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Resistin, adiponectin and visfatin; can adipocytokines predict gestational diabetes mellitus and early post partum metabolic syndrome?

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Abstract

Background: We investigated the association between three adipocytokines: resistin, adiponectinl, visfatin, and gestational diabetes mellitus (GDM) and early postpartum metabolic syndrome.
Methods: In a case-control study, 70 GDM patients and 76 healthy pregnant women were recruited from Endocrinology and Metabolism Research Center GDM Clinic, Tehran, Iran. Circulatory resistin, adiponectin and visfatin were measured in week 24–28th of pregnancy. All the participants followed until 6-12 weeks after delivery.
Results: The concentrations of all three adipocytokines were significantly different between GDM patients and healthy pregnant women. Visfatin concentration was higher in GDM patients (10.62±8.12 *vs.* 4.30±4.00 ng/ml, P< 0.01). Adiponectin concentration was lower in GDM patients (9.07±5.10 *vs.* 13.45±8.53 µg/ml, P<0.01). Resistin concentration was also lower in GDM patients (5.04±2.03 *vs.* 10.40±3.63 ng/ml, P<0.01). Postpartum follow-up showed that women developing metabolic syndrome had significantly lower adiponectin and resistin concentrations during pregnancy; however, visfatin concentration measured during pregnancy had no relation with postpartum development of metabolic syndrome. Nonetheless, after adjustment for age and pre-pregnancy BMI, logistic regression analysis did not show independent relation between adiponectin and resistin with development of postpartum metabolic syndrome.
Conclusion: Our results indicate that adipocytokines may associate with GDM and postpartum metabolic syndrome. However, the efficacy of their measurement during pregnancy as a predictor of postpartum metabolic syndrome is controversial.

Keywords: Gestational diabetic mellitus, Adipokines, Visfatin, Resistin, Adiponectin, Metabolic syndrome

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Introduction

Pregnancy is accompanied with physiological insulin resistance that fades away after delivery (1). In women with suboptimal beta-cell function, the increase in insulin secretion may not be sufficient to compensate the increased insulin resistance, resulting in gestational diabetes mellitus (GDM) (2). GDM is glucose intolerance that initiates or been primarily recognized during pregnancy and affects roughly 4-8% of all pregnancies (3,4).

In addition to the adverse outcomes associated with this complication, a history of GDM predisposes women to developing type 2 diabetes mellitus (DM2) with an 8–50% increased risk within 5 years following pregnancy. Nonetheless, GDM increases the long-term risk of developing hypertension and dyslipidaemia, and therefore atherosclerosis and coronary heart disease (5, 6).

Recently, researchers have been focused on several adipose tissue-related mediators implicated in the pathogenesis of insulin resistance (7). Adipose tissue now been known as a powerful endocrine organ due to production of adipokines, that are required for a number of physiological and metabolic processes (8). Dysregulation of adipokines production and/or secretion has been implicated in the pathophysiology of type2 diabetes mellitus, a metabolic complication closely related to gestational diabetes mellitus (GDM) (9). These bioactive substances include adiponectin (10), visfatin (11), resistin (12). Recently, several studies investigated the role of adipokines in the regulation of insulin resistance during pregnancy (1).

Adiponectin emerges from adipocyte and has insulin sensitizing properties (13). This adipokine has anti-diabetic, anti-atherogenic (14), anti-inflammatory (15) and angiogenic (16) properties. Circulating adiponectin is reduced in patients with obesity, coronary artery disease, and type2 diabetes (14). The role of this hormone has been identified in physiological adaptation to normal pregnancy and obstetric complications such as gestational diabetes (15). The results of some studies showed the role of adiponectin in the physiology of insulin resistance during pregnancy (1,13). Previous studies have shown hypoadiponectinemia during the 2nd trimester of pregnancies complicated by GDM, as compared to normal pregnancies (17), But still now there are some controversial findings about the change of maternal serum adiponectin during normal pregnancy (1). On the other hand, results of recent study demonstrated that difference in ethnicity can affect plasma concentrations of adiponectin in pregnancy and may be a potential factor contributing to the increased risk of diabetes (18).

