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Serum adiponectin and leptin in relation to risk for preeclampsia: results from a large case-control study

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ABSTRACT

Conditions resulting in insulin resistance, as well as metabolic, immune, and angiogenic perturbations, have been associated with an increased risk of preeclampsia (PE). Our purpose was to assess whether the adipose tissue–secreted hormones adiponectin, which has immune-modulating, metabolic, and angiogenic properties, and leptin, which reflects overall fat mass, are associated with PE risk. We performed a case-control design study within a hospital-based cohort of 368 pregnant women (106 with PE and 262 controls; mean age, 26.6 ± 6.8 years; mean gestational age at admission, 38.2 ± 2.8 weeks) between March 2005 and August 2007 at the Hospital of Pennsylvania University. Serum adiponectin and leptin were measured by radioimmunoassay. Statistical analysis of data was performed using simple and multiple regression analyses. No significant differences in adiponectin or leptin levels between preeclamptic and control pregnant women emerged in univariate analyses ($P = .57$ and $P = .15$, respectively). Among preeclamptic women, there were also no differences in adipokines between those with mild and severe disease. Serum adiponectin and leptin were not associated with higher risk of PE before and after adjustment for maternal age, race, primigravida, smoking status, body mass index at screening, gestational age at admission, history of PE, chronic hypertension, and gestational diabetes (odds ratio, 0.93; 95% confidence interval, 0.83-1.04 and odds ratio, 1; 95% confidence interval, 0.97-1.03, respectively). Maternal serum adiponectin and leptin levels, drawn at the time of PE diagnosis, were not associated with PE.

1. Introduction

Preeclampsia (PE) is characterized by the onset of high blood pressure and proteinuria after 20 weeks' gestation [1]. It occurs in about 5% to 10% of all pregnancies and results in substantial maternal and neonatal morbidity and mortality [1,2]. Preeclamptic women are at increased risk for developing coagulation defects, pulmonary edema, cerebral hemorrhage, blindness, seizures, hepatic and/or renal failure, and cardiovascular disease later in life [1,2], whereas infants born to preeclamptic

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women are prone to prematurity and more likely to be small for gestational age [1,2].

The etiology of the disease remains obscure. Several genetic, placental, metabolic, and immune factors giving rise to abnormal remodeling of the placental vasculature, ischemia, and endothelial cell dysfunction have been implicated in the etiopathogenesis of PE including insulin resistance [2-4]. Several conditions associated with insulin resistance such as hyperinsulinemia, glucose intolerance, gestational diabetes, polycystic ovary syndrome, maternal obesity, as well as excessive weight gain during pregnancy may predispose pregnant women to a substantially augmented risk of PE [5-8].

Adipose tissue is now broadly recognized as a functioning endocrine and paracrine organ secreting several bioactive adipokines, which regulate physiological and pathological processes, such as appetite, insulin sensitivity and resistance, inflammation, immunity, hematopoiesis, and angiogenesis [9]. The 2 best studied adipocyte-secreted hormones that circulate in the highest concentrations in the blood stream are leptin and adiponectin. Leptin has multiple physiologic functions, mainly in states of energy deficiency, in modulating satiety and energy homeostasis, but also in reproductive biology, ranging from placental angiogenesis to regulation of fetal development and growth [5,10-14]. Adiponectin is a pleiotropic, insulin-sensitizing, anti-inflammatory, and antiatherogenic adipokine; and hypoadiponectinemia is associated with obesity, insulin resistance, type 2 diabetes mellitus, hypertension [15], and obesity-related malignancies [6,16,17]

