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Vaspin and C-reactive protein levels in hyperemesis gravidarum

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Abstract. – OBJECTIVES: To determine vaspin and C-reactive protein (CRP) concentrations in hyperemesis gravidarum (HEG).

MATERIALS AND METHODS: Twenty-six women with HEG and 26 control subjects matched for gestational age and body mass index were examined. The levels of vaspin, CRP and lipid profile in all subjects were measured.

RESULTS: The vaspin levels were significantly higher in hyperemetic patients than in the healthy pregnant women (1308.3 ± 116.5 vs. 1145.9 ± 335.1 ng/ml, respectively) ($p < 0.05$). Women with HEG had significantly higher levels of CRP than the control group. Serum vaspin concentrations inversely correlated with total cholesterol, triglyceride, very low-density lipoprotein-cholesterol and low-density lipoprotein-cholesterol levels.

CONCLUSIONS: We found evidence of inflammation in HEG.

Key Words:
Hyperemesis gravidarum, vaspin, C-reactive protein.

Introduction

Adipose tissue acts as a true endocrine organ that secrets adipokines.

The family of adipokines is still growing. Recently, vaspin (visceral adipose tissue-derived serpin) was identified as a novel adipokine with insulin-sensitizing effects[1].

Seeger et al[2] revealed that serum vaspin levels were significantly higher in women and that gender was an independent predictor of circulating vaspin. Obesity, poor control of diabetes, increased glucose levels and impaired insulin sensitivity have been associated with increased vaspin[3].

Vaspin might be useful as a surrogate marker of lipid metabolism in pregnancy since vaspin was negatively correlated to lipid parameters (total cholesterol, triglycerides, and low-density lipoproteins) in the pregnant but not in the non-pregnant women[4]. On the other hand, serum lipid profile is altered in *hyperemesis gravidarum* (HEG)[5,6].

The importance of vaspin levels in people with HEG is not known. Our objective in this study was to measure the circulating levels of vaspin in HEG and make a comparison with age-matched control pregnant.

Materials and Methods

The Investigational Review Board approved this study and all subjects gave written informed consent.

A total of 26 patients with HEG were compared with 26 age- and BMI-matched healthy pregnant controls. HEG subjects were recruited consecutively. We defined HEG based on the criteria: (1) at least a 2.25 kg weight loss, (2) ketonuria > 80 mg/dl in a random urine specimen, (3) hypokalemia (potassium < 3.0 mEq/dl) or hyponatremia (sodium < 134 mEq/dl) requiring intravenous replacement, or (d) more than two visits to the Obstetric Emergency Department for HEG[7].

We recruited nonobese women with HEG aged 18-40 years who were nonsmokers in good health and who, for at least 1 month prior to each study, were not taking any medications known to affect hormone metabolism. All the participants had normal levels of aspartate and alanine aminotransferase. Women with liver, renal or heart failure or other chronic disease were excluded. Other exclusion criteria were BMI > 35 kg/m^2 and diabetes mellitus. The control group was selected from a cohort of healthy pregnant subjects.

Gestational age was determined from last menstrual period or ultrasound examination. BMI was obtained by dividing body weight in kilograms by the square of height in meters.

For all patients, the hormonal profile was performed after fasting for 8 hours. Blood samples were processed by centrifuge within 2 hours after withdrawal and were stored at -20°C until assayed. Glucose, triglycerides (TG), very low-density lipoprotein-cholesterol (VLDL-C), high density lipoprotein-cholesterol (HDL-C) were measured spectrophotometrically (Olympus Di-

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agnostica GmbH Hamburg/Germany; Olympus AU600). LDL-C was calculated by Friedewald equation [LDL-C = Total cholesterol-(HDL-C + Triglyceride/5)]. Insulin resistance was calculated with the formula of homeostatic model assessment for insulin resistance (HOMA-IR). It was calculated from insulin and glucose values using the formula of Matthews et al[8] (HOMA-IR = fasting plasma insulin (μU/ml) X fasting plasma glucose (mg/dl) / 405). CRP was measured using CardioPhase hsCRP (Dade Behring Marburg GmbH, Germany). Serum vaspin was measured using a commercially available kit (RayBio® Human Vaspin Enzyme Immunoassay Kit protocol, RayBiotech, Inc., Norcross, GA, USA). The minimum detectable concentration of vaspin is 26.2 pg/ml and detection range is 1-10,000 pg/ml. Intra-assay coefficient of variation is < 10% and inter-assay coefficient of variation is < 15%.

Statistical Analysis

Data were analyzed using Statistical Program for Social Sciences (SPSS) version 15.0 software for Windows (SPSS, Chicago, IL, USA). Normality was determined by the Kolmogorov-Smirnov test. Comparisons between groups were performed by parametric Student's *t* test and Mann-Whitney test. The strength of association between variables was calculated using Pearson's correlation test for parametric and the Spearman Rho correlation test for non-parametric variables. A p level of < 0.05 was considered significant.

Results

Table I shows the clinical characteristics and the hormonal profile. There were no statistically significant differences in age, parity, BMI, gestational age, total cholesterol, TG, VLDL, LDL and HDL levels between the two groups.