Another adipokine which has recently described is visfatin that seems to play an important role in regulation of glycemic homoeostasis (19). This adipokine with diabetogenic properties has been implicated in the pathophysiology of insulin resistance in patients with obesity and type2 diabetes mellitus as well as altered fetal growth (20). Findings of previous studies shown that circulating visfatin levels were elevated in patients with intrauterine growth retardation (21); whereas, comparison between women with GDM and healthy pregnant controls demonstrated both decreased and increased visfatin concentrations (22).

Resistin is another adipokine which seems to play a key role in the regulation of insulin resistance (23). During human pregnancy, resistin is expressed and secreted by the placenta (24) and resistin levels increase by the third trimester (25). There are few findings about its circulating level during pregnancies which be complicated by gestational diabetes (26).

Early postpartum screening studies provide an opportunity to decrease the risk of developing diabetes in women with history of GDM (27). Women with impaired glucose tolerance or postpartum metabolic syndrome have the highest risk of developing diabetes (28). The results of a previous study in Iranian women showed that 23% of women with previous history of GDM face to impair glucose tolerance (IGT) or diabetes later in the life (29). Adipokine levels during pregnancy may be useful predictors of developing postpartum metabolic syndrome among women with GDM, so we designed present study to investigate the association between plasma levels of adiponectin, resistin and visfatin with GDM and the association between serum

adipokines levels and risk of postpartum metabolic syndrome.

Methods

Study design and population

In a cross-sectional study, pregnant women who sought prenatal care during the first half of their pregnancies were recruited from prenatal clinic of one of the university hospitals affiliated to Tehran University of Medical Sciences. Previous known history of diabetes mellitus was the exclusion criterion. The study protocol was approved by ethics committee of Endocrinology and Metabolism Research Center (EMRC). After taking written informed consent, participants' information was collected, using a standard questionnaire that included patient demographic data, information regarding current pregnancy including gestational age according to the date of the last menstrual period confirmed by ultrasound in early pregnancy, medical history, infections and medications, past medical, obstetrical and family histories. Primary screening was done simultaneous with the first visit for prenatal care in high risk pregnant women. Risk factors included: age ≥ 30 years, pre-gestational body mass index (BMI) ≥ 27 kg/m2, polyuria, glucoseuria, proteinuria, parity ≥5, previous history of gestational diabetes, family history of diabetes mellitus, history of macrosomia, fetal death with no apparent cause, recurrent miscarriages and malformation in the previous pregnancies. Rest of the participants was studied via universal screening for GDM between 24th and 28th weeks of pregnancy using standard protocol.

Study protocol

The screening for diagnosis of GDM was performed using an OGCT-50g at 24-28th week of gestation with a cut-off value of 130 mg/dl one hour after glucose loading under non-fasting condition. Those with plasma glucose levels ≥130 mg/dl (7.2 mmol/l) were diagnosed as GDM if they had an impaired OGTT-100g. The diagnosis of gestational diabetes was confirmed when two or more measurements were equal or greater than 95, 180, 155, and 140 mg/dl respectively in fasting condition and one, two and three hours after taking oral glucose, as been explained by O'Sullivan & Mahan (30).

Laboratory measurements

Plasma glucose levels were measured using the glucose-oxidase enzymatic method, with a coefficient of variation (CV) <5%. The levels of insulin and c-peptide were measured at fasting. Insulin levels were detected via RIA using a Biosorce kit (Denmark); which inter-assay and intra-assay coefficients of variation (CV) were 8.2% and 7.1%, respectively. Circulatory resistin, adiponectin and visfatin were measured in 24–28th weeks of pregnancy. HbA1C measured using HPLC (High pressure liquid chromatography) exchange Ion method (DS5 England) Serum hsCRP was determined by immunoturbidometric assay (High sensitivity assay, by Hitachi 902).

Serum visfatin concentration was determined by ELISA method (Human visfatin ELISA kit, AdipoGen Pharmaceuticals, Belmont, Seoul, Korea), minimum detectable concentration was 30 pg/ml, Intra CV was 4.3 % and Inter CV was 7.5 %. Serum adiponectin concentration was determined by ELISA method (Human adiponectin ELISA kit, AdipoGen Pharmaceuticals, Belmont, Seoul, Korea), minimum detectable concentration was 100 pg/ml, Intra CV was 5.15 % and Inter CV was 3.82 %. Plasma resistin concentrations were determined with Human Resistin ELISA (LINCO Research Inc, St Charles, MO, USA), following the recommendations of the manufacturer. The sensitivity of the assay was 0.095 ng/ml and the inter- and intra-assay coefficients of variation were 5.9% and 5.8%, respectively.

