Resistin may not associate with gestational diabetes mellitus although insulin resistance

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Summary

Objective: Resistin is a potent regulator of glucose homeostasis which is thought to oppose the action of insulin in peripheral tissues. The aim of this study was to determine changes in resistin levels in gestational diabetes mellitus (GDM). *Material and Method:* Twenty women with GDM (mean age 32.28 ± 5.01 years old, and gestational age 32.2 ± 4.8 weeks) matched with 22 non diabetic pregnant women (NGDM) (mean age 30.30 ± 4.5 years old, and gestational age 34.8 ± 3.5 weeks) were included in the study. Body mass index (BMI) was calculated. Serum resistin levels were measured and insulin resistance was calculated with HOMA-IR. The Mann Whitney U test was used for statistical analysis. *Results:* BMI was 33.8 ± 6.2 kg/m^2 in the GDM group and 28.4 ± 6.2 kg/m^2 in the NGDM group ($p = 0.04$). Serum resistin levels were 8.7 ± 2.1 ng/ml in the GDM group and 8.1 ± 2.5 ng/ml in the NGDM group. Mean resistin level was not different between the two groups. HOMA-IR in GDM was higher than in the NGDM group (13.2 ± 12.2 vs 5.8 ± 5.1, $p = 0.02$, respectively). *Conclusion:* Although mean BMI in GDM was higher than in NGDM and insulin resistance in GDM was more marked than in NGDM, serum resistin levels in GDM were not found to be any different from NGDM.

Key words: Gestational diabetes mellitus; Resistin.

Introduction

Pregnancy is associated with substantial changes in maternal metabolism. Increasing concentrations of circulating diabetogenic hormones secreted by the fetoplacental unit, the enhanced maternal lipolysis and the increased maternal adiposity have been considered as major contributors of insulin resistance. The development of insulin resistance in late gestation is a process common to all human pregnancies [1].

The physiological mechanism of increasing insulin resistance during the pregnancy course and GDM has not been understood exactly. Numerous signalling molecules are released from white adipose tissue and placenta [2].

One of these bioactive peptides, collectively termed adipokines, is resistin, which is involved in mechanisms leading to insulin resistance [3]. Resistin is also mainly produced by monocytes and macrophages and to a lesser extent by adipocytes [4].

On the molecular level, resistin in vitro inhibits glucose uptake in myocytes by decreasing the activity of glucose transporter-4. In rodent models, administration of resistin decreases insulin-mediated glucose uptake, causing hepatic insulin resistance. However, the exact role of resistin in energy metabolism is still uncertain in humans [5, 6].

In addition, a recent animal study has shown that the administration of resistin to rodents increases insulin resistance, whereas the use of antiresistin protein could partially reverse this phenomenon [7]. In humans, however, this issue remains controversial [8].

The aim of the study was to evaluate the association of serum resistin levels with insulin resistance in gestational diabetes mellitus and to determine the possible contribution of resistin in metabolic changes of pregnancy.

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Materials and Methods

Twenty patients with gestational diabetes mellitus (GDM) and 22 patients without gestational diabetes mellitus (NGDM) were included in the study. The diagnosis of GDM was made according to the American Diabetes Association (ADA) when fasting glucose levels were greater than 95 mg/dl, and the second hour postprandial glucose levels were greater than 130 mg/dl. All patients with GDM were receiving insulin treatment at the time of the study.

Twenty-two pregnant women with NGDM, similar in terms of maternal (years) and gestational ages (weeks), were included as a control group. NGDM women had normal fasting glucose and second hour postprandial glucose levels. None of the NGDM patients had a family history of diabetes or took any medications except for minerals and vitamins.

Diagnosis of the pregnancy was made on the basis of history of missed menstruation and positive HCG (human chorionic gonadotropin) testing. Gestational age was calculated according to the last menstruation and confirmed with ultrasound examination.

None of the patients with GDM or NGDM had any systemic disease. Liver and renal functions of all patients were within normal limits and negative for islet cell antibodies; moreover they did not have any manifestations of infections, obesity, hypertension and hyperlipidemia.

Patients who had diabetes mellitus, infectious disease, chronic autoimmune disease, premature membrane rupture, polyhydramnios or oligohydramnios were excluded from the study. Written informed consent was obtained from all patients.

Body mass index (BMI) of the pregnant women was calculated with the following formula: W(kg)/H(m2) (W: weight, H: height). The homeostasis model assessment-insulin resistance index (HOMA-IR) was calculated with the following formula: HOMA-IR = fasting insulin (mU/l) x fasting glucose (mmol/l) /22.5 [9].

Sample collection

Fasting blood samples were taken from all women before delivery and all samples were centrifuged at 1500 g for 15 min.

Serum was stored at -80ºC until assay. Serum resistin levels were determined with ELISA (BioVendor-Laboratory Medicine; Czech Republic). Serum insulin, HbA1c and plasma glucose levels were measured with chemiluminescent (Roche E-170; USA), photometric (Cobas ntegra Roche; USA) and automated biochemical analyzer, respectively.

Data analysis

Mean and standard deviations (SD) were calculated for continuous variables. One-way ANOVA was used to calculate group characteristics. The Mann Whitney U test was used to evaluate the relationship between variables; p values < 0.05 were considered significant.

