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Serum levels of the adipokines, free fatty acids, and oxidative stress markers in obese and non-obese preeclamptic patients

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Summary

Purpose of investigation: To investigate the roles of adipokines, free fatty acid (FFA), and oxidative stress in obese and non-obese preeclamptic patients. *Materials and Methods:* Gestational age-matched obese preeclamptic (n=32), non-obese preeclamptic (n=32) ,and non-obese normotensive healthy (n=32) pregnant women were included in the study. Serum insulin, insulin resistance, leptin, nesfatin, ghrelin, chemerin, FFA levels, total antioxidant status, total oxidant status, and oxidative stress index were determined. *Results:* Leptin and nesfatin levels were significantly lower and ghrelin levels were significantly higher in the normotensive group as compared to the preeclamptic groups, while no difference was observed between obese and non-obese preeclamptic groups. Chemerin and FFA levels were significantly higher in obese preeclamptics as compared to non-obese preeclamptics and normotensive group. Total antioxidant status (TAS) levels were significantly higher in the normotensive group as compared to the preeclamptic groups, while no difference was observed between obese and non-obese preeclamptics. Total oxidative status (TOS) and oxidative stress index (OSI) levels were significantly lower in the normotensive group as compared to the preeclamptic groups, while no difference was observed between obese and non-obese preeclamptics. *Conclusion:* Serum levels of adipokines, TOS, and FFAs were significantly higher in pregnants with preeclampsia as compared to non-obese normotensive controls. Chemerin and FFA levels were significantly higher in obese preeclamptics as compared to non-obese preeclamptics.

Key words: Preeclampsia; Obesity; Free fatty acid; Adipokines.

Introduction

Preeclampsia is a serious cardiovascular complication of pregnancy characterized by hypertension, proteinuria, and generalized systemic vasoconstriction [1]. The disorder is diagnosed in the latter half of pregnancy, effects about 5% of pregnancies, and accounts for considerable mortality and morbidity [2]. Although several models have been proposed for the pathogenesis of preeclampsia, how this process occurs is not fully understood. Body mass index (BMI) is a classic obesity parameter and obesity is defined as BMI > 30 kg/m^2. It has already been shown that obesity leads to the development of insulin resistance and consequently to hyperinsulinemia. Clinical trials confirmed hyperinsulinemia as an important risk factor for the development of hypertension [3]. Although pathogenic mechanisms responsible for the coexistence of hypertension and obesity have not been completely explained, some authors indicate that hormonal and adipokine activity may play a role in the pathogenesis of both diseases [4].

Adipokines might play a role in the pathogenesis of preeclampsia. Increased concentrations of the appetite-suppressive adipokine leptin have been found to precede the clinical onset of preeclampsia. Moreover, leptin affects lipid metabolism, regulates food intake, modulates taste perception and the feeling of satisfaction after consumption, stimulates the sympathetic nervous system, and regulates the metabolism of insulin, glucose, and triglycerides [4]. Adipokine ghrelin, peptide hormone secreted by the stomach and duodenum, is involved in short-term regulation of appetite and reduces sympathetic activity [3, 4]. Adipokine chemerin is linked to facets of the metabolic syndrome in vitro and in vivo. Thus, chemerin mRNA expression is elevated in adipose tissue of mice on high-fat diet [5]. Adipokine nesfatin-1 is a recently discovered hormone that is derived from the previously described protein nucleobindin-2 [6]. Fasting nesfatin-1 levels were significantly lower in type 2 diabetic patients but its effects on gestational diabetes mellitus are unknown. Free fatty acids (FFAs) which also called non-esterified fatty acids are fatty acids that are not esterified to glycerol or another alcohol such as choline or cholesterol. In blood plasma or serum, FFAs are not free but bound to plasma albumin. Circulating FFAs are key regulators of glucose metabolism and have been shown to be increased in preeclamptic patients during and before the clinical onset of the disease [7].