Examinations after delivery

All participants followed until 6-12 weeks after delivery and fasting blood samples were collected for measurement of glucose. Total cholesterol (TC), high density lipoprotein (HDL) cholesterol and triglyceride (TG) levels were determined. Dyslipidemia was defined as the presence of abnormal levels in at least one of the mentioned lipid profile. Concerning American Diabetes Association (ADA) criteria (31), Fasting Blood Sugar (FBS) ≥126 mg/dl was considered as diabetes mellitus. The metabolic syndrome was defined according to WHO criteria (32).

Statistical analysis

Chi-square test was used to compare the frequency of variables and restrictive factors between two groups. To evaluate the association between adipokines concentrations and metabolic syndrome, regression models were used. We also explored the possibility of a non-linear relation between serum adipokine concentrations and the risk of GDM by fitting a multivariate logistic regression model that implemented the generalized additive model method as previously described. The level of significance was set at a probability of ≤0.05 for all tests.

Results

One hundred forty-six pregnant women participated in this study which 47% had gestational diabetes mellitus (GDM) (n=70) and resting were healthy pregnant women (n=76). The GDM group had higher mean age, pre-gravid BMI, and parity as compared with non-GDM group (Table 1). Fasting glucose and total cholesterol were significantly higher and HDL was lower in the GDM patients. The concentrations of all three adipocytokines were significantly different between GDM patients and healthy pregnant women. Visfatin concentration was higher in GDM patients (10.6±8.1 *vs.* 4.3±4ng/ml, P<0.01). Adiponectin concentration was lower in GDM patients (9±5.1 *vs.* 13.4±8.5 µg/ml, P<0.01). Resistin concentration was also lower in GDM patients (5±2 *vs.* 10.4±3.6 ng/ml, P<0.01).

Concerning metabolic syndrome at 6-12 weeks after pregnancy, 24% revealed classic syndrome.

In comparison, 32.6% of women with GDM had metabolic syndrome; whereas, 10.5% of normal pregnancies revealed syndrome (P=0.001). Postpartum follow-up showed that women who developed metabolic syndrome had significantly lower levels of adiponectin and resistin during pregnancy. However, visfatin concentration measured during pregnancy had no relation with postpartum metabolic syndrome. Indeed, logistic regression analysis did not show relation between adiponectin and resistin and development of postpartum metabolic syndrome, independent of age and BMI.

Table 1. Clinical characteristics and biochemical markers of pregnant women

characteristics	GDM (n=70)	Normal (n=76)
Age (years) §	32±5	27±7
Parity§	1.4±0.03	0.3±0.5
BMI-pre pregnancy (kg/m2)§	28.2±4.1	25.1±3.7
Fasting glucose (mg/dl) §	101.3±28.8	75.6±6.3
Total cholesterol(mg/dl)§	210±30.9	205.8±43.1
LDL (mg/dl)	110.9±23.2	113.2±27.8
HDL (mg/dl)§	52.7±8.8	53.4±14.8
TG (mg/dl)	177.3±90	183.8±81.7
CRP (mg/l)	3.4±4.4	2.8±2.2
HBA1C (%)	5.5±1.8	5.4±1.7
Adiponectin(µg/ml)§	9±5.1	4.30±4
Visfatin (ng/ml)§	10.6±8.1	4.3±4
Resistin (ng/ml)§	5±2	10.4±3.6

* Data presented as mean±SD

§ P-value between GDM and normal groups was significant (P<0.05).

