Study of possible relation between maternal serum resistin and insulin resistance in patients with preeclampsia

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Introduction
In humans, resistin antagonizes the effects of insulin on glucose metabolism in the liver and skeletal muscle, interacts with and reinforces inflammatory pathways, and may promote endothelial cell activation. Increased resistin levels have been associated with obesity, insulin resistance, metabolic syndrome, type 2 diabetes, and increased cardiovascular risk.

Objectives
Our study aimed to investigate the utility of maternal serum resistin in women with preeclampsia compared with normal pregnant women and its relation to insulin resistance.

Patients and methods
This study was carried out on 90 women who were divided into two groups: group I: preeclampsia (n = 60) and group II: healthy pregnant controls (n = 30). All individuals were subjected to the following after an informed oral and written consent was obtained: full assessment of history, clinical examination with a special focus on edema, blood pressure measurement, and maternal BMI [weight (kg)/height^2 (m^2)]. Gestational age was determined according to the date of the last menstrual period and confirmed by first-trimester ultrasound. Laboratory investigations including complete blood count, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, homeostasis model assessment-insulin resistance (HOMA-IR), and serum resistin were performed.

Results
Statistical comparison between preeclamptic patients (group I) and the healthy control group (group II) in terms of the different parameters studied showed a highly statistically significant increase in the patient group compared with the control group in systolic blood pressure, diastolic blood pressure, BMI, creatinine (CRE), aspartate aminotransferase, alanine aminotransferase, 50 g oral glucose challenge test, fasting blood glucose, fasting insulin, HOMA-IR, and resistin. In contrast, there was a highly statistically significant decrease in the patient group than the control group in haemoglobin (HB).

Conclusion
In this study, it was found that elevated serum resistin levels could be associated with exaggerated insulin resistance in patients with preeclampsia. Further studies are needed to clarify the role of resistin in the pathophysiology of preeclampsia and insulin resistance.

Keywords:
insulin resistance, preeclampsia, resistin

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Introduction

Resistin was discovered in 2001 by the group of Dr. Mitchell A. Lazar from the University of Pennsylvania School of Medicine [1]. It was called 'resistin' because of the insulin resistance (IR) observed in mice injected with resistin [2].

The discovery of the resistin gene and the fact that it encodes an adipocyte-derived hormone called resistin is consistent with the recognized role of adipose tissue as an endocrine organ. Many researches have been carried out on resistin since its initial description in 2001 [3]. Several follow-up studies have explored the role of resistin in obesity and type 2 diabetes and its underlying mechanisms. Other several studies showed that resistin may also play a pivotal role in inflammation and inflammation-related diseases [4].

Preeclampsia shares cardiovascular risk factors with the metabolic syndrome such as subclinical inflammation, IR, and obesity as resistin levels are enhanced in all these pathological conditions [5].

Preeclampsia is a disorder of widespread vascular endothelial malfunction and vasospasm that occurs after 20 weeks' gestation and can present as late as 4–6 weeks postpartum. It is clinically defined by hypertension with blood pressure 140/90 mmHg

or more accompanied by abnormal edema and/or proteinuria. It is considered severe if blood pressure and proteinuria are increased markedly or symptoms of end-organ damage, including fetal growth restriction, occurred [6].

In evaluating resistin and its association with insulin sensitivity in humans, several studies have identified positive correlations between resistin levels and IR *in vivo* and *in vitro*. In addition, serum resistin levels were increased by ~20% in type 2 diabetes mellitus patients [7]. In contrast, other studies have reported no associations between serum resistin levels and markers of IR in type 2 diabetes mellitus patients or insulin-resistant patients [8].

Homeostasis model assessment (HOMA) is a model of the relationship between glucose and insulin dynamics that predicts fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of IR and b-cell function. Insulin levels depend on the pancreatic b-cell effect on glucose concentrations, whereas glucose concentrations are regulated through insulin-mediated glucose production by the liver. Thus, deficient b-cell function will echo a decreased response of b-cell to glucose-stimulated insulin secretion [9].