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Table 1. — *Baseline characteristics of the study population. Age, BMI, SBP, DBP, gestational age, fasting glucose, fasting insulin, HOMA-IR, CRP, creatinine, HDL, and cholesterol.*

	Group 1 (obese preeclamptic)	Group 2 (non-obese preeclamptic)	Group 3 (non-obese normotensive)	*p* value	
Age (years)	31.28 ± 6.00	31.28 ± 8.05	31.03 ± 7.12	0.987	
BMI (kg/m^2)	34.2 (30.4 - 57.6)	24.6 (20.8 - 24.9)	24.5 (21.2 - 24.9)	0.0001	*p* (1-2) = 0.0001 *p* (1-3) = 0.0001 *p* (2-3) = 0.214
SBP (mmHg)	165 (140 - 240)	160 (140 - 220)	120 (100 - 130)	0.0001	*p* (1-2) = 0.369 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
DBP (mmHg)	100 (80 - 160)	100 (80 - 120)	73 (60 - 80)	0.0001	*p* (1-2) = 0.721 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
Gestational age at blood sampling (days)	35.0 (25 - 39)	34.5 (25 - 40)	35.5 (26 - 38)	0.837	
Fasting glucose (mg/dl)	80.31 ± 13.17	75.63 ± 13.65	74.75 ± 11.55	0.181	
Fasting insulin (microU/ml)	10.02 (3.77 - 58.00)	6.31 (1.27 - 47.25)	6.56 (1.20 - 43.00)	0.070	*p* (1-2) = 0.008 *p* (1-3) = 0.036 *p* (2-3) = 0.428
HOMA-IR	2.15 (0.57 - 13.18)	1.35 (0.19 - 11.43)	1.06 (0.18 - 10.30)	0.016	*p* (1-2) = 0.038 *p* (1-3) = 0.007 *p* (2-3) = 0.409
C-reactive protein (mg/dl)	1.08 ± 0.37	0.79 ± 0.33	0.29 ± 0.21	0.0001	*p* (1-2) = 0.005 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
Creatinine (mg/dl)	0.63 (0.47 - 1.62)	0.61 (0.41 - 0.95)	0.55 (0.44 - 1.46)	0.004	*p* (1-2) = 0.657 *p* (1-3) = 0.003 *p* (2-3) = 0.006
HDL (mg/dl)	55.22 ± 18.81	59.00 ± 20.08	53.88 ± 8.92	0.448	
Cholesterol (mg/dl)	208.66 ± 40.69	179.56 ± 29.99	156.81 ± 17.49	0.0001	*p* (1-2) = 0.009 *p* (1-3) = 0.0001 *p* (2-3) = 0.031
Triglycerides (mg/dl)	215.88 ± 32.82	189.22 ± 47.43	167.22 ± 38.82	0.0001	*p* (1-2) = 0.009 *p* (1-3) = 0.0001 *p* (2-3) = 0.031

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high-density lipoprotein.
Values for median (range) or mean ± SD are shown.

Maternal endothelial dysfunction is widespread and may explain all clinical signs of preeclampsia [8]. In the past several years, evidences have been accumulating that there is a second important biochemical imbalance in preeclampsia; that is, women with preeclampsia have an increased oxidative stress and lipid peroxidation and at the same time have a deficiency in several important antioxidants [9].

Adipokines were studied both in preeclampsia and in obesity; however, there has not yet been a study comparing obese and non-obese preeclamptic patients in the literature. In the present study, the authors aimed to investigate the roles of adipokine and FFA levels on the development of preeclampsia and on the development of obesity in preeclampsia. In addition, they aimed to investigate total antioxidant and oxidant status in the study groups.

Materials and Methods

Study design

This prospective study was approved by the local Institutional Review Board and confirmed written consent forms were obtained from all the participants. Obese preeclamptic, non-obese preeclamptic and non-obese normotensive healthy pregnant women in their third trimester, admitted to the Department of Obstetrics and Gynecology of the present tertiary center, between March 2012 and July 2012 constituted the two study groups and the control group, respectively. Cases with multiple pregnancy, diabetes mellitus, gestational diabetes, gestational hypertension, psychiatric disorders, cancer, stroke, severe hepatic or renal disease, acute cardiovascular events, platelet disorders, endocrine diseases, hyperlipidemia, fetal infections, fetal anomalies, rupture of membranes, and autoimmune diseases were excluded from the study.