Until recently, few studies, mainly cross-sectional in their design without adjustment for known risk factors of PE and with limited number of participants (ie, ranging from 37 to 200) in different trimesters of pregnancy, have evaluated changes in serum adiponectin and leptin in preeclamptic women and gave rise to conflicting results [18-22]. Because no previous large study has jointly evaluated adiponectin and leptin in relation to PE taking into account other known risk factors of PE, we attempted to explore whether these adipose tissue–secreted hormones are associated with PE risk. We hypothesized that hypoadiponectinemia might be present in PE because lower adiponectin levels are linked to insulin resistance, impaired endothelium-dependent vasodilatation, and reduced blood flow, and predict risk for hypertension [15]. As a matter of fact, previous evidence from a nested case-control study carried out on a large cohort of pregnant women revealed a strong association between first-trimester hypoadiponectinemia and subsequent risk of hypertensive disorders including PE [23]. In this case-control study, we investigated the role of serum adiponectin and leptin levels in the etiopathogenesis of PE using a multivariate model adjusting for maternal age, race, primigravida, smoking status, body mass index (BMI), gestational age at admission, history of PE, chronic hypertension (CHTN), and gestational diabetes.

2. Material and methods

We performed a case-control design study within a hospital-based cohort of 368 pregnant women between March 2005 and August 2007 at the Hospital of the University of Pennsylvania. Cases were pregnant women with PE. Controls were women presenting for delivery at term (≥37 weeks) without PE.

All women admitted to Labor and Delivery with PE were eligible for enrollment and invited to participate in the study. Women with available serum, drawn at the time of diagnosis on labor and delivery, were included in this study, nested in the overall study. Cases were identified based on maternal criteria for PE. *Mild preeclampsia* was defined as elevated blood pressure (140/90 mm Hg or greater on 2 measurements that were obtained 6 or more hours apart, or 160/105 mm Hg or greater at time of admission) with proteinuria equal +1 on urine dip [1,24]. *Severe preeclampsia* was defined as blood pressure 160/105 mm Hg with greater than +1 on urine dip or at least 140/90 mm Hg on 2 occasions 6 hours apart and any one of the following: platelets less than 120 000/mL, aspartate aminotransferase greater than 45 U/L, alanine aminotransferase greater than 60 U/L, and/or creatinine greater than or equal to 1 mg/dL [1,24]. Severe disease also included women diagnosed with HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome or eclampsia; women who required intravenous antihypertensive medications before delivery, as a surrogate for blood pressure values persistently in the severe range; or women who had iatrogenic preterm delivery (<37 weeks) due to the severity of their disease [1,24].

We identified 106 cases during the study period who met all the inclusion and exclusion criteria. Two hundred sixty-two pregnant women (controls) were prospectively enrolled during the same period from women presenting for delivery at term (≥37 weeks) for scheduled induction of labor, scheduled cesarean delivery, spontaneous rupture of membranes, or term labor. It is important to note that all patients were enrolled at the time of PE diagnosis that coincides with the time of delivery for the majority of them. If PE diagnosis was established preterm, then pregnant women were followed to their delivery. There were no exclusion criteria for either cases or controls in the overall study. Patients with multiple gestations or gestational hypertension (blood pressure ≥140/90 mm Hg on 2 measurements ≥6 hours apart without proteinuria) or no available serum were excluded from this case-control study. All study participants were fully informed and gave written consent for their participation. University of Pennsylvania Institutional Review Board approval was obtained before enrollment.

Trained research nurses collected information on height, race, ethnicity, history of CHTN, and family history by patient interview at the time of enrollment. Other history including obstetric, demographic, prenatal delivery, and neonatal information was collected from prenatal and hospital chart abstraction by trained research nurse abstractors. A separate individual performed data entry. The primary investigator (SKS) reviewed all data sheets for completeness, consistency, and accuracy. Small for gestational age was defined using actual birth weight and the Alexander growth curve to determine percentile fetal growth for gestational age [25].