Serum vaspin was significantly higher in HEG subjects (1308.3 ± 116.5 vs. 1145.9 ± 335.1 ng/ml, respectively) ($p < 0.05$). Biochemical analyses indicated that women with HEG had significantly higher levels of CRP than the control group [10.1 (5-20) vs. 9 (1.4-14) mg/l].

Serum vaspin concentrations inversely correlated with total cholesterol (r = –0.377, $p = 0.006$) TG (r = –0.417, $p = 0.002$), VLDL (r = –0.388, $p = 0.004$) and LDL levels (r = –0.362, $p = 0.008$). We found no correlation between vaspin and age (r = –0.005, $p = 0.973$) and vaspin and CRP levels (r = –0.080, $p = 0.571$).

Discussion

Oxidative stress and inflammation are considered to have a crucial role in the pathophysiologic mechanism of HEG[9]. Paraoxonase-1 (PON-1) activity was found lower in hyperemetic patients. Decreased PON-1 activity might be related to increased oxidative stress and inflammation in pregnant women with HEG[9]. Mediators of an inflammatory response were altered in women with HEG, including increased CRP[9].

Vaspin is a newly described adipocytokine expressed predominantly in visceral white adipose tissues. Vaspin may also act as a pro-inflammatory cytokine[10]. Vaspin levels were found lower in pregnant women than in non-pregnant controls[4]. Serum vaspin levels were increased in women with polycystic ovary syndrome[11]. Metformin treatment decreased serum vaspin levels[12]. In this study, our objective was to measure the circulating levels of vaspin in HEG and make a comparison with age-matched control pregnant.

Table I. Demographic and biochemical characteristics of the two groups.

	Control group (n=26)	Study group (n=26)	p
Age (years)*	25.9 ± 3.8	26.9 ± 4.8	0.413
GA (weeks)**	8 (8-11)	8 (6-16)	0.081
Parity**	0.5 (0-3)	1 (0-2)	0.387
BMI (kg/m^2)*	22.6 ± 3.3	23.3±3.1	0.426
TG (mg/dl)**	98.5 (75-191)	91 (40-229)	0.534
Total cholesterol (mg/dl)*	120.6 ± 17.4	117.0 ± 22.4	0.511
HDL-C (mg/dl)**	44 (35-55)	42.5 (32-58)	0.300
VLDL-C (mg/dl)*	29.4 ± 7.4	26.8 ± 11.5	0.343
HOMA-IR**	0.6 (0.1-1.6)	0.6 (0.1-2.4)	0.971

Abbreviations: BMI: Body mass index; GA: Gestational age; HOMA-IR: Homeostatic model assessment for insulin resistance; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; VLDL-C: Very low density lipoprotein cholesterol. *Values are mean ± standard deviation; **Values are median (minimum-maximum).

The dehydration, electrolyte and metabolic changes are well recognized in HEG[13,14]. To our knowledge, vaspin levels in HEG never have been evaluated. In the present study, women with HEG had significantly higher vaspin levels, compared to BMI-matched healthy controls. We also found that women with HEG had significantly higher levels of CRP than the control group. Although we found no correlation between vaspin and CRP levels, Seeger et al[2] revealed that CRP levels were independently associated with this adipokine in chronic hemodialysis patients. The results of our study showed that the presence of the increased vaspin and CRP levels in women with HEG could contribute to pathophysiologic mechanism of hyperemesis gravidarum. The increase of serum vaspin and CRP may be the sign of the inflammatory process. The mechanism is speculative as to the etiology for elevated vaspin in HEG. It is possible that the augmented serum vaspin concentration may be due to a diminished catabolism of vaspin by the liver, or another cause. Vaspin may be increased due to the fetal production.

We also found no significant differences in total cholesterol, TG, VLDL, LDL and HDL levels between the hyperemetic patients and controls. In the study of Aksoy et al[6] serum total cholesterol, TG, LDL-C, and apo B levels were not different between the HEG patients and controls ($p > 0.05$), HDL-C and apo A1 levels were lower in HEG patients than in normal pregnant. In another study[5], again we found no significant differences in TG levels, apo-B/apo-A, HDL/apo-A, cholesterol/HDL ratios between the hyperemetic patients and controls but decreased levels of total cholesterol and LDL cholesterol in hyperemetic patients.

Similar to the study of Seeger et al[2], in our study, serum vaspin levels did not correlate with markers of insulin sensitivity (HOMA-IR). Furthermore, like Giomisi et al[4], we found negative association between vaspin levels and lipid profile. Serum vaspin concentrations inversely correlated with total cholesterol, TG, VLDL and LDL levels.

To our knowledge, this is the first report that evaluates serum vaspin levels in HEG. Our study drives the attention to vaspin and CRP levels in HEG. Although our data is limited, the results of our study showed the presence of the increased vaspin and CRP levels in women with HEG. The meanings of increased serum vaspin levels in women with HEG currently are unclear. Although the association does not establish a causal relationship, high vaspin levels in women with HEG may contribute to the development of emesis in these patients. But, because this was a pilot investigation, long term and larger trials will be needed to confirm our findings and investigate whether other adipocytokines, such as interleukin-6, adiponectin, leptin, and visfatin are altered in hyperemetic women.

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