Preeclampsia diagnosis was done as to criteria defined by the report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [10]. BMI was calculated as weight before pregnancy divided by squared height. Obesity was defined as BMI > 30 kg/m^2. Maternal ages, gravity, parity, abortions, height, weight, systolic blood pressures

Table 2. — *Comparison of chemerin, leptin, nesfatin, ghrelin, and FFA between study groups.*

	Group 1 (obese preeclamptic)	Group 2 (non-obese preeclamptic)	Group 3 (non-obese normotensive)	*p* value	
Chemerin (μg/l)	234.03 ± 26.41	218.84 ± 17.40	163.39 ± 13.77	0.0001	*p* (1-2) = 0.024 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
Leptin (μg/l)	11.12 ± 4.48	8.58 ± 4.36	5.84 ± 2.59	0.0001	*p* (1-2) = 0.063 *p* (1-3) = 0.0001 *p* (2-3) = 0.010
Nesfatin (ng/ml)	0.32 (0.15 - 1.17)	0.30 (0.13 - 0.65)	0.21 (0.13 - 0.46)	0.001	*p* (1-2) = 0.221 *p* (1-3) = 0.0001 *p* (2-3) = 0.012
Ghrelin (ng/ml)	0.53 ± 0.22	0.55 ± 0.19	0.79 ± 0.26	0.0001	*p* (1-2) = 0.730 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
FFA (mmol/l)	0.80 (0.35 - 1.87)	0.68 (0.38 - 1.93)	0.57 (0.31 - 0.89)	0.0001	*p* (1-2) = 0.045 *p* (1-3) = 0.0001 *p* (2-3) = 0.009

(SBP), and diastolic blood pressures (DBP) of the study group were recorded.

Outcome parameters

A venous blood sample was obtained after an overnight fast. Each collected blood sample was immediately centrifuged at 4,000 rpm +4 ^{0}C for ten minutes and then transferred into an Eppendorf tube. Samples were transferred on ice and kept in -70°C deepfreeze until the end of the study, which was completed in four months. Insulin resistance was calculated with the use of homeostasis model of insulin resistance (HOMA-IR) = {[fasting insulin (μU/ml)] × [fasting glucose (mmol/l)]}/22.5 [11]. The plasma leptin, nesfatin, ghrelin, chemerin, and FFAs levels were determined using the enzyme-linked immunsorbent assay (ELISA) method. Plasma insulin was measured by a chemiluminescence method. C-reactive protein (CRP) was assessed by immunonephelometry. Total antioxidant status (TAS) was measured by Erel's methods [12]. Total oxidant status (TOS) was measured by Erel's methods [13]. The TOS level to TAS level ratio was regarded as the oxidative stress index (OSI) [14].

Routine biochemistry parameters (serum creatinine, glucose, cholesterol, and triglycerides) were determined by photometric method.

Statistical analyses

Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 19.0 for Windows. A normal distribution of the quantitative data was checked using Kolmogorov-Smirnov and Levene tests. Parametric tests used in the study were One Way Anova for independent groups, Fisher's LSD test for the homogeneous variances and Games-Howell test for the non-homogeneous variances. Non-parametric tests used in the study were Kruskal-Wallis H test for independent groups, Bonferroni-corrected Mann-Whitney U test for post hoc comparisons. The distribution of categorical variables in both groups was compared using Pearson chi-square test. The relative importance of independent variables was assessed by stepwise binary logistic regression analysis using the forward Wald method. The cut-off points were calculated by the MedCalc software as the points with the best sensitivity-specificity balance. Data are expressed as mean ± SD or median (interquartile range), as appropriate. Statistical significance was assumed for $p < 0.05$.

Results

Gestational age-matched obese preeclamptic (n=32), non-obese preeclamptic (n=32), and non-obese normotensive healthy (n=32) pregnant women were included in the study. Table 1 summarizes the clinical characteristics of the groups studied during pregnancy. Age, gestational age at blood sampling, fasting glucose levels, and high density lipoprotein (HDL) levels were not significantly different between groups. SBP, DBP and creatinine levels were significantly lower in the normotensive group as compared to both obese and non-obese preeclamptic groups. Measures of insulin sensitivity (fasting insulin and HOMA-IR) in the obese group was significantly higher than both non-obese preeclamptic and non-obese normotensive groups. CRP, cholesterol, and triglyceride levels were significantly different among groups, each parameter being highest in the obese preeclamptics and lowest in the non-obese normotensive patients.

