CEOG Clinical and Experimental Obstetrics & Gynecology

The possible role of serum leptin in preeclampsia

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Summary

Background: It is theorized that adipokines play a critical role in the pathophysiology of preeclampsia, particularly with their pro-inflammatory and inflammatory features. *Aim:* To investigate serum leptin levels in pregnancies complicated with preeclampsia and severe preeclampsia. *Materials and Methods:* Maternal serum leptin levels were analyzed by solid phase enzyme amplified sensitivity immunoassay (EASIA) method in 23 patients with mild preeclampsia, 29 patients with severe preeclampsia, and 28 healthy pregnant controls. *Results:* Mean serum leptin levels did not differ statistically between patients with mild preeclampsia, severe preeclampsia, and the controls (10.77 ng/ml, 13.40 ng/ml, and 8.43 ng/ml, respectively). Also, there was no relationship between serum leptin levels and the gestational ages of the participants. *Discussion:* Serum leptin levels are not associated with preeclampsia. Leptin measurements are not affected with the gestational age. The role of leptin in the pathophysiology of preeclampsia should be evaluated cautiously.

Key words: Preeclampsia; Severe preeclampsia; Adipokine; Leptin.

Introduction

At the present time, the pathophysiology of preeclampsia is still obscure. Recent studies suggest that adipokines may play an important role during pregnancy, and therefore, may have a role in the pathologic basis of this rigorous disorder [1-3]. Principally, adipokines that are secreted from the adipose tissue are known to regulate the secretion of insulin [4]. Thus, they control the metabolism of the organism. Additionally leptin, one of the adipokines, has functional and structural similarities to interleukin-6 (IL-6) family of cytokines [5, 6]. It is introduced as a pro-inflammatory cytokine. Leptin is also a pro-angiogenic and mitogenic factor, the actions of which are reinforced through crosstalk with IL-1 family of cytokines. It is well-established that leptin is involved in the regulation of the inflammatory response [6-8]. This may explain its potential participation in development of preeclampsia [6-8]. The placenta is one of the major sources for leptin [9]. There are evidences that the production of placental leptin is reinforced with hypoxia [10, 11]. Leptin is thought to ensure adequate nutrient transfer for placental–fetal use [12]. Regulation of the leptin mechanism is said to be discrete in pregnancies in which fetal growth and development is pathologic, compared to physiologic regulations in normal pregnancies [13-15]. Placental insufficiency is associated with a significant increase in placental leptin production, suggesting that leptin may be an index of fetal stress and placental dysfunction [16], but it is not evidently concluded that serum leptin levels increase in patients with preeclampsia. Therefore, in this study, the authors sought to determine serum leptin levels in patients with preeclampsia in accordance with the severity of the disorder.

Materials and Methods

Participants

Fifty-two preeclamptic women [23 patients with mild preeclampsia (MPE) and 29 patients with severe preeclampsia (SPE)] and 28 normotensive pregnant controls were recruited from patients managed at the antenatal clinics of the Obstetrics and Gynecology Department of Uludag University between April 2009 and May 2011. All participants were Caucasian third-trimester singleton pregnants with average socioeconomic status. The attendees of the control group were followed up with blood pressure measurements beyond the sixth week after delivery to ensure that they did not develop chronic hypertension.

Definition of exposure and study population

Preeclampsia was defined as demonstration of systolic blood pressure measurement above 140 mm Hg and diastolic blood pressure reading above 90 mm Hg on at least two different occasions more than six hours apart in a previously normotensive women after 20th gestational weeks at her pregnancy, in association with proteinuria above 300 mg/l in a 24-hour urine collection [17]. SPE was defined as presence of one of the following criteria: systolic blood pressure measurement above 160 mm Hg or diastolic blood pressure measurement above 110 mm Hg on two occasions at least six hours apart, more than five grams urinary protein excretion in 24 hours, less than 500 ml of urinary discharge in 24 hours, increased serum creatinine levels above 1.2 mg/dl, presence of microangiopathy demonstrated with thrombocyte counting lower than <100,000/mm^3 or increased lactate dehydrogenase more than 600 u/l, presence of cerebral or visual disturbances, pulmonary edema or cyanosis, epigastric or right upper quadrant pain [17]. Body mass index

Revised manuscript accepted for publication September 1, 2014

Table 1. — *Patient demographics.*

	MPE group (n=23)	SPE group (n=29)	Control group (n=28)	*p*
Age (years)	26 (19-33)	26 (19-43)	30 (22-39)	<0.05*, <0.05§, 0.305#
Gravidity	1 (1-4)	1 (1-5)	2 (1-5)	0.111*, <0.05§, 0.367#
Parity	0 (0-3)	0 (0-4)	0 (0-2)	0.263*, <0.05§, 0.154#
Gestational age (weeks)	36 (28-38)	36 (28-40)	39 (36-41)	<0.001*, <0.001§, 0.001#
BMI (kg/m^2)	28.84 (16.6-44.44)	28.76 (22.76-41.45)	28.71 (21.83-45.17)	0.442

*Statistical significance of the difference between control and MPE groups.
§Statistical significance of the difference between control and SPE groups.
#Statistical significance of the difference between MPE and SPE groups.
BMI: body mass index; MPE: mild preeclampsia; SPE: severe preeclampsia.