Many studies use the HOMA-IR as the diagnostic criteria for IR [10]. IR was considered to be present in cases with HOMA 3.0 or more [11].

Aim

The aim of the present study was to investigate the clinical utility of maternal serum resistin in women with preeclampsia compared with normal pregnant women and its relation to IR.

Patients and methods

Study design

The study was carried out at both Clinical Pathology and Obstetrics and Gynecology Departments, Ain Shams University hospitals in the period between October 2013 and April 2014. Informed consents were obtained from all participants before enrollment in the study. The study was carried out on 90 women. They were divided into the following groups: group I (n = 60): preeclampsia group and group II (n = 30): healthy pregnant group as controls. All individuals included in this study were subjected to the following: full assessment of history focusing on information on the current pregnancy including age, and medical and obstetric history.

Exclusion criteria

Significant endocrine disorder in the current pregnancy or in the past, systemic involvement such as hypertension, renal, or liver function disturbances.

Clinical assessments

A thorough clinical examination was performed, with a special focus on edema, blood pressure measurement, maternal BMI [weight (kg)/height^2 (m^2)]. Gestational age (GA) was determined according to the date of the last menstrual period and confirmed by first-trimester ultrasound.

Laboratory assessments

Samples

Blood Samples: 6 ml of venous blood was collected under complete aseptic precautions from each participant and the same was done for other samples withdrawn after overnight fasting (8–12 h). The blood collected was transferred to an EDTA tube for complete blood count and a plain test tube for serum separation. After complete clot formation, samples were centrifuged at 1500*g* for 15 min. The separated serum was divided into two aliquots. One was designated for the immediate assay of serum glucose, serum transferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], creatinine, and blood urea nitrogen (BUN). The other aliquot was stored at −20°C for subsequent assay of resistin. The separated 8–12 h fasting serum was used for the assay of fasting glucose and fasting insulin levels for detection of IR. Hemolyzed samples were discarded; repeated freezing and thawing was avoided.

Analytical methods: Complete blood count was performed using Max M Coulter (Beckman Coulter Inc., Nyon, Switzerland).

(1) Routine laboratory tests including fasting glucose, AST, ALT, BUN, and creatinine were carried out on a Synchron PRO Autoanalyzer (Beckman Instruments Inc., Fullerton, California, USA).
(2) 50 g glucose challenge test, as recommended by the American Diabetes Association (ADA), was performed regardless of the time or the nature of the last meal. Women were administered 50 g of glucose by mouth and serum glucose was measured at 1 h. A positive test was a plasma venous glucose concentration at least 7.8 mmol/l (≥140 mg/dl) [12].
(3) Measurement of serum resistin and fasting serum insulin: they were assayed using commercially available enzyme-linked immunosorbent assay (ELISA) kits supplied by Assaypro Company (St Peters, Missouri, USA) for resistin and DRG International Inc., (Mountain Avenue, Springfield,

New Jersy, USA). for insulin. Both assays use the quantitative sandwich enzyme immunoassay technique in which the microtiter wells are coated with a murine monoclonal antibody specific for resistin in the first kit and a monoclonal antibody directed toward a unique antigenic site on the insulin molecule in the second one. Standards and samples are sandwiched by the immobilized antibody and a biotinylated polyclonal antibody specific for resistin and insulin, respectively, which is recognized by a streptavidin–peroxidase conjugate. All unbound material is then washed away and a peroxidase enzyme substrate is added. The color development is stopped and the intensity of the color is measured. The mean absorbance value for standards and samples were calculated. A standard curve was constructed for each analyte and using the mean absorbance value for each sample, the corresponding concentration of resistin (ng/ml) was determined from the standard curve. The reported reference level of fasting insulin in healthy individuals is (2–25 mIU/ml) [13]. Concentrations of resistin were expressed in ng/ml.