Leptin and nesfatin levels were significantly lower and ghrelin levels were significantly higher in the normotensive group as compared to the preeclamptic groups, while no difference was observed between obese and non-obese preeclamptic groups (Table 2). Chemerin and FFAs levels were significantly different between each group, each parameter being highest in the obese preeclamptics and lowest in the non-obese normotensive patients (Figure 1).

TAS levels were significantly higher in the normotensive group as compared to the preeclamptics, while no difference was observed between obese and non-obese preeclamptic groups (Table 3). TOS and OSI levels were significantly lower in the normotensive group as compared to the preeclamptics, while no difference was observed between obese and non-obese preeclamptic groups (Figure 2).

Estimates of preeclampsia risk according to the risk factors were calculated by logistic regression. Preeclampsia

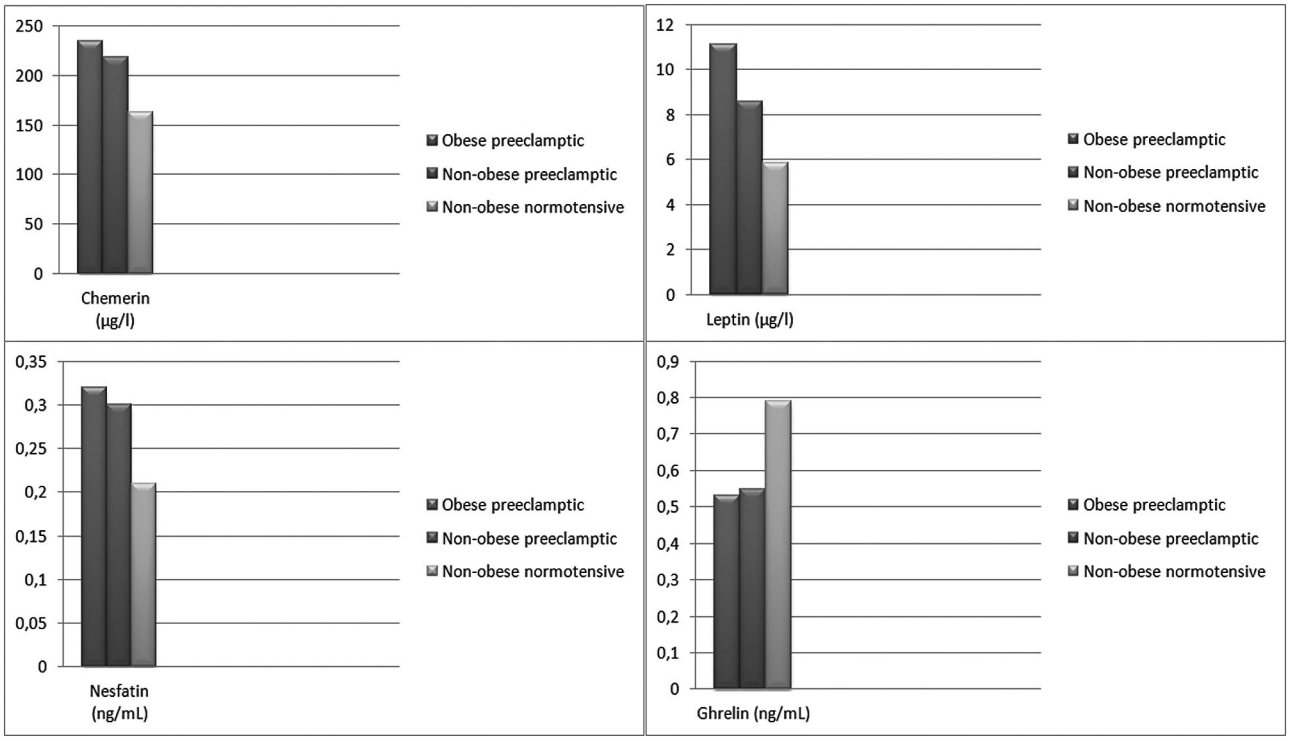

Figure 1. — Chemerin, leptin, nesfatin, and ghrelin levels among the study groups.