Maternal whole blood was collected from each subject within 24 hours of enrollment. After centrifugation, serum samples were aliquoted and placed at –80°C. For each subject, commercially available assays were used to measure levels of

adiponectin and leptin by personnel who were blinded to the case-control status. Serum adiponectin was determined by radioimmunoassay (LINCO Research, St Charles, MO) with a sensitivity of 1 ng/mL, an intraassay coefficient of variation of 1.8% to 6.2%, an interassay coefficient of variation of 6.9% to 9.3%, and a recovery rate of 99% to 103% for adiponectin. Serum leptin levels were measured using radioimmunoassay (LINCO Research). For leptin, the sensitivity of the assay was 0.5 ng/mL, with an intraassay coefficient of variation of 3.4% to 8.3% and an interassay coefficient of variation of 7.0% to 9.3%.

2.1. *Statistical analysis*

Statistical analysis of the data was performed using SPSS (Chicago, IL) version 17 for Windows statistical software package. Initial data were assessed through simple cross-tabulations and by using χ^2 test and Fisher exact test for categorical variables, *t* test for normally distributed variables, and Mann-Whitney *U* test for not normally distributed variables. The normality hypothesis was tested by Kolmogorov-Smirnov test, measures of asymmetry, and Shapiro-Wilk test. To compare means of cases among different subgroups, 1-way analysis of variance test for normally distributed variables or Kruskal-Wallis test for not normally distributed variables was conducted. Post hoc pairwise comparisons were performed using the Bonferroni method. Analysis of covariance was used to determine if cases and controls differ in serum leptin or adiponectin levels after accounting for gestational age and/or weight gain during pregnancy. The Pearson or Spearman correlation coefficients (*r*) were used as measurements of correlation for continuous normally or not normally distributed variables, respectively. Multivariable logistic regression analysis was performed to evaluate independent predictors of PE (mainly adiponectin or leptin), with results reported as odds ratios (ORs) with 95% confidence intervals (CIs). For all tests performed, a 2-sided *P* value < .05 was considered as significant.

3. Results

Clinical and demographic characteristics of 106 PE patients and 262 controls are depicted in Table 1. Maternal age and the proportion of African American race were similar between cases and controls. There were fewer primigravida women with PE than controls (*P* = .009). Cases had significantly higher systolic blood pressure (SBP) at first visit (prenatal care-screening visit) than controls (*P* = .03), but there were no significant differences in diastolic blood pressure (DBP) and mean blood pressure (MBP). Body mass index, body height, body weight, as well as body weight gain during pregnancy did not differ between cases and controls (>.05). Women in the PE group had a lower mean gestational age at delivery and therefore gave birth to smaller for gestational age and smaller birth weight infants when compared with control pregnant women (*P* < .001, *P* = .027, and *P* < .001 respectively). Preeclamptic women were more likely to have a history of PE (*P* = .001), gestational diabetes (*P* = .02), and renal disease (*P* = .03) compared with controls.

Table 1 – Clinical and demographic characteristics of PE (n = 106) and control (n = 262) patients

Variables	Preeclamptic patients	Control patients	*P* value
Maternal age (y)	26.2 ± 6.4	26.8 ± 6.9	.5
Race (n, %)			
African American	84 (79.2)	201 (76.7)	.53
White	19 (17.9)	45 (17.2)	
Asian	1 (0.9)	8 (3)	
Latino	0 (0)	4 (1.5)	
Other	2 (1.9)	4 (1.5)	
Primigravida (n, %)	38 (35.8)	58 (22.1)	.009
SBP at first visit (mm Hg)	114.8 ± 12.1	111.8 ± 12	.03
DBP at first visit (mm Hg)	70.5 ± 9.6	69.7 ± 8.7	.45
MBP at first visit (mm Hg)	85.2 ± 9.6	83.7 ± 8.9	.15
BMI at first visit (kg/m^2)	29.3 ± 9.3	29.3 ± 8.2	.95
Body height (m)	1.63 ± 0.07	1.63 ± 0.08	.55
Body weight at first visit (kg)	76.7 ± 21.7	77.5 ± 20.5	.75
Body weight gain during pregnancy (kg)	10.9 ± 7.9	9.7 ± 7.8	.23
Gestational age at admission (wk)	36.1 ± 4.2	39 ± 1.3	<.001
Gestational age at delivery (wk)	36.5 ± 3.4	39.1 ± 1.3	<.001
Infant birth weight (g)	2671 ± 755	3296 ± 468	<.001
Small for gestational age infants (n, %)	24 (22.6)	34 (12.9)	.027
Mode of delivery (n, %)			
Vaginal delivery	63 (59.4)	182 (69.5)	.07
Cesarean delivery	43 (40.6)	80 (30.5)	
Current smokers (n, %)	13 (12.3)	26 (9.9)	.5
Adiponectin (μg/mL)	9.3 ± 4.4	9.6 ± 5.2	.57
Leptin (ng/mL)	21 ± 15.9	23.8 ± 18.1	.15
1-h glucose tolerance test (mg/dL)	104.3 ± 24.6	101.2 ± 25.6	.33
Gestational age at 1-h glucose tolerance test (wk)	26.1 ± 5.2	26.2 ± 5.3	.87
Gestational diabetes diagnosed during pregnancy (n, %)	5 (4.7)	3 (1.1)	.02
History of PE (n, %)	19 (17.9)	20 (7.6)	.001
History of prepregnancy diabetes (n, %)	4 (3.8)	8 (3)	.75
History of CHTN (n, %)	11 (10.4)	14 (5.3)	.08
History of preterm delivery (n, %)	3 (2.8)	4 (1.5)	.06

