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Changes in serum adropin, salusin alpha and salusin beta, vaspin, and preptin in hyperemesis gravidarum

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Summary

Purpose: To investigate serum levels of adropin, salusin alpha and salusin beta, vaspin, and preptin in pregnant women with hyperemesis gravidarum (HG) and uncomplicated pregnancies. *Materials and Methods:* Thirty-three pregnant women with HG (group 1) and 30 pregnant women with uncomplicated pregnancies (group 2) who were referred to the University Obstetrics-Gynecology clinic were enrolled in this present study. Fasting serum samples were obtained and measured for adropin, salusin alpha and salusin beta, vaspin, and preptin. The hormones levels were studied by using ELISA method. *Results:* Statistically significant difference was found between groups 1 and 2 according to adropin, salusin alpha and salusin beta, vaspin, and preptin levels (all $p < 0.05$). There were increased levels of salusins and adropin and decreased levels of vaspin and preptin in women with HG. *Conclusion:* This study suggests a possible role of these peptides, which may clarify the etiopathogenesis of HG.

Key words: Hyperemesis gravidarum; Adropin; Salusin alpha and salusin beta; Vaspin; Preptin.

Introduction

Hyperemesis gravidarum (HG) is a condition of severe nausea or vomiting that may require hospitalization due to various complications during pregnancy [1]. It is a multifactorial condition and associated with multiple factors including endocrine diseases, hepatic dysfunction, changes in lipid metabolism, upper gastrointestinal system dysmotility, and psychological factors [2].

Throughout gestation, the well-known normal ranges of several laboratory parameters are altered due to the broad spectrum of physiological changes, as well as proinflammatory and procoagulant effects of pregnancy. Serum lipid profile is also altered in HG [3, 4].

Adipokines act as paracrine factors within white adipose tissue, and as endocrine hormones on the liver, muscles, and central nervous system in the regulation of energy homeostasis [5]. Adropin attenuates components of the metabolic distress associated with obesity independently of effects on body weight or weight loss [6]. Salusin alpha and salusin beta act in maternal endocrine and/or paracrine fashion. Serum salusin alpha and beta are decreased and correlate positively with cord blood levels in gestational diabetes mellitus (GDM) [7].

Preptin, consists of 34 amino acids and originates from proinsulin-like growth factor II (pro IGF II). Maternal serum and cord blood preptin levels were shown to be higher in patients with GDM than control pregnant women [8].

Vaspin, is a newly discovered adipocytokine secreted mainly by visceral adipose tissue that has insulin-sensitizing effects. It may play a role in GDM and fetal development [9].

There seems to be a connection between the hormones involved in energy regulation and HG [2]. Currently, the significance of possible changes in blood levels of adropin, salusin alpha and salusin beta, vaspin, and preptin during pregnancy with HG is not well known. In this manner, the present authors' objective in this study was to invesitgate the relationship between HG and circulating levels of these peptides in a controlled clinical setting.

Materials and Methods

Thirty-three pregnant women with HG (group 1) and 30 pregnant women with uncomplicated pregnancies (group 2) who were referred to the University Obstetrics-Gynecology clinic were enrolled in the present study. The study was approved by the local Ethics Committee. All research procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent/permission was obtained from all parent participants.

Diagnosis of HG was based on the presence of severe vomiting (more than three times per day without any other obvious cause), an inability to maintain oral nutrition, weight loss, and at least one positive ketonuria according to American College of Obstetrics and Gynecology (ACOG) [10].

Patients with systemic illnesses, maternal age > 40 years, multiple pregnancies, women with a history of cranial trauma, metabolic, psychiatric or medical disorders (e.g. peptic ulcer), and history of chronic medication intake (e.g. non-steroidal anti-in-

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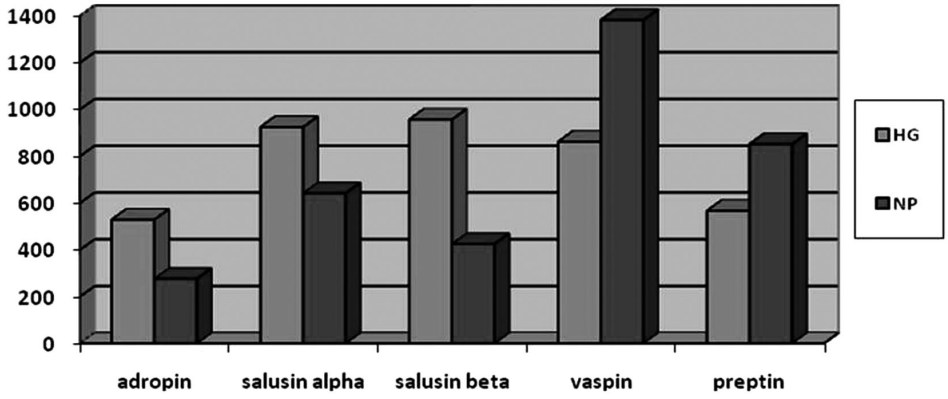

Figure 1. — Comparision of serum peptides levels in hyperemesis gravidarum (HG) and normal pregnancy (NG).

flammatory drugs) were excluded from the study.

An ultrasound scan including fetal biometry, placental site, amount of amniotic fluid, and any relevant obstetric condition (e.g., twin pregnancy, molar pregnancy or missed abortion) was performed for all cases.

Fasting venous blood samples were taken from all subjects. Extracted serum was stored at -70°C for further analyses. Venous blood was then obtained for the measurement of adropin, salusin alpha and salusin beta, vaspin, and preptin levels.