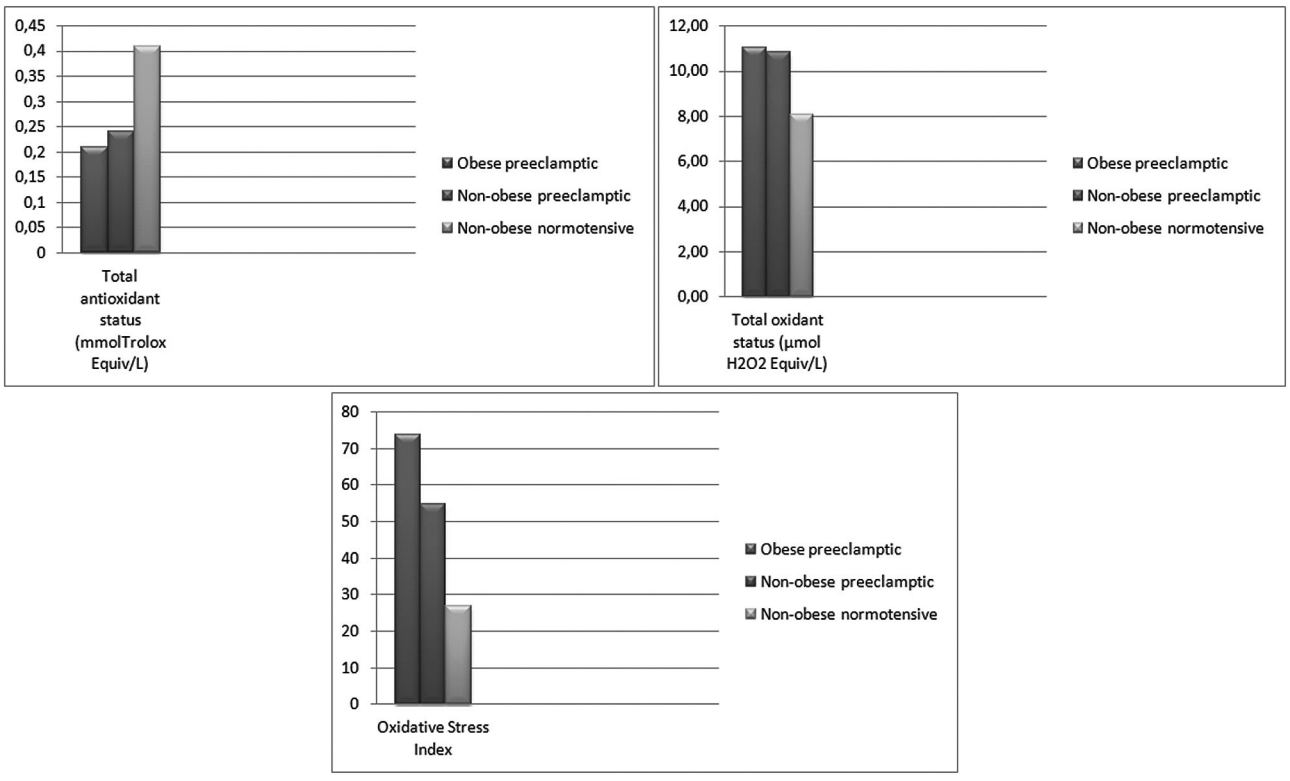

Figure 2. — Total antioxidant status, total oxidant status, and oxidative stress index among the study groups.

Table 3. — *Comparison of total antioxidant status, total oxidant status, and oxidative stress index between study groups.*

	Group 1 (obese preeclamptic)	Group 2 (non-obese preeclamptic)	Group 3 (non-obese normotensive)	*p* value	
Total antioxidant status (mmolTrolox Equiv/L)	0.21 ± 0.18	0.24 ± 0.13	0.41 ± 0.19	0.0001	*p* (1-2) = 0.489 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001
Total oxidant status (μmol H2O2 Equiv/L)	11.04 (4.90 - 37.14)	10.86 (3.49 - 38.91)	8.05 (5.48 - 13.83)	0.008	*p* (1-2) = 0.968 *p* (1-3) = 0.012 *p* (2-3) = 0.005
Oxidative stress index	73.88 (13.16 - 1187.67)	54.78 (16.34 - 590.00	26.80 (7.21 - 53.62)	0.0001	*p* (1-2) = 0.493 *p* (1-3) = 0.0001 *p* (2-3) = 0.0001