Data are expressed as percentage (number) or mean ± standard deviation. Mean blood pressure = DBP + (SBP – DBP)/3.

Serum concentrations of leptin and adiponectin in the PE group and in the control group did not differ significantly (9.3 ± 4.4 vs 9.6 ± 5.2 μg/mL for adiponectin, *P* = .57; 21 ± 15.9 vs 23.8 ± 18.1 ng/mL for leptin, *P* = .15). Serum leptin and adiponectin were similar in both groups after adjusting for gestational age (for leptin: estimated marginal mean [EMM] ± standard error [SE], 21.4 ± 1.9 in cases vs 23.6 ± 2.16 ng/mL in controls, F = 0.92, *P* = .34; for adiponectin: EMM ± SE, 9.11 ± 0.55 in cases vs 9.6 ± 0.32 μg/mL in controls, F = 0.65, *P* = .42). Serum leptin and adiponectin did not differ significantly between cases and controls after adjusting for gestational age and weight gain during pregnancy (for leptin: EMM ± SE, 21.25 ± 2.04 in cases vs 23.9 ± 1.21 ng/mL in controls, F = 1.16, *P* = .28; for adiponectin: EMM ± SE, 9.06 ± 0.55 in cases vs 9.53 ± 0.31 μg/mL in controls,

Table 2 – Unadjusted and adjusted ORs with 95% CIs for PE risk according to serum adiponectin or leptin in 106 preeclamptic pregnant women and 262 controls

Variables	Unadjusted ORs (95% CI)	P value	Adjusted ORs (95% CI) [a]	P value
Adiponectin				
1 μg/mL more	0.99 (0.94-1.03)	0.61	0.93 (0.83-1.04)	.21
Leptin				
1 ng/mL more	0.99 (0.98-1)	0.18	1 (0.97-1.03)	.96

[a] Adjusted for maternal age, race, primigravida, smoking status, BMI at screening, gestational age at admission, history of PE, CHTN, gestational diabetes, and serum adiponectin or leptin.

