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Preliminary report: serum levels of retinol-binding protein 4 in preeclampsia

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Abstract

The objective of the study was to investigate serum levels of the adipokine retinol-binding protein 4 (RBP4) in patients with preeclampsia (PE) as compared with healthy controls of similar gestational age. Retinol-binding protein 4 serum levels were quantified by enzyme-linked immunosorbent assay in control (n = 20) and PE (n = 16) patients. Mean maternal RBP4 concentrations were not significantly different in PE (24.5 mg/L) as compared with controls (22.3 mg/L). Furthermore, RBP4 did not correlate to clinical and biochemical measures of pregnancy outcome, renal function, glucose, and lipid metabolism, as well as inflammation. Our results do not support a role of RBP4 in the pathogenesis of PE.

1. Introduction

Preeclampsia (PE) is a serious cardiovascular complication in pregnancy that shares risk factors with the metabolic syndrome including insulin resistance and obesity [1]. As a consequence of a preeclamptic pregnancy, mother and newborn have a significantly increased future risk for metabolic and cardiovascular diseases [1]. We and others have demonstrated that dysregulation of various adipocyte-secreted factors—so-called adipokines—occurs in PE and might play an important role in the pathogenesis of the disease [2-8]. Recently, retinol-binding protein 4 (RBP4) was introduced as a novel insulin resistance–inducing adipokine that is up-regulated in human insulin resistance and obesity [9,10]. However, regulation of RBP4 has not been determined in PE.

2. Subjects and methods

Sixteen white pregnant women with PE were recruited from the Department of Obstetrics, University of Leipzig. *Preeclampsia* was defined as gestational blood pressure elevation greater than 140 mm Hg systolic or greater than 90 mm Hg diastolic accompanied by proteinuria in women who were normotensive before 20 weeks of gestation according to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [11]. The control group consisted of 20 normotensive pregnant white women who were admitted to the Department of Obstetrics of the University of Leipzig for indications including cervical insufficiency and placenta previa. Patients with cardiac and renal diseases, diabetes mellitus, as well as gestational diabetes mellitus (GDM) were excluded from the study. At the time of the blood sampling, none of the women was in labor. Body mass index (BMI) was calculated as weight before pregnancy divided by squared height and was representative for the patients treated in the Department of Obstetrics. The study protocol was approved by the local Ethics Committee. All patients gave written informed

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Table 1
Characteristics of the study population

	Control	PE
n	20	16
RBP4 (mg/L)	22.3 ± 5.5	24.5 ± 7.6
Age (y)	27.7 ± 6.0	31.9 ± 5.9*
BMI (kg/m^2)	20.7 ± 2.6	22.4 ± 3.6
SBP (mm Hg)	106 ± 15	167 ± 21*
DBP (mm Hg)	66 ± 11	103 ± 15*
Gestational age at blood sampling (d)	214 ± 15	209 ± 32
Gestational age at delivery (d)	243 ± 26	217 ± 30*
Birth weight of infants (g)	2296 ± 735	1265 ± 897*
Creatinine (μmol/L)	55 ± 12	70 ± 13*
FG (mmol/L)	3.57 ± 0.57	3.95 ± 0.89
FI (pmol/L)	77.36 ± 98.40	59.01 ± 50.44
HOMA-IR	1.94 ± 3.14	1.49 ± 1.20
FFA (mmol/L)	0.44 ± 0.29	0.96 ± 0.55*
Cholesterol (mmol/L)	7.49 ± 3.10	6.87 ± 1.73
TG (mmol/L)	2.79 ± 1.44	3.38 ± 1.30
Leptin (μg/L)	27.99 ± 12.19	77.14 ± 50.15*
Adiponectin (mg/L)	6.66 ± 2.01	13.71 ± 7.38*
CRP (mg/L)	3.09 ± 4.61	23.91 ± 31.08*
Antihypertensive treatment (%)	0 (0)	8 (50)*
α-Methyldopa (%)	0 (0)	8 (50)*
β-Blocker (%)	0 (0)	2 (13)

Means ± SD or the total number and percentage of patients taking a medication are shown. Continuous parameters were analyzed by Mann-Whitney U test, and categorical parameters were analyzed using the χ^2 test. CRP indicates C-reactive protein; DBP, diastolic blood pressure; FFA, free fatty acids; SBP, systolic blood pressure; TG, triglycerides.