Serum adropin, salusin alpha and salusin beta, vaspin, and preptin levels were studied using adropin, salusin alpha and salusin beta, vaspin, and preptin kits by the enzyme-linked immunosorbent assay (ELISA) method according to the manufacturer's instructions.

The statistical analyses of the present study were conducted using Statistical Package for Social Sciences version 17.0 package program. Group 1 and 2 subjects were compared by using multivariate analysis. A value of $p < 0.05$ was considered statistically significant. All clinical parameters were expressed as mean ± SD, as well as percentages (for categorical variables).

Results

The mean age of group 1 was 26.05 ± 5.06 years and the mean age of the group 2 was 26.93 ± 6.42 years. No statistically significant difference was found between this study groups in terms of age ($p > 0.05$).

During the study, the mean gestational ages of the groups were 10.45 ± 2.54 and 10.43 ± 2.73 weeks, respectively. No statistically significant difference was found between groups 1 and 2 in terms of gestational age ($p > 0.05$)

There was a statistically significant difference between groups 1 and 2 according to serum adropin, salusin alpha and salusin beta, vaspin, and preptin levels (all $p < 0.05$) (Figure 1, Table 1). There were increased levels of salusins and adropin and decreased levels of vaspin and preptin in women with HG.

Table 1. — *Comparison of groups 1 and 2 according to laboratory parameters.*

	Group 1 n=33 Mean± SD	Group 2 n=30 Mean± SD	Group 1 *vs.* group 2 *p* value
Adropin (pg/ml)	529.3±150.87	276.6±96.	0.0001
Salusin-alpha (pg/ml)	925.6±300.2	642.1±351.6	0.003
Salusin-beta (pg/ml)	957.3±425.8	680.1±460.3	0.003
Vaspin (pg/ml)	862.1±468.1	1382.3±511.3	0.0001
Preptin (pg/ml)	567.8±262.0	852.4±303.6	0.003

Discussion

HG is a disease of nausea, vomiting, and anorexia in pregnancy resulting in dehydration and weight loss. Peptides involved in the regulation of energy metabolism in women with HG compared to normal pregnant women may be expected to be altered. In addition, pregnancy may affect the levels of these peptides and hyperemesis may play a role in this regulation. As far as the present authors know, this is the first study to report the serum levels of adropin, salusin alpha and salusin beta, vaspin, and preptin in HG.

HG diagnosis is based on the presence of vomiting for a prolonged duration in the anamnesis, an inability to tolerate food, and liquid intake resulting in dehydration. There is no effective specific treatment for HG, and the exact pathogenesis and etiology remain unclear. It is associated with multiple factors including metabolic and hormonal changes.

Homeostasis of energy is regulated by genetic factors, food intake, and energy expenditure. When energy input is greater than expenditure, the balance is positive, which can lead to weight gain and obesity. When the balance is negative, weight lost occurs. Regulation of this homeostasis is multi-factorial, involving many orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) peptide hormones [11].

HG shares many clinical features with other debilitating eating disorders associated with chronic negative energy balance, such as anorexia nervosa, malnutrition, chronic infectious disease, and cachexia. High levels of ghrelin has been shown previously in some of these disorders, which

are characterised by anorexia, loss of appetite, nausea and/or vomiting, wasting, and loss of weight similar to HG [12]. Albayrak *et al.* reported that levels of total ghrelin, acylated ghrelin, PYY-3, and the total ghrelin / leptin ratio were significantly higher in HG group [13].

Wren *et al.* reported that blood ghrelin levels of the HG patients increase after fasting [14]. In a similar study Gungor *et al.* revealed that nesfatin-1 concentrations in the HG group were higher compared to the control group whereas leptin concentrations during pregnancy were lower in the HG group as compared to the control group. However, they showed that the two groups did not differ with regards to acyl and des-acyl ghrelin and obestatin [15]. Another study suggested that serum levels of asymmetric dimethylarginine in pregnant women with HG indicate the role of endothelial dysfunction in the pathogenesis of HG [16].

In this study, the authors found significantly increased levels of salusins and adropin in women with HG. Aydin *et al.* demonstrated in their study that salusin alpha and beta were significantly lower in both plasma and colostrums of GDM than healthy lactating women (7). In an another study Beigi *et al.* reported that low serum adropin concentration is associated with GDM [17]. So both these peptides may act as an endocrine fashion in HG pathogenesis and they seem to be anorexigenic peptides.

In the present study there was decreased levels of vaspin and preptin in women with HG. This may be explained by homeostasis of energy that is regulated by food intake and energy expenditure. A related article showed that women with GDM had significantly higher plasma and colostum preptin concentrations than healthy lactating women during the colostral and transitional milk period [7].

There is a connection between the hormones involved in energy regulation and HG, increased salusins and adropin levels, and decreased vaspin and preptin levels may have stimulated decreased appetite and food intake, weight loss, and negative energy balance in HG.

Another study showed that levels of copeptin, adropin, and irisin in the colostrum were significantly higher than those in transitional and mature milk samples from healthy women. The authors indicated that these peptides could influence the regulation of metabolic pathways and the postnatal growth and development of different organs in the newborn [18]. Özkan *et al.* showed that leptin, preptin, and acylated ghrelin levels increased with higher body mass index [19]. Indeed, one would expect to see inverse correlations between ghrelin or related peptides with BMI to propose a possible cause-effect relationship between ghrelin and HG since weight loss is a sign of HG.

Conclusions

To the present authors' knowledge, this is the first report that evaluates serum adropin, salusin alpha and salusin beta, vaspin, and preptin levels in HG patients. Additional studies with large population in this area should clarify what, if any role, these proteins provide in diagnosing and monitoring the disease.

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