F = 0.51, P = .48). When categorizing preeclamptic women into those with mild (n = 23) and severe (n = 83) disease, there were no significant differences in serum adiponectin or leptin (9.7 ± 4.7 μg/mL in mild PE vs 9.2 ± 4.3 μg/mL in severe PE for adiponectin, P = .51; 20.3 ± 16 ng/mL in mild PE vs 21.2 ± 15.9 ng/mL in severe PE for leptin, P = .72). Among cases, no significant correlations were observed between adiponectin and leptin or other parameters such as BMI; body weight; height; and screening SBP, DBP, and MBP. Only serum adiponectin levels were negatively correlated with infant birth weight (r = –0.2, P = .04). Among controls, serum leptin correlated positively with screening DBP (r = 0.21, P = .001) and MBP (r = 0.183, P = .004). Moreover, no significant differences in adiponectin and leptin levels emerged when we further categorized preeclamptic women as overweight/obese (BMI ≥25) and nonoverweight (BMI <25). When categorizing all pregnant women as overweight/obese (BMI ≥25) and nonoverweight (BMI <25), only leptin was significantly higher in overweight/obese women than in nonoverweight pregnant women (24.7 ± 18.02 ng/mL in overweight pregnant women vs 19.8 ± 17.07 ng/mL in nonoverweight pregnant women, P = .016).

Table 2 summarizes the ORs for PE risk by adiponectin and leptin concentrations, with and without covariate adjustment. Pregnant women with increasing leptin concentrations did not present significantly higher odds for PE before (OR, 0.99; 95% CI, 0.98-1; P = .18) and after adjustment for maternal age, race, primigravida, smoking status, BMI at screening, gestational age at admission, history of PE, CHTN, gestational diabetes, and serum adiponectin (OR, 1; 95% CI, 0.97-1.03; P = .96). In contrast, subjects with higher adiponectin concentrations tended to present lower odds for PE risk (though not significant at 0.05) after adjustment for the aforementioned covariates including serum leptin (OR, 0.93; 95% CI, 0.83-1.04; P = .21). Only history of PE and gestational age at admission were significant predictors of PE risk (OR, 3.6; 95% CI, 1.12-11.3; P = .03 and OR, 0.53; 95%, CI 0.36-0.78; P < .001, respectively).

4. Discussion

We sought to determine whether serum adiponectin is associated with an increased risk of PE after adjusting for leptin levels that reflect body fat mass, maternal age, race, primigravida, smoking status, BMI at screening, gestational age at admission, history of PE, CHTN, and gestational diabetes. The results of the current investigation revealed no statistically significant associations between serum adiponectin and PE. Other important observations were that leptin was not associated with PE and that neither adiponectin nor leptin differed significantly between mild and severe cases. We have also found that history of PE and gestational age were significant predictors of PE risk in agreement with previous evidence demonstrating associations with PE [1,2,7].

Increased risk of PE has been noted in relation to several conditions associated with insulin resistance, including gestational diabetes, polycystic ovary syndrome, maternal obesity, and excessive weight gain during pregnancy [8]. The pathophysiology that links maternal obesity with PE and pregnancy-induced hypertension is a subject of intensive research with insulin resistance playing a pivotal role [26]. Although insulin resistance increases in the normal course of pregnancy to facilitate the diversion of glucose to the fetus and support the rapid fetal and placental growth [8], increase of insulin resistance beyond a certain point may become deleterious, contributing to the development of gestational diabetes, pregnancy-induced hypertension, and PE [26]. Recent reports have suggested that insulin signaling and angiogenesis are intimately related [27] and aberrations in angiogenesis and insulin resistance may lead to alterations in critical cellular functions, endothelial cell injury, and consequently augmented risk of developing PE [21]. Insulin resistance in pregnancy and pregnancy complications is mainly attributed to placental hormones and increased maternal adiposity, but the underlying mechanisms remain to be fully elucidated [26].

Adiponectin, the most abundant adipose-tissue specific protein, is a pleiotropic, insulin-sensitizing, anti-inflammatory, and antiatherogenic adipokine [17]. Serum values of adiponectin are lower in insulin-resistant states, including type 2 diabetes mellitus, obesity, obesity-related cancers, and coronary artery disease [16,17]. Adiponectin plays an important role in angiogenesis and exhibits powerful anti-inflammatory properties: it inhibits the inflammatory cytokine network down-regulating tumor necrosis factor-a–induced expression of endothelial adhesion molecules, tumor necrosis factor-a expression in macrophages and adipose tissue, macrophage-to-foam cell transformation, and smooth muscle proliferation [28]. Moreover, it uses caspase-mediated endothelial cell apoptosis, underscoring a possible role of adiponectin in PE that is generally linked to endothelial cell malfunction [6].

