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Serum levels of the adipokine fibroblast growth factor-21 are increased in preeclampsia

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ABSTRACT

Background: Preeclampsia (PE) is a serious cardiovascular complication in pregnancy, which is associated with an increased future metabolic and cardiovascular risk for mother and newborn. Fibroblast growth factor (FGF)-21 was recently introduced as a novel adipokine improving glucose metabolism in vitro and in vivo.

Material and methods: We investigated serum FGF-21 levels in patients with PE ($n = 51$) as compared to healthy, age-matched controls ($n = 51$) during and 6 months after pregnancy. Furthermore, association of FGF-21 with markers of renal function, glucose and lipid metabolism, as well as inflammation, was elucidated in all individuals.

Results: Median maternal FGF-21 serum concentrations adjusted for body mass index and gestational age at blood sampling were significantly, almost 3-fold increased in PE patients (309.6 ng/l) as compared to healthy, age-matched pregnant women (105.2 ng/l) ($p < 0.001$). Furthermore, FGF-21 concentrations were independently and positively correlated with triglycerides whereas an independent and negative association was observed with glomerular filtration rate and low density lipoprotein (LDL) cholesterol in pregnant women. Moreover, FGF-21 serum levels significantly decreased in former PE patients 6 months after pregnancy approaching levels found in control patients.

Conclusions: Maternal FGF-21 serum concentrations are significantly increased in PE during pregnancy. Furthermore, triglycerides, glomerular filtration rate, and LDL cholesterol are independent predictors of circulating FGF-21 in pregnant women.

1. Introduction

Preeclampsia (PE) is a multi-system disorder of pregnancy, which is characterized by new-onset hypertension and proteinuria during the second half of gestation [1]. Since it affects 2–7% of all pregnancies, PE represents a leading cause of maternal and fetal morbidity and mortality. Furthermore, the future risk for vascular and metabolic disease is significantly increased in mother and child after a preeclamptic pregnancy [1].

The pathogenesis of PE is not fully understood, but has been better elucidated in recent years. In fact, a dysbalance of angiogenic and anti-angiogenic factors including soluble fms-like tyrosine kinase 1 and endoglin appears to be critical in the development of PE [2–5]. Furthermore, metabolic risk factors including adipocyte-secreted proteins – so-called adipokines – are implicated in the pathogenesis of the disease. Here, concentrations of the adipokine leptin are increased in PE and precede the clinical onset of the disease [6]. Recent results indicate that this hyperleptinemia might be a compensatory response to increase nutrient delivery to the placenta by promoting amino acid uptake and enhancing blood supply to the placenta [7,8]. Furthermore, 2-fold upregulation of the proinflammatory adipokine tumor necrosis factor (TNF) α was observed in PE women [9]. Studies in pregnant rats showed that this increase in TNFα concentrations was sufficient to increase mean arterial pressure by 27 mmHg [10]. A 3-fold increase in maternal interleukin (IL)-6 levels could also be detected in women with PE [9]. Furthermore, elevation of circulating IL-6 levels was observed from first to third trimester in PE women but not in healthy controls [11].

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Fibroblast growth factor (FGF)-21 has recently been identified as a novel adipokine, which enhances insulin sensitivity and regulates lipid metabolism. Thus, FGF-21 significantly stimulated glucose uptake in 3T3-L1 adipocytes [12]. Furthermore, the adipokine improved pancreatic β-cell function and survival by activation of p44/42 mitogen-activated protein kinase [13]. Moreover, FGF-21-transgenic animals were resistant to diet-induced obesity [12] and therapeutic administration of this adipokine reduced plasma glucose concentrations in ob/ob and db/db mice [12], as well as in rhesus monkeys [14]. Downregulation of FGF-21 in the liver resulted in the development of fatty liver disease and dyslipidemia [15]. In addition, three independent papers suggested that FGF-21 is an important mediator of the metabolic effects of peroxisome proliferator-activated receptors (PPARs) α agonists [15–17]. Most recently, FGF-21 was also introduced as a key mediator of the physiological and pharmacological actions of PPARγ [18].

Since PE shares various risk factors with the metabolic syndrome, it is of major interest to elucidate whether adipokines influencing glucose and lipid metabolism, as well as vascular disease, are dysregulated in and contribute to PE and its complications. Recent studies convincingly demonstrate that leptin [19], TNFα [9], and IL-6 [9] are involved in the pathogenesis of this pregnancy disorder. In contrast, FGF-21 potently improves glucose and lipid metabolism [12–18], however, a potential contribution of this adipokine to the pathogenesis of PE has not been assessed so far. In the current study, we, therefore, sought to investigate for the first time whether levels of maternal FGF-21 are increased during and 6 months after pregnancies complicated by PE. For this purpose, we determined circulating FGF-21 in 51 women with PE and 51 normotensive, age-matched controls during and after pregnancy and correlated FGF-21 serum levels with biochemical and clinical markers of renal function, glucose and lipid metabolism, as well as inflammation.

