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Original Research

Circulating vaspin and IL-6 concentrations in second trimester pregnancy with gestational diabetes

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Summary

Objective: This study aims to compare serum vaspin and IL-6 concentrations between pregnant women with gestational diabetes mellitus (GDM) and normal glucose tolerance (NGT), as well as with non-pregnant healthy subjects (NC). *Materials and Methods:* A total of 85 women were included into this study. These patients were divided into groups: GDM group (n=30), patients who had GDM, NGT group, (n=28), pregnant women with normal oral glucose tolerance test (OGTT) values, NC group (n=27), and non-pregnant controls. Vaspin and IL-6 concentrations were measured by enzyme-linked immunosorbent assay (ELISA). *Results:* Serum vaspin levels did not differ between women with GDM (5.1 ± 2.36 ng/ml) and NGT (5.43 ± 1.88 ng/ml), but were significantly higher than those in the NC group (2.03 ± 2.34 ng/ml, $p < 0.01$). Circulating vaspin did not significantly correlate with markers of adiposity (BMI) and insulin resistance (fasting plasma glucose, homeostasis model assessment of insulin resistance) in the GDM and NGT groups. However, vaspin was positively correlated to total cholesterol and triglycerides in these two groups, and was significantly negatively correlated with serum IL-6 levels in the GDM group. *Conclusions:* Serum vaspin concentrations were elevated in pregnant women irrespective of the status of their glucose tolerance. Vaspin may be a marker of lipid metabolism, and may be affected by proinflammatory cytokines such as IL-6 during pregnancy.

Key words: Gestational diabetes mellitus; Pregnancy; Vaspin; IL-6; Lipid metabolism.

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy [1], is a state of chronic insulin resistance (IR) that occurs in 2-5% of pregnant women [2]. The reported prevalence of GDM varies between 0.6% and 20% of pregnancies, depending on the screening method, gestational age, and the population studied [3]. Recently, several cytokines including leptin, C-reactive protein (CRP), TNF-α, adiponectin, and visfatin have been associated with GDM [3, 4].

Visceral adipose tissue-specific serpin (vaspin) is a newly discovered adipocytokine, which is mainly secreted by visceral adipose tissues, and has insulin-sensitizing effects [5]. It was identified as a member of the serine protease inhibitor family, which was originally discovered in visceral adipose tissue of an animal model of type-2 diabetes mellitus (T2DM) [5]. Vaspin protein expression and its serum levels increase at the peak of obesity and IR, and decrease with the exacerbation of diabetes in rats [5]. Human vaspin protein comprises of 415 amino acids, and homology analysis indicated that vaspin has 40.4% identity with α1-antitrypsin [5]. Human serum vaspin concentrations positively correlate with age, BMI, and IR; all of which are abrogated in patients with T2DM [6]. The association between circulating vaspin and insulin sensitivity remains controversial in T2DM [7-9].

In normal pregnancy, vaspin is expressed in the placenta. Its expression increases during pregnancy, reaching its highest level at the end of gestation [10]. Therefore, it was hypothesized that circulating vaspin levels increased in pregnancy. However, one study reported that at 24-30 weeks of gestation, normal pregnant women showed significantly lower vaspin serum levels compared to non-pregnant controls [11]. In another study, it was revealed that vaspin levels slowly decreased from the second trimester to postpartum in GDM. In the third trimester of pregnancy, it has been reported that vaspin levels are positively correlated to insulin levels, homeostasis model assessment of insulin resistance (HOMA-IR) and triglycerides in GDM women [12]. However, a more recent study revealed that the maternal serum levels of vaspin increased in women with GDM in the second trimester of pregnancy, compared to normal controls [13]. Therefore, it was hypothesized that vaspin may play a role in GDM.

Several studies have demonstrated that high interleukin-6 (IL-6) levels are associated with GDM [14-16]. El-Mesallamy *et al.* [17] demonstrated that serum vaspin was significantly positively correlated with serum IL-6 levels in T2DM. Thus, the aim of this study was to compare serum vaspin and IL-6 concentrations between GDM and pregnant women with normal glucose tolerance (NGT), as well

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as with non-pregnant healthy subjects (NC).

Materials and Methods

Fifty-eight pregnant women with gestational age between 24 and 28 weeks were admitted at the Obstetrics and Gynecology Department of this Hospital between January 2013 and June 2013. Among these patients, 30 patients had GDM (GDM group) and 28 age-matched pregnant patients had normal oral glucose tolerance test (OGTT) values (NGT group). In addition, 27 age-matched non-pregnant women, who had their annual check-up examination at the Medical Examination Center of this Hospital, were recruited and served as controls (NC group) (Table 1). GDM was diagnosed between 24 and 28 weeks of gestation when subjects had one or more values above the threshold for a 75-gram two-hour OGTT, according to the diagnostic criteria of the International Association of Diabetes and Pregnancy Study Group (IADPSG). The normal values between 24 and 28 weeks of gestation were as follows: fasting glucose < 5.1 mmol/L (92 mg/dL), one hour < 10.0 mmol/L (180 mg/dL) and two hours < 8.5 mmol/L (153 mg/dL) [18].

All subjects were non-smokers and did not receive any drugs known to affect carbohydrate metabolism. Patients with a history of diabetes mellitus and/or abnormal glucose readings before pregnancy, pregnancy-induced hypertension, pre-eclampsia, and other pregnancy complications were excluded. All participants were in good health, without any known disease.

The protocol was approved by the Human Ethics Committee of our Hospital. All patients who participated in the study provided a written informed consent.