Table 2. — *Mean serum leptin levels of the study participants.*

	MPE group (n=23)	SPE group (n=29)	Control group (n=28)	*p*
Serum leptin (ng/ml)	10.77 (1.55-49.33)	13.4 (2.07-46.35)	8.43 (2.36-43.48)	0.155

MPE: mild preeclampsia; SPE: severe preeclampsia

(BMI), past medical and obstetric history of the participants, previous interventions and applied medications were recorded. BMI was calculated by using the formula of weight in kilograms divided by square of height in meters. Women with multiple pregnancies, chronic hypertension, diabetes mellitus, pre-existing vascular, and chronic renal diseases were excluded from the study. The study was approved by the Uludag University Research Ethics Committee. Informed consent was obtained from all the pregnant women participating the study.

Technique

Peripheric venous blood collection was performed prior to onset of parturition in the period between 08:00 am and 09:00 am following a 12 hours of fasting. Serum samples were drained into cryo tubes and stored at -80°C until assayed, following the centrifugation of blood samples at 3,000 rpm for ten minutes. Solid phase enzyme amplified sensitivity immunoassay (EASIA) method was used to analyze serum leptin levels via a leptin EASIA kit.

Statistical analysis

Continuous variables were given in medians with minimum and maximum values. Categorical variables were given in numerals, and supplied with percentages in parentheses. Kruskal-Wallis H test was used in the comparisons of groups consisting continuous variables. In addition, Mann-Whitney U-test was performed in the analyses of subgroups. Correlation analysis was conducted, and Pearson correlation coefficient was calculated for the definition of the strength of possible associations. Pearson's chi-squared test was used in the comparisons of groups consisting categorical variables. Statistical analyses were conducted by Statistical Package for the Social Sciences (SPSS) 22.0. A *p*-value smaller than 0.05 was accepted as the statistical significance.

Table 3. — *Correlation analyses between mean serum leptin levels and body mass index, serum sampling time and systolic, diastolic, and mean arterial blood pressures.*

		Serum leptin			
		MPE group	SPE group	Controls	All participants
BMI	*p*	0.120	0.128	0.001	0.001
	r	—	—	0.661	0.414
Sampling time	*p*	0.178	0.126	0.557	0.441
	r	—	—	—	—
Systolic BP	*p*	0.783	0.929	0.832	0.278
	r	—	—	—	—
Diastolic BP	*p*	0.278	0.774	0.556	0.305
	r	—	—	—	—
Mean arterial BP	*p*	0.625	0.916	0.818	0.337
	r	—	—	—	—
Fetal weight	*p*	0.644	0.710	0.084	0.169
	r	—	—	—	—

BMI: body mass index; BP: blood pressure; MPE: mild preeclampsia; SPE: severe preeclampsia.

Results

The clinical characteristics of the subgroups are summarized in Table 1. The median ages of the patients with MPE, SPE and control participants were 26 years (19-33), 26 years (19-43), and 30 years (22-39), respectively. There was no statistical significance with respect to the ages between patients with mild and severe preeclampsia, but patients with MPE and controls, and SPEs and controls. The differences of gravidity and parity were statistically significant solely between the patients with SPE and controls. The differences between median gestational ages of the patients with MPE (36 weeks), SPE (31 weeks), and the control participants (39 weeks) were statistically significant (Table 1).

The median values of BMI in MPE, SPE, and control groups were 28.84 kg/m^2 (16.6–44.44), 28.76 kg/m^2 (22.76–41.45), and 28.71 kg/m^2 (21.83–45.17), respectively. None of the differences between the groups in terms of BMI was statistically significant (Table 1).

Mean serum leptin level was 8.43 ng/ml (2.36–43.48) in control participants, 10.77 ng/ml (1.55–49.33) in patients with MPE, and 13.4 ng/ml (2.07–46.35) in patients with SPE. The differences between all groups were found statistically insignificant (Table 2).