2. Materials and methods

2.1. Study population

One hundred and two women with PE ($n = 51$) and normal pregnancy (controls, $n = 51$) were recruited from the Department of Obstetrics, University of Leipzig, for the current study. PE was defined as gestational blood pressure elevation >140 mmHg systolic or >90 mmHg diastolic accompanied by proteinuria in women who were normotensive before 20 weeks of gestation as described in more detail in [20]. Body mass index (BMI) was calculated as weight before pregnancy divided by squared height and the BMI ranged from 16.9 to 43.0 kg/m^2. Age of the patients was between 18 and 40 years. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as described [21]. Renal function was assessed as glomerular filtration rate (GFR) estimated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. Patients with diabetes mellitus or kidney disease were excluded from the study. Six months after delivery, fasting blood samples from 89 (44 former patients with PE; 45 former controls) out of 102 women were collected. Again, all women underwent a clinical examination. The study protocol was approved by the local Ethics Committee and all patients gave written informed consent before taking part in the study.

2.2. Assays

All blood samples were obtained after an overnight fast and none of the women was in labour at the time of blood sampling. Serum was immediately separated by centrifugation at 4000*g* for 10 min and frozen at −80 °C. Circulating FGF-21 (Biovendor, Modrice, Czech Republic), adiponectin (Mediagnost, Reutlingen, Germany), and leptin (Mediagnost, Reutlingen, Germany) were determined with enzyme-linked immunosorbent assays (ELISA) according to the manufacturers' instructions. Serum creatinine, fasting glucose (FG), fasting insulin (FI), free fatty acids (FFA), total, high density lipoprotein (HDL), and low density lipoprotein (LDL) cholesterol, triglycerides (TG), and C-reactive protein (CRP) were determined by standard laboratory methods in a certified laboratory.

2.3. Statistical analysis

Data were analyzed with SPSS software version 20.0 (IBM, Armonk, USA). Differences in circulating FGF-21 levels between control and PE patients during pregnancy or after pregnancy were assessed by Mann–Whitney-*U* test. Before performing this non-parametric test, all variables were adjusted for BMI and gestational age at blood sampling during pregnancy and for BMI and time from delivery after pregnancy. Changes in FGF-21 serum concentrations within the same individual during and after pregnancy were identified using Wilcoxon signed-rank test for related samples. Univariate correlation analyses were performed using Spearman's rank correlation method followed by Bonferroni adjustment for multiple testing. Since outliers for FGF-21 were present in our data set, medians are given in Table 1 and non-parametric tests (Mann–Whitney-*U* test, Spearman's rank correlation method, Wilcoxon signed-rank test) were performed instead of their parametric counterparts (unpaired Student's *t*-test, Pearson's correlation method, paired Student's *t*-test). To adjust the effects of covariates and identify independent relationships, multivariate linear regression analyses were performed. Distribution was tested for normality using Shapiro–Wilk *W* test. Non-normally distributed parameters were logarithmically (lg) transformed before multivariate analyses. A *p*-value of <0.05 was considered as statistically significant in all analyses.

Table 1
Baseline characteristics of the study population. BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; FFA, free fatty acids; FG, fasting glucose; FGF-21, fibroblast growth factor-21; FI, fasting insulin; GFR, glomerular filtration rate; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low density lipoprotein; PE, preeclampsia; SBP, systolic blood pressure; TG, triglycerides. Values for median (interquartile range) are shown.

	Control	PE
n	51	51
FGF-21 (ng/l)	105.2 (199.9)	309.6 (487.6)[a]
Age (years)	30 (7)	30 (11)
BMI (kg/m^2)	22.0 (4.3)	22.7 (5.9)
SBP (mmHg)	115 (19)	159 (28)[a]
DBP (mmHg)	70 (15)	100 (18)[a]
Gestational age at blood sampling (days)	197 (26)	208 (37)[b]
Gestational age at delivery (days)	274 (31)	216 (37)[a]
Birth weight (g)	3115 (1216)	1190 (945)[a]
Creatinine (μmol/l)	54 (10)	66 (16)[a]
GFR (ml/min)	121.8 (10.1)	105.1 (24.9)[a]
FG (mmol/l)	3.6 (0.9)	3.8 (1.4)[a]
FI (pmol/l)	58.9 (38.3)	73.9 (64.4)
HOMA-IR	1.3 (1.0)	1.7 (2.1)
FFA (mmol/l)	0.4 (0.3)	0.8 (0.5)[a]
Cholesterol (mmol/l)	6.5 (1.7)	6.7 (1.8)
HDL cholesterol (mmol/l)	1.8 (0.7)	1.8 (0.6)
LDL cholesterol (mmol/l)	3.9 (1.3)	3.4 (1.3)[a]
TG (mmol/l)	2.2 (1.1)	3.4 (1.2)[a]
CRP (mg/l)	2.5 (3.8)	8.2 (14.8)[a]
Leptin (μg/l)	20.4 (11.8)	41.0 (36.9)[a]
Adiponectin (mg/l)	7.4 (4.0)	11.7 (10.0)[a]

[a] Indicates $p < 0.05$ as compared to control as assessed by Mann–Whitney-*U* test after adjustment for BMI and gestational age at blood sampling.
[b] Indicates $p < 0.05$ as compared to control as assessed by Mann–Whitney-*U* test.