Table 2. Baselines characteristics and biochemical markers after pregnancy

Variable	Women with MS**	Women without MS
Age (years)	31±5	30±6
BMI (kg/m2)§	32.6±5.2	28.6±3.9
fasting glucose (mg/dl)§	129.5±40.6	93.7±10
Total cholesterol (mg/dl)	228.2±23.7	188.6 ±23.5
LDL (mg/dl)	122.2±12.5	93±13.6
HDL (mg/dl)	48.6±7.4	55.50±8
TG (mg/dl)	210.2±91.8	138±81
CRP (mg/l)	4±5.2	3.4±5.8
HBA1C (%)§	5.2±2.2	5±0.5
Adiponectin (µg/ml)	6.9±2.2	9.8±5.3
Visfatin (ng/ml)	11.5±7.8	11.2±9
Resistin (ng/ml)	4.4±2.2	5.5±1.5

* Data presented as mean±SD
** Metabolic syndrome
§ P-value between MS and normal groups was significant (P<0.05)

Discussion

A vast majority of evidences have focused on the role of adipose tissue in the initiation and development of insulin resistance in non-pregnant and pregnant women which support the role of adipokines in the physiology and pathophysiology of insulin resistance during pregnancy. The responsible mechanism for the development of diabetes is unclear; but, obesity-related factors are strongly implicated (33).

Some studies have been demonstrated difference in circulating adiponectin levels between pregnant and non-pregnant women. These findings present adiponectin as a physically influential hormone which involves in hormonal changes during pregnancy; also, there are several findings regarding differences between normal pregnant women and gestational diabetics (15). Lower concentrations of adiponectin have consistently been reported in patients with gestational diabetes as compared to healthy pregnancy (15, 34). We also found a lower concentration of adiponectin in women with GDM compared to normal pregnant women.

Our finding of lower plasma resistin concentrations in comparison between normal pregnant women and patients with gestational diabetes are consistent with results of Megia *et al.* (35); which, this difference indicates the association between adipokines and insulin resistance during pregnancy and development of GDM throughout this period and propose that circulating resistin changes may be associated with the pregnancy-induced insulin resistance (26).

Our finding on elevated visfatin in women with GDM is consistent with report of Krzyzanowska *et al.* (22) and inconsistent with reports by Akturk (36) and Telejko (37). The findings of previous studies demonstrated that recombinant human PBEF treatment of human fetal membranes and amniotic epithelial WISH cells cause a significant increase in three key inflammatory cytokines (38); which may be involved in GDM pathogenesis in this way.

Recently performed study investigated the early postpartum metabolic syndrome in women with gestational diabetes mellitus (GDM) to determine predictive factors for subsequent diabetes (28) revealed women with impaired glucose tolerance or "prediabetes" has the highest risk. As well as, earlier studies have demonstrated that the production of some adipokines is affected during obesity, type 2 diabetes mellitus and metabolic syndrome

(39). Our finding showed that decrease in resistin and adiponectin plasma concentrations during pregnancy accompany the higher risk of later developing metabolic syndrome. Adiponectin is released by adipose tissue; so, an increase in fat mass leads to down-regulation of adiponectin (40); these finding suggest that adipose tissue may exert a negative feedback on adiponectin production. Mc Lachlan (15) reported that adiponectin levels don't change from pregnancy to postpartum . Also, Vitoratos *et al.* (41) and Winzer *et al.* (42) postpartumly determined adipokine levels in normal pregnant women and women who been diagnosed with gestational diabetes mellitus (GDM) and revealed adiponectin was significantly lower in women with GDM than in controls during pregnancy and postpartum.

Although we found an association between lower resistin and adiponectin plasma concentrations and postpartum developing metabolic syndrome, it was removed after adjustment for age and BMI; nonetheless, after adjusting for potential covariates, there was no significant association. High fat mass and adipocyte hypertrophy in pregnant women may explain decrease in adiponectin during GDM afflicted pregnancies.

In conclusion, our data provides evidence that plasma resistin and adiponectin decrease, and circulating visfatin increase in women with GDM as compared to healthy pregnancy women. Also, our results demonstrated the association between postpartum metabolic syndrome and decreased levels of resistin and adiponectin; however, it was not independent of BMI and age.

One of the limitations of current study was small sample size, but to our knowledge, this study is the first one that beside simultaneous measuring three adipokines, suggests that proposed factors involved in insulin resistance pathogenesis during pregnancy and after delivery, may predict the vulnerability of further developing metabolic syndrome and diabetes.

Conclusively, more studies are warranted to elucidate the precise mechanisms involved in pathophysiology of GDM adverse outcomes.

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Disclosure Statement

No author has any conflict of interest.

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