* $P < .05$ as compared with control.

consent before taking part in the study. In all patients, blood was obtained after an overnight fast within 3 days of admittance to the Department of Obstetrics. In the PE patients, blood was drawn within 3 days of the diagnosis of PE. Retinol-binding protein 4 (Immundiagnostik, Bensheim, Germany), adiponectin (Mediagnost, Reutlingen, Germany), and leptin (Mediagnost) were determined with enzyme-linked immunosorbent assays according to the manufacturers' instructions. All other parameters were measured in a certified laboratory by standard laboratory methods. Statistical analyses were performed with SPSS software version 11.5 (SPSS, Chicago, IL) as indicated in the legend of Table 1 and in the text.

3. Results

Clinical characteristics of the subgroups studied are shown in Table 1. Retinol-binding protein 4 serum concentrations were not significantly different between PE patients (24.5 ± 7.6 mg/L) as compared with healthy pregnant controls of similar gestational age (22.3 ± 5.5 mg/L) (Table 1). Furthermore, RBP4 levels were not significantly different between PE and control subjects after adjustment for gestational age at blood sampling, gestational age at delivery, and birth weight of infants (data not shown). Using Spearman rank correlation method, RBP4 did not correlate with markers of renal function (creatinine), adiposity (BMI, leptin), insulin resistance (fasting glucose [FG], fasting insulin [FI], homeostasis model assessment of insulin resistance [HOMA-IR], adiponectin), lipid metabolism (cholesterol, triglycerides), and inflammation (C-reactive protein) in univariate analyses (data not shown). In addition, gestational age at blood sampling, gestational age at delivery, and birth weight of infants were not significantly associated with circulating RBP4 in uni- and multivariate analyses (data not shown).

4. Discussion

In the current study, circulating RBP4 levels are determined for the first time in PE. We demonstrate that RBP4 concentrations are not significantly different between PE patients as compared with healthy controls of similar gestational age. Furthermore, the adipokine is not associated with gestational age at blood sampling, gestational age at delivery, as well as birth weight of infants. These results indicate that RBP4 is not involved in the pathogenesis of PE. In contrast to RBP4, several other adipokines have recently been suggested to contribute to PE. Thus, increased concentrations of the appetite-suppressive adipokine leptin are found in PE that precede the clinical onset of the disease [2]. This hyperleptinemia appears as a compensatory response to increase nutrient delivery to the underperfused placenta [6]. Furthermore, the proinflammatory adipokine tumor necrosis factor α is increased about 2-fold in PE patients [7]. Interestingly, studies in pregnant rats show that this increase in tumor necrosis factor α is sufficient to increase mean arterial pressure by 27 mm Hg [8]. Furthermore, we have recently demonstrated for the first time that the adipokines adipocyte fatty acid–binding protein [3] and visfatin [5] are significantly increased in PE patients.

In the current study, we demonstrate that circulating RBP4 is not associated with markers of adiposity, insulin resistance, and lipid metabolism. Studies determining the association between RBP4 and metabolic disease in pregnancy to date have focused on GDM with controversial results. Thus, Chan and coworkers [12] demonstrate that serum RBP4 concentrations are significantly higher in women with GDM as compared with a healthy control group. Furthermore, BMI independently predicts circulating RBP4 in the patients studied [12]. In contrast, Krzyzanowska and coworkers [13] demonstrate that RBP4 concentrations measured by enzyme-linked immunosorbent assay or Western blotting are significantly decreased in GDM. In accordance with our findings, a significant correlation between RBP4 and BMI, FG, FI, and HOMA-IR cannot be shown in both control and GDM patients [13]. Taking these data into consideration, RBP4 does not appear to be involved in metabolic homeostasis in pregnant women.

Taken together, we show for the first time that RBP4 serum levels are not significantly different between PE

patients and controls and are not associated with markers of pregnancy outcome, renal function, adiposity, insulin resistance, lipid metabolism, and inflammation. Further work is needed to better elucidate the pathophysiologic significance of RBP4 in pregnancy-related complications.

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