(4) HOMA score to determine IR: it is calculated using the formula: HOMA score = [fasting glucose (mg/dl) × fasting insulin (mU/l)]/405. IR was considered to be present in cases with HOMA 3.0 or more [11].

Statistical analysis

Statistical analysis was carried out using software SPFF (SPSS, IBM Inc., Armonk, New York, USA). Parametric data were expressed as mean and SD ($\bar{X} \pm$ SD), whereas nonparametric data were expressed as median and interquartile range. Comparative statistics were computed using Student's *t*-test for parametric data and Wilcoxon's rank-sum for nonparametric data. Correlation analysis was carried out using Pearson's correlation test (r) for parametric data and Spearman's rank correlation (r_s) for nonparametric data. P values less than 0.05 were considered significant, whereas values less than 0.001 were considered highly significant. Receiver operating characteristic (ROC) curve analysis was carried out to assess the overall diagnostic performance of each test.

Results

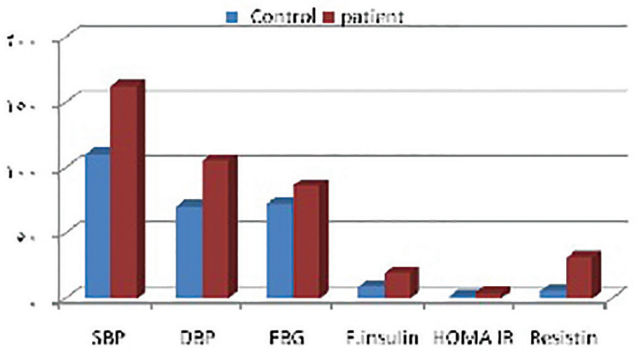
Statistical comparison between preeclamptic patients (group I) and the healthy pregnant control group (group II) in the different parameters studied, as shown in Table 1 and Fig. 1, showed a highly statistically significant increase in the patient group than the control group in systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, CRE, AST, ALT, 50 g glucose test, fasting blood glucose (FBG), fasting insulin, HOMA-IR, and resistin. In contrast, there was a highly statistically significant decrease in the patient group than the control group in HB. A statistically significant increase in the patient group than the control group was also found for BUN, whereas there was a statistically significant decrease in the patient group than the control group in platelet (PLT); there was also no statistically significant difference in age and GA.

Table 1 Comparison between preeclamptic patients (group I) and the control group (group II) in the different parameters studied using Student's *t*-test for parametric data and the Wilcoxon rank-sum test for nonparametric data

Parameters	Group I (n = 60)	Group II (n = 30)	P value
Age (years)	25 ± 4.5	25 ± 3.5	>0.05
GA (weeks)	28 ± 2.5	27 ± 2.5	>0.05
SBP (mmHg)	162 ± 10	110 ± 11	<0.01
DBP (mmHg)	105 ± 7	70 ± 8	<0.01
BMI	28 ± 3	25 ± 3.81	<0.01
50 g glucose test (mg/dl)	129 ± 7	109 ± 5	<0.01
Creatinine (mg/dl)	0.85 ± 0.22	0.64 ± 0.19	<0.01
Bun (mg/dl)	12 ± 7	9 ± 4	<0.05
AST (IU/l)	26 ± 11	18 ± 4	<0.01
ALT (IU/l)	31 ± 14	23 ± 10	<0.01
PLT (×10³/μl)	195 ± 50	253 ± 197	<0.05
HB (g/dl)	10.24 ± 1.70	12.11 ± 0.78	<0.01
FBG (mg/dl)	86 ± 7	28 ± 7	<0.01
HOMA-IR	4.24 ± 1.01	1.64 ± 0.80	<0.01
Resistin (ng\ml)[a]	31.22 (10.5–52.4)	5.37 (1.88–8.86)	<0.01
Fasting insulin (μU/ml)	19.40 ± 4.14	8.93 ± 3.50	<0.01

Data are expressed as $\bar{X} \pm$ SD for parametric data; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; FBG, fasting blood glucose; GA, gestational age; HOMA-IR, homeostasis model assessment-insulin resistance; PLT, platelet; SBP, systolic blood pressure, [a]Median and (interquartile range), $P > 0.05$, nonsignificant difference; $P < 0.05$, significant difference; $P < 0.001$, highly significant difference.