Table 4. — *Estimates of preeclampsia risk according to the risk factors (Binary Logistic Regression, Forward Wald Model; CI = Confidence Interval).*

	p value	Odds Ratio (95% CI)
C-reactive protein	0.048	6.297 (1.014 - 39.125)
Cholesterol	0.007	9.800 (1.840 - 52.630)
Creatinine	0.001	21.280 (3.530 - 125.000)
Chemerin	0.0001	701.022 (53.373 - 9207.522)

Table 5. — *Estimates of obesity risk in preeclamptic patients according to the risk factors (Binary Logistic Regression, Forward Wald Model; CI = Confidence Interval).*

	p value	Odds Ratio (95% CI)
HOMA-IR	0.016	12.344 (1.597 - 95.416)
Cholesterol	0.012	16.651 (1.871 - 148.192)
Triglycerides	0.012	62.706 (2.438 - 1612.828)

development ratio was 6.297 times higher when CRP blood level was over 0.48 mg/dl ($p = 0.048$); 9.800 times higher when cholesterol blood level was over 180 mg/dl ($p = 0.007$); 21.280 times higher when creatinine blood level was over 0.62 mg/dl ($p = 0.001$); 701.022 times higher when chemerin level was over 183.98 μg/l ($p = 0.0001$) (Table 4). Obesity development ratio in preeclamptic patients was 12.344 times higher when HOMA-IR index was over 0.95 ($p = 0.016$); 16.651 times higher when cholesterol blood level was over 184 mg/dl ($p = 0.012$); 62.706 times higher when triglyceride blood level was over 180 mg/dl ($p = 0.012$) (Table 5).

Discussion

In the current study, the authors demonstrated that maternal serum levels of chemerin, leptin, nesfatin, and FFAs were significantly higher, while ghrelin levels were significantly lower in preeclampsia patients as compared to non-obese normotensive controls during pregnancy. They also demonstrated that maternal serum levels of leptin, nesfatin, and ghrelin levels did not differ between obese and non-obese preeclamptic groups, while chemerin and FFAs levels were significantly higher in obese preeclamptics as compared to non-obese preeclamptic patients. TAS levels were significantly lower, while TOS levels were significantly higher in preeclampsia patients as compared to non-obese normotensive controls. TAS and TOS levels did not differ between obese and non-obese preeclamptic groups.

A growing body of evidence strongly supports the association between preeclampsia and common metabolic complications: 1) obesity is an independent risk factor for preeclampsia [15]; 2) patients with insulin resistance are more likely to develop preeclampsia [16]; 3) preeclampsia is also associated with hypertriglyceridemia, hypercholesterolemia, increased concentrations of FFAs, and reduced HDL concentrations [17]; and 4) women who had preeclampsia have an increased risk for metabolic syndrome-related morbidity and mortality later in life [18]. In the present study, patients with preeclampsia and the normotensive control group were compared in terms of factors predisposing to preeclampsia. Preeclampsia development ratio was 6.297 times higher when CRP blood level was over 0.48 mg/dl; 9.800 times higher when cholesterol blood level was over 180 mg/dl; 21.280 times higher when creatinine blood level was over 0.62 mg/dl. Despite the compelling evidence for the association between obesity-related complications and preeclampsia, the mechanism by which excess adipose tissue exerts its deleterious effect and predisposes pregnant women to develop preeclampsia remains unknown.

Development of insulin resistance in the third trimester of pregnancy, together with adipose tissue accumulation, is a possible adaptation of the maternal metabolism to optimize fetal nutrition. Obesity is associated mainly with insulin receptor resistance, resulting from the impairment of insulin binding to tissue receptors, especially in adipose tissue and muscles [19]. Hyperinsulinemia, like hyperleptinemia, contributes to activation of the sympathetic nervous system, and subsequently to the increase in blood pressure [20, 21]. The authors found significantly higher HOMA-IR in obese preeclamptic patients than both non-obese preeclamptic and non-obese normotensive healthy subjects. This differ-

ence could result from both hypertension and the obesity in this group. Furthermore, in the present study, obese and non-obese preeclamptic patients were compared in terms of factors predisposing to obesity. Obesity development ratio was 12.344 times higher when HOMA-IR index was over 0.95; 16.651 times higher when cholesterol blood level was over 184 mg/dl; 62.706 times higher when triglyceride blood level was over 180 mg/dl.

