiponectinemia and those complications have indicated by some authors [32,43,44]. The study performed on Caucasians and Pima Indians showed the inverse relationship among the fasting glucose level, insulin level, percentage of body fat and waist-to-hip circumference with circulating adiponectin concentration.

Insulin resistance may lead to hypoadiponectinemia in obesity and type 2 diabetes [44]. Maeda et al. [45] demonstrated that the removal of fatty acid from plasma was reduced in adiponectin knockout mice.

A previous study, which performed on rhesus monkeys showed a drop in adiponectin levels and found an association between hypoadiponectinemia and insulin resistance [46]. In another study, administration of adiponectin in rodent improved glucose regulation and lipid oxidation [40,41].

Our results were in conflict with several previous studies [47-50], which worth mentioning. For example, Saucedo et al. [47] demonstrated that there was no difference in concentration of adiponectin between women with GDM and normal pregnant women. Also Matyjaszek-Matuszek et al. [49] indicated that there was no significant difference in term of adiponectin level in GDM groups vs. non-GDM.

However, a number of studies show that significant differences exist, paradisi et al, display no considerable difference in concentration of adiponectin in GDM and control groups. This difference maybe explains by small numbers of participants or a different method of adiponectin measurement [51].

In our research, after matching for maternal age, gestational age and BMI, we found that women with the lowest level of adiponectin are at higher risk of GDM. Strengths of our research were the strong capacity to control the inclusion and exclusion criteria by complete interview. Moreover, blood samples of all participants were collected and stored in the same situation and all participants were instructed about the condition before the test. Additionally, our study had a strong capacity to exclude subjects with pre-gestational diabetes. All biochemical and clinical assessments were carried out by the systematized Method.

Also, we know that our investigation has some drawbacks which should be commented. The most important one is the small numbers of participants. Also, we did not have information about the levels of adiponectin before pregnancy. Moreover, the concentration of adiponectin is changed by many factors like placenta's hormone levels but we were not able to assess it during pregnancy [52]. Another restriction of the current study was lack of information about percent body fat, waist circumference, and physical activity.

In conclusion, in this case-control survey, we evaluated the concentration of adiponectin in mid-pregnancy in pregnant women with GDM and healthy pregnant women. We showed that subjects with GDM had significantly lower concentration of serum adiponectin and a higher level of fasting blood glucose.

This finding may propose that the adiponectin is used as a diagnostic tool for detecting metabolic dysfunction like GDM. More investigations with a larger sample are necessary to recognize the role and mechanism of adiponectin in GDM.

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