Figure 1



Comparison between control and patient groups in the mean values of systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), fasting insulin, homeostasis model assessment-insulin resistance (HOMA-IR), and resistin.

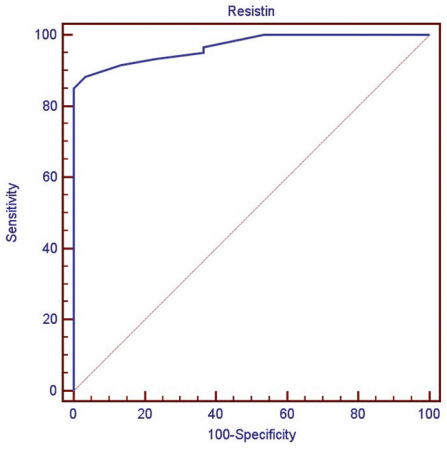
A correlation study between resistin and the other studied parameters in preeclamptic patients carried out using Spearman's rank correlation coefficient test (r_s) is shown in Table 2; a significant positive correlation was found between resistin and SBP, DBP, HOMA-IR, GA, 50 g glucose test, fasting insulin, FBG, AST, BUN, and ALT, and a nonsignificant correlation was found between resistin and age, GA, BMI, CRE, HB, and PLT. The same table shows another correlation study between HOMA-IR and the other parameters studied in preeclamptic patients using the Pearson correlation test (r), which showed a significant positive correlation between HOMA-IR and resistin, DBP, GA, GA, 50 g glucose test, fasting insulin, FBG, and ALT, and a nonsignificant correlation between HOMA-IR and age, SBP, BMI, CRE, BUN, AST, HB, and PLT.

ROC curve analysis was carried out to assess the diagnostic utility of resistin in discriminating preeclamptic patients from the control group. The best diagnostic cut-off level for resistin was 10 ng/ml.

This had a diagnostic sensitivity of 88.33%, a specificity of 96.76%, a negative predictive value (NPV) of 80.6%, and a positive predictive value (PPV) of 98.1%. The area under the curve was 96.7 as shown in Fig. 2.

ROC curve analysis was carried out to assess the diagnostic utility of HOMA-IR in discriminating preeclamptic patients from the control group. The best diagnostic cut-off level for HOMA-IR was 2.05 ng/ml, yielding a diagnostic sensitivity of 98.33%, a specificity of 86.67%, an NPV of 96.3%, and a PPV of 93.7%. The area under the curve was 97.3 as shown in Fig. 3.

Figure 2



Receiver operating characteristic curve analysis showing the diagnostic performance of resistin in discriminating preeclamptic women from healthy controls.

Discussion

Preeclampsia is a multisystem disorder that causes considerable maternal and fetal morbidity and mortality. It is defined as the sudden onset of hypertension presenting after the 20th week of gestation (≥140/90 mmHg) accompanied by abnormal edema and/or proteinuria [14].

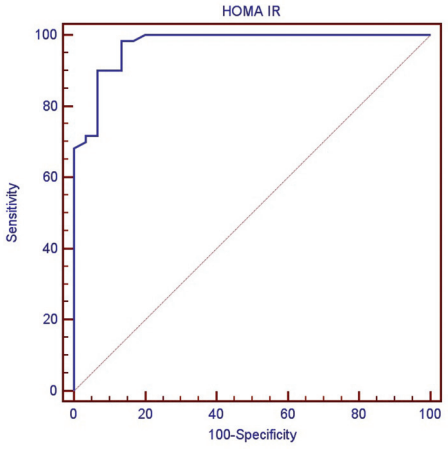
Although preeclampsia remains a disease of theories, previous studies have indicated that preeclampsia