In this investigation, we hypothesized that lower adiponectin might be present in PE because hypoadiponectinemia is associated with impaired endothelium-dependent vasodilatation and reduced blood flow, and is an independent risk factor for hypertension [15]. In our study, although preeclamptic women showed a slightly lower adiponectin than the control group, we did not observe any statistically significant difference in serum adiponectin between cases and controls both in univariate analysis and after adjustment for possible confounders. This finding is in accordance with 2 previous smaller studies showing no change in adiponectin values [29,30]. But controversial data exist in the literature regarding adiponectin as predictive marker of PE. A decrease [18,22,23], no change [29,30], and even an increase in maternal adiponectin levels have been reported [18,19,31]. In addition, in a

small study with different women in different trimesters of pregnancy, Herse et al [32] found that serum adiponectin increased throughout normal pregnancy but was lower in women with PE. The results of our study may be attributable to (*a*) the case-control design nested within a hospital-based cohort study (the majority of previous studies are cross-sectional); (*b*) the larger size of our study (N = 368), whereas the other studies have a limited number of participants ranging from 37 to 200; and (*c*) possibly, the greater percentage of African American pregnant women in our study compared with previous reports. However, the findings of this study suggest that adiponectin levels may not be an important contributor to the pathogenesis of PE. Whether or not placental adiponectin synthesis and secretion contribute to maternal serum adiponectin levels remains to be elucidated given that placental expression of messenger RNA adiponectin was found to be weaker than it was in adipose tissue [18]. Whether the relative amounts of adiponectin isoforms are altered in pregnancy-associated hypertensive disorders is not known and remains to be elucidated, but we have shown no major differences in terms of insulin resistance [33].

We found no difference in serum leptin levels between preeclamptic women and controls both in univariate analysis and after controlling for potential confounders. This is in agreement with other studies that did not detect any significant differences [18,34]. We also found similar leptin levels in pregnant women with mild or severe PE in accordance with a previous study [34]. Preeclamptic placentas are characterized by several vascular alterations and are associated with hypoxic stress [2]. It has been considered that leptin is upregulated in PE, reflecting an induced compensatory response to augment nutrient delivery to an underperfused and hypoxic placenta [2]. However, it seems that there is no consensus regarding leptin levels in PE: some investigators found no change [18,34], whereas others detected an increase [18,32,35,36] and even a reduction [37]. Nevertheless, in some of these cross-sectional studies, the results were not adjusted for maternal BMI and other important known risk factors for of PE; or leptin levels were measured during early pregnancy. In particular, even if participants of some previous studies were matched for age and BMI, results on adipokines were not adjusted in multivariate models for important confounders such as gestational age, race, parity, history of PE, CHTN, gestational diabetes, etc.

Our findings must be interpreted in the context of the study design. When using a case-control design, there is potential for selection bias, particularly in the selection of controls. It is challenging to match for all covariates, and it is possible that uncontrolled differences between groups may mask an association of adipokines with PE. Our controls came from the same study base as our cases. This, as well as the random selection of controls, reduces selection bias. Furthermore, other methodological strengths of the present investigation include (1) the larger sample size (N = 368) compared with other studies of adipokines and PE, (2) the strict criteria for inclusion of cases and control subjects, and (3) the adjustment for many known potential risk factors for PE, which further reinforces the observed null associations. The assessment of adiponectin and leptin was made using state-of-the-art technology and in a blinded fashion that also eliminates uncontrolled confounding from this source.

In summary, the results of our case-control study do not support an association between the 2 well-known adipokines, adiponectin and leptin, and risk for PE. Further research, including mechanistic, prospective, and longitudinal studies, is required to determine exactly if and when adiponectin and leptin concentrations are altered in PE and whether adiponectin per se and/or any of its isoforms and/or leptin may play a causal role in the pathogenesis of PE.

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