Results

Mean maternal age of the 20 patients with GDM and 22 patients with NGDM was 32.28 ± 5.01 and 30.30 ± 4.5 years old, respectively.

Descriptive statistics of BMI, resistin levels, HOMA-IR, gestational age, and HbA1c are presented in Table 1.

Gestational age did not differ in the GDM group (32.2 ± 4.8 weeks) from the NDGM group (34.86 ± 3.5 weeks).

BMI of the patients with GDM and NGDM was 33.8 ± 6.2 kg/m^2 and 28.4 ± 6.2 kg/m^2, respectively. However mean values of BMI were statistically different between the two groups (p = 0.04). Serum resistin levels were 8.7 ± 2.1 ng/ml in the GDM group and 8.1 ± 2.5 ng/ml in the NGDM group. The difference between the GDM and NGDM groups was not statistically significant in terms of mean resistin levels.

HOMA-IR in the GDM group was higher than in the NGDM group (13.2 ± 12.2 vs 5.8 ± 5.1, p = 0.02, respectively).

$HBA1_c$ value was (6.08% ± 1.9) higher in the GDM group than in the NGDM (5.01% ± 0.5) group (p = 0.04).

Table 1. — *Clinical characteristics*.

	GDM (n = 20)	NGDM (n = 22)	Significance
Maternal age (years)	32.28 ± 5.0	30.30 ± 4.5	NS
Gestational age (weeks)	32.2 ± 4.8	34.86 ± 3.5	NS
BMI (kg/m^2)	33.8 ± 6.2	28.4 ± 6.2	p = 0.04
Resistin (ng/ml)	8.7 ± 2.1	8.1 ± 2.5	NS
HOMA-IR	13.2 ± 12.2	5.8 ± 5.1	p = 0.02
$HbA1_c$ (%)	6.08 ± 1.9	5.01 ± 0.5	p = 0.04

BMI: Body mass index. NS: Non significant. HOMA-IR: Homeostasis model assessment-insulin resistance index.

Discussion

In 2-8% of pregnant women, the insulin response is inadequate and thus GDM develops [10]. The development of insulin resistance in late gestation is a process common to all human pregnancies in order to provide sufficient energy and nutrients to the fetus [11].

Furthermore, insulin resistance has been proposed to increase in preeclampsia and play a role in the pathogenesis of such disorder. A chronic inflammatory process in adipose tissue may also contribute to obesity-induced insulin resistance during the course of pregnancy. Adipose tissue monocytes and macrophages play an important role in the production of inflammatory cytokines – e.g., TNF-a and resistin, eventually leading to insulin resistance [12]. In this study, none of the patients with GDM and NDGM had preeclampsia or any other chronic inflammatory diseases.

Resistin, a newly discovered cytokine, is produced to a lesser extent in adipocytes, and expressed abundantly in monocytes and macrophages. In animal studies, administration of resistin to mice induces insulin resistance. The physiological effect of the resistin in humans is not well known. Increased serum resistin levels have been reported in obesity, although controversial reports exist on its role in diabetes and insulin resistance in humans [4-6].

Palik *et al*. [13] reported hyperresistinemia in patients with GDM during the course of pregnancy. Cortelazzi *et al*. [14] reported higher reistin levels in normal pregnant women than in nonpregnant controls. Magie *et al*. [15] reported lower resistin levels in GDM than in NGDM women. Lappas *et al*. [16] reported that there was no difference in the release of resistin between normal pregnant women and women with GDM.

In our study, however, mean BMI in GDM was higher than in NGDM and insulin resistance in GDM was more marked than in NGDM, although the serum resistin levels in GDM did not differ from NGDM. According to these results, it seems that obesity may be an important factor in insulin resistance, independent of resistin levels in GDM.

The circulating resistin level tends to increase in obesity and appears to impair glucose tolerance. A recent animal study has shown that the administration of resistin to rodents increased insulin resistance, while use of antiresistin protein partially reversed this phenomenon [4-6].

In humans, however, this issue remains controversial. In a study carried out earlier, it was suggested that resistin mRNA expression in adipocytes was increased in obese subjects, but subsequent reports were unable to confirm any association between obesity and resistin expression [17-19].

Similarly, Kawashima *et al*. [8] performed a series of experiments and found that exogenous insulin treatment caused a substantial reduction of resistin mRNA in a time- and dose-dependent fashion in 3T3-L1 adipocytes. Increased serum resistin levels were found in obesity, but some controversy exists concerning its role in type II diabetes, insulin resistance and hypertension in humans [8].

Serum insulin resistance was calculated with HOMA-IR. Silha *et al*. [20] showed a significant association between resistin and HOMA-IR levels. In our study there was not any correlation between resistin and HOMA-IR levels in patients with GDM and the NGDM group.

Although mean BMI in GDM was higher than in NGDM and insulin resistance in GDM was more marked, serum resistin levels in GDM were not found any differ-

ent from NGDM. We can conclude that other inflammatory cytokines in obesity may be an important factor in insulin resistance between mechanisms of gestational diabetes mellitus. Therefore, more comprehensive studies should be carried out in order to establish the exact effect of resistin on pregnancy, obesity and GDM, considering the other factors.

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