The present findings are in accordance with the hypothesis that fat-secreted factors play a role in the pathogenesis of preeclampsia. Adipose tissue has an endocrine function, secreting several metabolically active proteins, termed adipokines [22]. During pregnancy, the placenta is an additional source of adipokines [23]. The physiological significance of adipokine upregulation in preeclampsia remains unclear so far. Chemerin induces insulin resistance in human skeletal muscle cells [24]. In agreement with these in vitro findings, experiments in rodents demonstrate convincingly that administration of chemerin impairs glucose tolerance, lowers serum insulin levels, and decreases basal glucose uptake in diabetic mice in vivo [25]. Leptin may play an important role during pregnancy. Studies have shown that leptin levels rise between the first and the last two trimesters of pregnancy and return to pre-pregnancy levels within the first days postpartum [26]. In agreement with the present study, it has previously been shown that circulating leptin is increased in preeclamptic women [27]. Normal human pregnancy results in a pronounced physiologic hyperlipidemia involving a gestational rise in blood triglycerides and cholesterol. Women with preeclampsia display additional alterations in blood lipids, reflecting a disordered lipid and lipoprotein metabolism [28]. In the majority of these studies, however, preeclampsia either was not defined or was combined with non-proteinuric gestational hypertension or included women with superimposed chronic hypertension. Lorentzen *et al.* and Endresen *et al.* analyzed sera obtained from women in late pregnancy after an eight- to ten-hour fast [29, 30]. Serum triglyceride and FFAs concentrations in women with preeclampsia were higher than those in women with uncomplicated pregnancy. In agreement with other investigators, the present authors found that serum levels of chemerin, leptin, nesfatin, and FFAs levels were significantly higher in preeclampsia patients as compared to non-obese normotensive controls. In our study, serum levels of ghrelin were lower in patients with preeclampsia. The action of leptin is antagonistic to that of ghrelin and serum ghrelin levels were negatively correlated with blood pressure [31]. Ghrelin may represent a compensatory hypotensive mechanism in preeclamptic women [32, 33]. In addition, triglyceride levels were significantly different between each group, each parameter being highest in the obese preeclamptic group, and lowest in the non-obese normotensive group.

Pregnancy itself is a condition of increased oxidative stress due to increased mitochondrial activity and reduced scavenging potential [34]. Elevated levels of oxidative stress status in pregnancy were shown in many studies. This status is aggravated in pregnancies with preeclampsia. Preeclampsia is characterized by increased oxidative stress and decreased antioxidants [35]. In preeclamptic women, maternal circulating levels, placental tissue levels and production rate of lipid peroxides are increased and several antioxidants are markedly decreased [36]. In the present study, antioxidants were higher and oxidative stress markers were lower in the normotensive group as compared to the preeclamptic groups, while no difference was observed between obese and non-obese preeclamptic groups.

Some limitations of the study need to be discussed: the patient groups were small and some results could not reach or were bordering on statistical significance. Therefore, further detailed studies based on a larger population are needed for a more comprehensive evaluation.

Conclusions

The authors demonstrated that maternal serum levels of adipokine and FFAs were significantly higher in preeclampsia patients as compared to non-obese normotensive controls. Adipokine levels did not differ between obese and non-obese preeclamptic groups, while chemerin and FFAs levels were significantly higher in obese preeclamptics as compared to non-obese preeclamptic patients. The present findings support the hypothesis that adipokine and FFAs play a role in the pathogenesis of preeclampsia and Chemerin and FFAs are also associated with obesity in preeclamptic patients. TAS levels were significantly lower, while TOS levels were significantly higher in preeclampsia patients as compared to non-obese normotensive controls. TAS and TOS levels did not differ between obese and non-obese preeclamptic groups and these findings suggest that preeclampsia is associated with increased oxidative stress and decreased antioxidants.

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