Table 2 Correlation study between resistin/homeostasis model assessment-insulin resistance and the other parameters studied in preeclamptic patients

Parameter	Resistin		HOMA-IR	
	r_s	*P* value	*r*	*P* value
HOMA-IR/resistin	0.544	<0.001	0.544	<0.001
Age (years)	−0.090	>0.05	−0.085	>0.05
GA (weeks)	0.474	<0.001	0.260	<0.05
SBP (mmHg)	0.575	<0.001	0.234	>0.05
DBP (mmHg)	0.626	<0.001	0.334	<0.001
BMI	0.202	>0.05	0.153	>0.05
50 g glucose test (mg/dl)	0.494	<0.001	0.606	<0.001
FBG (mg\dl)	0.331	<0.05	0.840	<0.001
Fasting insulin (μU/ml)	0.469	<0.001	0.812	<0.001
CRE (mg/dl)	−0.096	>0.05	−0.023	>0.05
BUN (mg/dl)	0.292	<0.05	0.076	>0.05
AST (IU/l)	0.558	<0.001	0.234	>0.05
ALT (IU/l)	0.505	<0.001	0.311	<0.05
PLT (×10³/μl)	−0.056	>0.05	−0.089	>0.05
HB (g/dl)	0.183	>0.05	0.062	>0.05

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; DBP, diastolic blood pressure; FBG, fasting blood glucose; GA, gestational age; HOMA-IR, homeostasis model assessment-insulin resistance; PLT, platelet; *r*, Pearson's correlation coefficient, r_s, Spearman's correlation coefficient; SBP, systolic blood pressure; $P > 0.05$, nonsignificant difference; $P < 0.05$, significant difference; $P < 0.001$, highly significant difference.

Figure 3



Receiver operating characteristic curve analysis showing the diagnostic performance of homeostasis model assessment-insulin resistance (HOMA-IR) in discriminating preeclamptic women from healthy controls.

is associated with endothelial dysfunction, a hypercoagulable state, metabolic abnormalities, an inflammatory response, and atherosclerosis [15]. The etiology of these conditions remains elusive and multiple factors are implicated in the pathogenesis of preeclampsia, among these mechanisms, IR. Many studies have been carried out to elucidate the precise mechanism of exaggerated IR in preeclampsia, focusing on identifying circulating adipokines such as leptin, adiponectin, and resistin in the pathogenesis of preeclampsia [16].

Resistin is one of the adipocytokine hormones secreted by the adipose tissue and mononuclear cells. The main role of adipocytokines is signaling key organs to maintain metabolic homeostasis and their dysfunction has been causally linked to a wide range of metabolic diseases [17]. Resistin is a potent regulator of glucose homeostasis that is thought to oppose the action of insulin in peripheral tissues; it impairs glucose intake by adipocytes, increases plasma glucose concentration, and thus decreases insulin [18].

HOMA was first developed in 1985 by Matthews. HOMA describes glucose–insulin homeostasis by means of a set of simple, mathematically derived nonlinear equations. The approximating equation for IR has been simplified and uses a fasting plasma sample in which glucose (FBG) and insulin (fasting insulin) are measured, together with a constant [19].

In the light of the previous postulation, the aim of the present study was to investigate the clinical utility of maternal serum resistin in women with preeclampsia compared with normal pregnant women, and to investigate the potential role of resistin as a mediator of IR.

This study was carried out on 90 women. They were divided into the following groups: group I (n = 60): preeclampsia group and group II (n = 30): healthy pregnant group as controls. They were attending the Obstetrics Outpatient Clinic as they had preeclampsia during the third trimester of pregnancy; in addition, 30 healthy pregnant controls matched for age and GA to the patient group were included.

Our results showed a highly statistically significant increase in serum levels of resistin and HOMA-IR in preeclamptic women compared with their matched controls. This is in agreement with Haugen and colleagues [20–22], who reported that serum resistin levels were significantly elevated in women with preeclampsia compared with normal pregnant women.

