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The predictive value of the first-trimester maternal serum chemerin level for pre-eclampsia

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ABSTRACT

Chemerin is a novel adipokine linked to inflammation. The cross-sectional studies have reported that maternal chemerin serum concentrations are significantly increased in pre-eclampsia. However, limited data are available regarding the cause-effect relationship between chemerin and pre-eclampsia. The aim of this prospective observational study was to evaluate predictive significance of the first-trimester maternal serum chemerin levels for pre-eclampsia and to further confirm the hypothesis that chemerin is an important causative factor in the pathogenesis of pre-eclampsia. 518 pregnancy women were recruited. The first-trimester maternal serum chemerin levels were determined using enzyme-linked immunosorbent assay. The first-trimester maternal serum chemerin levels were statistically significantly elevated in women with pre-eclampsia compared with those without pre-eclampsia and in severe pre-eclampsia women compared with mild pre-eclampsia women. Serum chemerin levels remained positively associated with plasma C-reactive protein levels using a linear regression model. A logistic-regression analysis demonstrated that body mass index and serum chemerin levels appeared to be the independent predictors of pre-eclampsia. A receiver–operating characteristic curve analysis identified that serum chemerin levels predicted pre-eclampsia with high predictive value. The predictive value of the chemerin concentrations was similar to that of body mass index. Chemerin improved the predictive value of body mass index statistically significantly. Thus, our results suggest that high serum chemerin levels are associated with inflammation and pre-eclampsia independently, as well as chemerin may play a role as predictive biomarker for pre-eclampsia and be an important causative factor in the pathogenesis of pre-eclampsia.

Introduction

Pre-eclampsia is a pregnancy-specific multisystem disorder, which is characterized by new-onset hypertension, edema, and proteinuria that develop after 20 weeks of gestation in previously normotensive women [17,27,28]. It is one of the most serious complications during pregnancy and is a major cause of maternal mortality and morbidity [11,31,32]. Despite the considerable morbidity and mortality, the cause of pre-eclampsia is partially elucidated. It is currently believed that pre-eclampsia is caused by multiple factors, including vasospasm, endothelial dysfunction, inflammation, improper angiogenesis and oxidative stress [5,8,18,19].

Chemerin, named also as tazarotene-induced gene protein 2 or retinoic acid receptor responder protein 2, is a novel adipocytokine that is mainly expressed in adipocytes, liver, placenta, and ovary [3,14,22,25]. Chemerin attracted great interest for its proposed roles in adaptive and innate immunity, inflammation, lipid and carbohydrate metabolism and its association with obesity and diabetes [3,7,24]. Recent cross-sectional studies have reported that maternal chemerin serum concentrations are significantly increased in pre-eclampsia [6,29]. However, limited data are available regarding the cause-effect relationship between chemerin and pre-eclampsia. The aim of this prospective observational study was to evaluate prognostic significance of the first-trimester maternal serum chemerin levels for pre-eclampsia and to further confirm the hypothesis that chemerin is an important causative factor in the pathogenesis of pre-eclampsia.

Materials and methods

Study population

A prospective observatory study was performed on 518 pregnant women who had been referred to the prenatal clinic of

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the Jinhua People's Hospital in Jinhua, China, between April 2012 and July 2012. The study protocol was approved by the Medical Ethics and Human Clinical Trial Committee of the Jinhua People's Hospital. Written informed consent was obtained from the study subjects. These pregnancy women were aged 17–40 years with a mean age of 25.2 ± 4.7 years. The mean body mass index was 22.8 ± 2.6 kg/m^2 (17.0–31.5 kg/m^2). 65 (12.6%) women had history of smoking. 415 (80.1%) women have experienced high school education. 90 (17.4%) women were unmarried. 458 (88.4%) women had prenatal vitamin use. 25 (4.8%) women had maternal history of pre-eclampsia. 215 (41.5%) women had family history of chronic hypertension. 128 (24.7%%) women had family history of diabetes mellitus. The mean gestational age at blood sampling was 74.5 ± 4.2 days (64–83 days). The systolic blood pressure at blood sampling, 115.0 ± 10.6 mmHg (87–130 mmHg); the diastolic blood pressure at blood sampling, 71.1 ± 8.5 mmHg (51–84 mmHg); the mean blood glucose level, 4.3 ± 0.9 mmol/L (3.1–7.0 mmol/L); the mean plasma C-reactive protein level, 5.2 ± 2.0 mg/L (1.1–10.7 mg/L); the mean white blood cell count, 6.8 ± 1.9 × 10^9/L (4.2–11.5 × 10^9/L); the mean blood hemoglobin level 120.0 ± 16.2 g/L (69–149 g/L); the mean blood platelet count, 166.7 ± 41.1 × 10^9/L (101–282 × 10^9/L). None of these patients had previous systemic disorders or drug use (except usual supplementation, including folic acid), chronic hypertension, diabetes mellitus, renal disorders, recent or present fever or infectious disease, malignancies, autoimmune diseases and multiple pregnancies.