We did not find any statistically significant relationship between serum leptin levels and systolic, diastolic, and mean arterial blood pressures within each group (Table 3). Serum leptin levels did not change between gestational weeks at which blood sampling was carried out in all patients and within study groups (Table 3, Figure 1). Furthermore, no statistical significance was found with respect to the gestational age, when serum leptin levels were adjusted for BMI, systolic blood pressure, diastolic

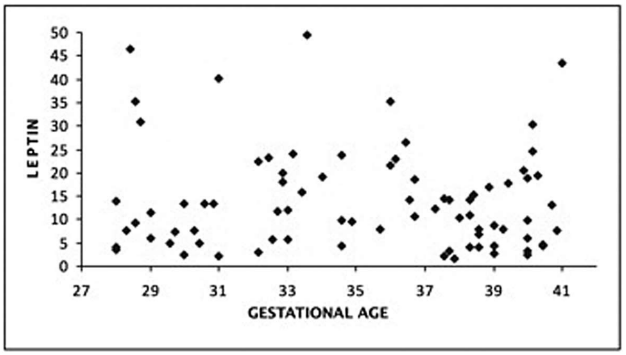

Figure 1. — Correlation between serum leptin measurements and gestational age at which serum sampling was performed in all study participants. Serum leptin measurements are given in ng/ml.

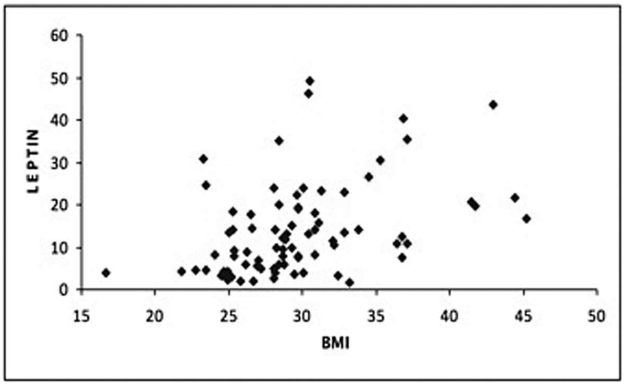

Figure 2. — Correlation between serum leptin measurements and body mass index in all study participants. Serum leptin measurements are given in ng/ml, BMI: body mass index (kg/m²).

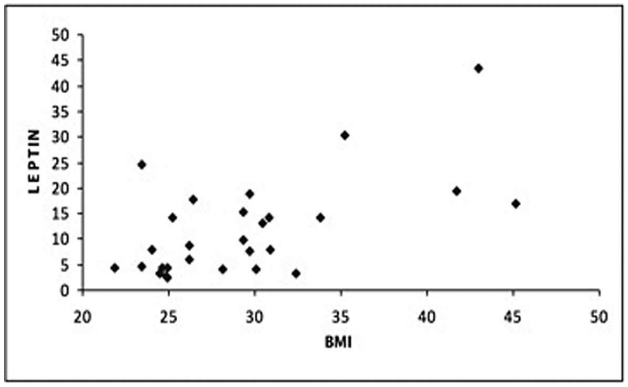

Figure 3. — Correlation between serum leptin measurements and body mass index in control group. Serum leptin measurements are given in ng/ml. BMI: body mass index (kg/m²).

blood pressure, and mean arterial blood pressure (data not shown).

A positive linear correlation was found between serum leptin measurements and BMI when the authors evaluated all patients (r = 0.414) (Table 3, Figure 2). In none of the groups but in the controls, a positive linear correlation could be demonstrated between BMI and serum leptin levels when each group was analyzed separately (r = 0.661) (Table 3, Figure 3). Serum leptin levels and BMI were found to inversely correlate in patients with MPE and SPE, yet it did not reach statistical significance (p = 0.120 and p = 0.128, respectively).

The differences between mean values of fetal weights between patients with MPE and healthy controls, and patients with SPE and healthy controls were statistically significant ($p < 0.001$, $p < 0.001$). There was no correlation between serum leptin measurements and the fetal weights within the groups (Table 3).

Discussion

In this study, we could not establish a statistically significant difference in serum leptin levels between patients with preeclampsia and healthy pregnancies. Although the difference of gestational ages of the study participants between all three groups were statistically different, it is demonstrated that gestational ages of the participants had no influence on the serum leptin measurements. Similar to the present study, Teppa *et al.* [18] and Kafulafula *et al.* [19] demonstrated that leptin levels were not correlated with gestational age. The means of the gestational ages of the patients with preeclampsia and control participants in those studies were 36.6±0.4 and 38.2±0.3 weeks, and 34.4±8.3 and 35.5±4.6 weeks, respectively. Like the latter two, some other studies emphasized serum leptin measurements not to be effected by the gestational age in the third trimester of pregnancy [20, 21]. In pregnancy, by the application of Northern blot analysis, leptin is shown to be primarily expressed in the first-trimester chorionic villous tissue, and to a lesser degree in the third-trimester chorionic tissue, amnion cells and villous vascular endothelial cells [22, 23]. During pregnancy, circulating leptin levels show a trend towards an increase, especially during the second trimester, and a plateau during the third trimester, while after labor, they decline sharply to the non-pregnant levels [21, 24, 25]. In this study, the gestational ages that the serum samplings were conducted in all three groups were in coverage of the previously mentioned studies. In parallel to the present study, other investigators also failed to demonstrate any significant difference concerning serum leptin levels between pre-eclamptic and normotensive women during the third trimester [26]. Furthermore, Laml *et al.* have suggested that serum leptin levels were significantly lower in pre-eclamptic pregnant women than in women with normal pregnancies, while no differences were identified between the two groups concerning the leptin levels in cord blood [27].