As resistin plasma concentrations depend on glomerular filtration and increase with progressive renal impairment, altered renal function in preeclampsia might contribute toward elevated circulating resistin levels [23].

Although the exact function of resistin in the pathophysiology of preeclampsia remains unclear, the elevated serum resistin levels might be associated with exaggerated IR by the extensive systemic inflammatory response in preeclampsia [20–22].

Extensive systemic inflammation is a well-known characteristic of preeclampsia, and monocyte activation is one of the associated features of systemic inflammation [24]. Monocytes may be the source of the increased serum resistin concentrations in preeclampsia. Recent studies also suggested that resistin has proinflammatory properties [25]. Unfortunately, we did not investigate mononuclear cell activation or other proinflammatory adipokines, such as TNF-a and IL-6, in this study. Future investigation is needed to determine whether the different genetic expression of monocytes is related to circulating resistin concentrations in women with preeclampsia. Resistin impairs glucose intake by adipocytes and increases plasma glucose concentrations, thus decreasing insulin sensitivity [22]. In contrast, other studies report lower circulating resistin levels in preeclampsia group compared with normotensive healthy pregnant women of similar GA. The authors hypothesize that lower levels of resistin in preeclampsia group might be related to a reduction in placental production of the adipokine because of the smaller size of the placenta [26,27]. This view is supported by the detection of resistin mRNA expression in the human placenta, together with the absence of significant changes in resistin expression in adipose tissue during gestation [26]. Hendler *et al.* [28] did not find a difference in circulating resistin concentrations between pregnant women with and without preeclampsia.

Our correlation study showed a significant positive correlation between both resistin and HOMA-IR and SBP as well as DBP. The results are consistent with the findings of Haugen and colleagues [20,21], who also reported a significant positive correlation between mean SBP and mean DBP, the indices of preeclampsia, and both resistin and HOMA-IR levels in preeclamptic groups.

Our correlation study also showed a nonsignificant correlation between both resistin and HOMA-IR and BMI. This is in agreement with Silha *et al.* [29] and Heilbronn *et al.* [30], who reported no relationship between resistin serum levels and percentage body fat, visceral adiposity, and BMI. In contrast, Azuma *et al.* [31] reported higher serum resistin levels

in obese patients compared with lean patients, which positively correlated with the changes in BMI and visceral fat area.

The best diagnostic cut-off level of resistin for discriminating preeclamptic patients versus healthy pregnant controls was 10 ng/ml. This had a diagnostic sensitivity of 88.33%, a specificity of 96.67%, a PPV of 98.1%, and an NPV of 80.6%. This sensitivity and specificity is supported by the results of Al-Refai [32], who reported sensitivity and specificity of 90 and 98%, respectively, for resistin at the cut-off level of 12 ng/ml.

Assessment of the diagnostic performance of HOMA-IR in preeclamptic patients versus healthy pregnant controls showed that the best diagnostic cut-off level was 2.05. This had a diagnostic sensitivity of 98.3%, a specificity of 86.67%, a PPV of 93.7%, and an NPV of 96.3%. This sensitivity and specificity is supported by the results of Haugen *et al*. [21], who reported sensitivity and specificity of 90 and 80%, respectively, for resistin at a cut-off level of 3.2.

The results of this study indicated increased serum resistin concentrations in women with preeclampsia compared with the levels found in women with normal pregnancies. This finding suggests that elevated serum resistin levels may represent exaggerated IR in preeclampsia.

Conclusion and recommendation

Serum resistin can be considered a promising marker in the diagnosis of preeclampsia, with an excellent diagnostic efficiency; also, it was found that elevated serum resistin levels may represent the exaggerated IR in preeclampsia. Further studies are needed to clarify the origin of the elevations in resistin in patients with preeclampsia and the role of resistin in the pathophysiology of preeclampsia and IR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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