Assessment

We recorded some information including maternal age, maternal pre-pregnancy body mass index, maternal smoking status, high school education, status of marriage, prenatal vitamin use, maternal history of pre-eclampsia, family history of chronic hypertension, family history of diabetes mellitus, gestational age at blood sampling and maternal arterial blood pressure at blood sampling. Pre-eclampsia was determined by increased blood pressure (>140/90 mmHg) that occurred in a pregnant woman after 20 weeks of amenorrhea, accompanied by proteinuria (≥0.3 g/24 h) as defined by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [20]. Severe pre-eclampsia was diagnosed if one or more of the following were present: blood pressure of 160/110 mmHg or higher, excretion of 5 g or more of protein in a 24-h urine sample or a urine dipstick showing 3+ or 4+ in a random urine sample, oliguria of less than 500 mL in 24 h, pulmonary edema or cyanosis, visual or cerebral disturbance, impaired liver function, thrombocytopenia, epigastria or right upper quadrant pain and hemolysis, elevated liver enzymes, low platelets syndrome. Patients were grouped according to mild and severe pre-eclampsia. Women who met the criteria for pre-eclampsia but not severe pre-eclampsia were diagnosed as having mild pre-eclampsia.

Immunoassay methods

In the first trimester, after an overnight fasting, 5 mL of venous peripheral blood was collected from each patient. Isolated serum aliquots were stored at −70 °C for further analysis. Serum chemerin levels were measured in duplicate using a commercial enzyme immunoassay kit (Millipore, USA) according to manufacturer's instructions. The person carrying out the assays was completely blinded to the clinical information.

Statistical analysis

All statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). All quantitative or categorical variables were expressed as the mean ± standard deviation or the number (percentage) respectively, unless otherwise stated. Chi-square tests and *t* tests were performed for intergroup comparisons as appropriate. Bivariate correlations were analyzed by Spearman's or Pearson's correlation coefficient and followed by a multivariate linear regression. The relation of chemerin to pre-eclampsia was assessed in a logistic-regression model with odds ratio (OR) and 95% confidence interval (CI). The receiver–operating characteristic (ROC) curves were used to determine the best threshold of chemerin values to predict pre-eclampsia with calculated area under curve (AUC). In a combined logistic-regression model, the additive benefit of chemerin to body mass index was estimated. A *P* value of <0.05 was considered significant for all test.

Results

The change of serum chemerin levels

41 (7.9%) women suffered from pre-eclampsia, of which 18 (43.9%) women had severe pre-eclampsia and 23 (56.1%) women had mild pre-eclampsia. Fig. 1 showed that serum chemerin levels were statistically significantly elevated in all women with pre-eclampsia (312.1 ± 112.7 ng/mL), in severe pre-eclampsia women (365.5 ± 116.5 ng/mL) or in mild pre-eclampsia women (270.3 ± 91.8 ng/mL), compared to women without pre-eclampsia (181.4 ± 78.6 ng/mL, all $P < 0.001$); in addition, serum chemerin levels were also statistically significantly elevated in severe pre-eclampsia women compared with mild pre-eclampsia women ($P < 0.001$).

Correlative analysis

Table 1 showed that serum chemerin levels were highly associated with body mass index, family history of chronic hypertension, family history of diabetes mellitus, systolic blood pressure, diastolic blood pressure, blood glucose and C-reactive protein levels. When the above variables were introduced into the linear regression model, serum chemerin levels remained positively associated with plasma C-reactive protein levels ($t = 13.978$, $P < 0.001$) in Fig. 2.

Pre-eclampsia prediction

In Table 2, the univariate analysis showed that pre-eclampsia was associated highly with age, body mass index, family history of chronic hypertension, family history of diabetes mellitus, systolic blood pressure, diastolic blood pressure, blood glucose, C-reactive protein levels and serum chemerin levels. Table 3 showed their OR and 95% CI values. When was configured a

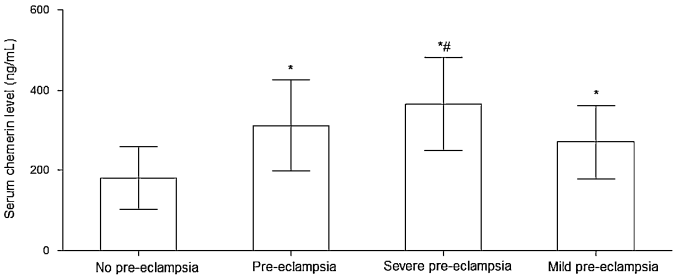

Fig. 1. The change in first-trimester maternal serum chemerin levels of 518 pregnant women. Data are expressed as mean ± standard deviation and differences between groups were analyzed by *t* test. Compared with no pre-eclampsia, $^*P < 0.001$; compared with mild pre-eclampsia, $^\#P < 0.001$.