Principally, leptin is derived from, and a representative of adipose tissue [18]. Accordingly, serum leptin levels were shown to correlate positively with BMI in men and nonpregnant women in the previous studies in which the mutual effects of BMI and serum leptin were investigated [28, 29]. On the other hand it is theorized that, in a pregnancy state, BMI does not evidently reflect the fat ratio of the body because of the increased plasma volume, oozed intravascular fluid out to the extravascular space, presence of amniotic fluid, placenta and its components, and the fetus [30, 31]. Contrary to the latter concerns, it was found in the studies that serum leptin levels correlated positively with BMI in normotensive pregnant women, as it was in the nonpregnant individuals [30, 32]. Similar to this finding, the present study showed a positive linear correlation between BMI and serum leptin measurements amongst the normotensive study participants ($r = 0.661$, $p < 0.001$). In addition, we could not demonstrate a statistically significant relationship between BMI and serum leptin measurements among the patients with MPE and SPE ($p = 0.120$ and $p = 0.128$, respectively). This finding was in accordance with the work of Molvarec *et al.* [30] and Eleuterio *et al.* [31], but partly opposing the studies of Kafulafula *et al.* [19] and Sattar *et al.* [33], which demonstrated a statistically significant correlation between BMI and serum leptin levels in both of the groups including patients with preeclampsia and normotensive individuals.

Insufficient endovascular invasion of the cytotrophoblasts, which leads to placental hypoxia, is thought as the main/major pathophysiological process in development of preeclampsia. Hypoxia was shown to increase production [34-37] and excretion of placental leptin [38]. The evidences from above mentioned studies address leptin as a part of fetal adaptation mechanisms against deteriorated placental perfusion, and therefore, help to explain possible alterations of serum levels of leptin of mother or the fetus. Although the differences between mean values of maternal serum leptin in all three groups did not differ significantly in the present study, the differences of mean values of fetal weights between patients with MPE and healthy controls, and patients with SPE and healthy controls were statistically significant. This finding was an expected one because of the premature delivery of the fetuses in the group of patients with MPE and SPE. However, when we evaluated the weights of the infants in each group separately, we did not find any correlation between weight of the infant and maternal serum level of leptin. This finding was compatible with the results of Sucak *et al.* [39] but opposite to the results of Mise *et al.* [40].

Although some of the studies reported a relationship between serum concentrations of leptin and blood pressure, some others did not [41 - 43]. In this study, we could not demonstrate any statistically significant relationship between leptin and systolic BP, diastolic BP, and mean arterial BP, as well. The studies in which a relationship was reported asserted the presence of hemoconcentration, which is an important adherent of preeclampsia, as the causative factor for this relationship [44]. However, other studies could not demonstrate a correlation between hemoconcentraion and increased levels of maternal leptin [18, 35]. In one of those studies, Teppa *et al.* measured total fraction of leptin [18]. Unbound fraction of leptin (rather than bound fraction) was found to be increased when they separated bound and unbound fractions by chromatography in that study. This finding stands against the hemoconcentration theory. Thus, there is no sufficient data demonstrating relationship of hemoconcentraion and leptin levels in preeclamptic patients.

The gradually increasing production rate of leptin by the human placenta towards gestation, as well as the fluctuations observed during pregnancies complicated with preeclampsia could support the concept that leptin represents an important metabolic factor functionally linked with human pregnancy [45]. Studies investigating leptin levels in maternal serum of the patients with preeclampsia yielded different results. There are many studies that reported increased levels of leptin in preeclampsia [46 - 49], however, others declared no change [26, 50, 51] or decrement [27] in leptin levels in preeclampsia. It seems that there are several mechanisms in regulation of leptin in preeclampsia. The discrepancy in the studies could be attributed to multiple factors which affect serum levels of leptin including the influence of weight gain on pregnancy itself, and the ethnicity. Certain confounding factors such as the differences in study designs, patient selection criteria, and non-homogenous patient groups may also contribute to these inconsistent results. Further researches will provide new insights into the physiological mechanisms of leptin in the pregnant women and its possible role in complex disorders like preeclampsia.

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