Venous blood samples were collected from all subjects after an eight-hour overnight fasting. Blood samples were collected in tubes without anticoagulants, centrifuged at 3,000 rpm for 10 minutes, and stored at -80°C until analysis. Blood glucose, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC) were analyzed at the Biochemical Laboratory of this Hospital. Plasma glucose and lipids were determined through routine methods using an automatic analyzer. Plasma insulin was measured by chemiluminescence assays. Serum vaspin and IL-6 were determined by enzyme-linked immunosorbent assay (ELISA, sensitivity 0.1 ng/ml, intra-assay coefficient of variation [CV] < 10%, inter-assay CV < 10%). Insulin sensitivity was determined using the HOMA index through the formula: HOMA-IR = fasting insulin (FINS, μU/mL) × fasting plasma glucose (FPG, mM) / 22.5.

For clinical and anthropometrical variables, normally distributed data were reported as mean ± standard error (SE). For variables with non-Gaussian distribution, values are reported as median (25-75th percentile). Parametric methods were used for normally distributed parameters, and comparisons between groups were performed using one-way analysis of variance (ANOVA). Non-parametric analyses were performed for non-normally distributed parameters, and comparisons between groups were performed using the Kruskal-Wallis test with post-hoc Mann-Whitney *U*-test. Correlation analyses were performed with Spearman's or Pearson's correlation coefficients, depending on the distribution of the variables. *P* values < 0.05 were considered statistically significant. All statistical analyses of the study were performed using SPSS version 13.0.

Table 1. — *Clinical and biochemical characteristics of the population studied.*

	GDM (n=30)	NGT (n=28)	NC (n=27)	*p* value
Age (years)	29.27 ± 2.43	28.93 ± 3.16	29.67 ± 4.14	>0.05*,**,***
Gestational age (weeks)	26.91 ± 2.07	25.98 ± 1.47		>0.05
Pre-pregnant BMI (kg/m^2)	24.08 ± 3.94	22.61 ± 2.58	23.11 (4.03)	>0.05*,**,***
Current BMI (kg/m^2)	27.94 ± 3.11	27.08 ± 2.82		NS
Fasting glucose (mmol/l)	5.48 ± 0.69	4.54 ± 0.28	5.16 ± 0.42	<0.01*,***
				>0.05**
One hour	10.87 ± 1.84	7.42 ± 1.33	7.58 ± 0.83	<0.01*
				<0.05**
Two hours	8.55 ± 1.76	6.2 ± 0.92	6.75 ± 0.68	<0.01*
				<0.05**
Total cholesterol (mg/dl)	5.52 ± 0.87	5.85 ± 0.78	4.62 ± 0.67	>0.05*
				<0.01**,***
Triglycerides (mg/dl)	2.79 ± 0.77	2.52 ± 0.71	0.86 ± 0.49	>0.05*
				<0.01**,***
LDL-cholesterol (mg/dl)	3.34 ± 0.77	3.4 ± 0.62	2.27 ± 0.47	>0.05*
				<0.01**,***
HDL-cholesterol (mg/dl)	1.75 ± 0.44	1.94 ± 0.39	1.5 ± 0.35	>0.05*
				<0.01**,***
Insulin (mU/ml)	14.03 ± 5.57	11.49 ± 4.18	8.88 ± 3.75	=0.05*
				<0.01**,***
HOMA-IR	3.45 ± 1.46	2.32 ± 0.86	2.03 ± 0.87	<0.01*,**
				>0.05***
Vaspin (ng/ml)	5.1 ± 2.36	5.43 ± 1.88	2.03 ± 2.34	>0.05*
				<0.01**,***
Il-6 (pg/ml)	296.96 ± 122.38	286.80 ± 97.66	234.38 ± 90.86	>0.05*
				<0.01**,***

*All parameters are given mean + standard deviation and minimum-maximum values. Comparisons are shown between groups as *: GDM and NGT, **:GDM and NC ***: NGT and NC. n: subject number, p values statistically evaluated as p > 0.05 insignificant and p < 0.05 significant.*

Table 2. — *The correlation of vaspin with other parameters*

	GDM		NGT		NC	
	r	*p*	*r*	*p*	*r*	*p*
FPG	-0.38	0.06	-0.25	0.20	-0.08	0.69
Insulin	-0.34	0.07	0.14	0.49	-0.42	0.03*
HOMA-IR	-0.35	0.06	0.09	0.66	-0.41	0.03*
TC	0.42	0.02*	0.71	0.00*	0.05	0.81
TG	0.51	0.00*	0.38	0.046*	-0.26	0.19
HDL	0.13	0.49	0.34	0.07	0.14	0.48
LDL	0.33	0.08	0.04	0.82	0.12	0.56

** $p < 0.05$. GDM: gestational diabetes mellitus; HDL:high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; LDL:low-density lipoprotein cholesterol; NGT: normal glucose tolerance; NC: non-pregnant women with normal glucose tolerance.*

Table 3. — *The correlation IL-6 with other parameters.*

	GDM		NGT		NC	
	r	*p*	*r*	*p*	*r*	*p*
Pre-pregnant BMI	0.44	0.02*	-0.02	0.93	-0.27	0.18
Current BMI	0.45	0.01*	-0.07	0.74	-	-
FPG	0.54	0.00*	0.52	0.01*	0.02	0.91
Insulin	0.07	0.71	-0.19	0.34	-0.01	0.96
HOMA-IR	0.04	0.85	-0.21	0.29	0.03	0.90
TC	-0.25	0.19	0.09	0.66	-0.16	0.43
TG	-0.50	0.01*	-0.17	0.39	-0.21	0.29
HDL	-0.29	0.12	0.28	0.15	0.04	0.84
LDL	-0.24	0.21	0.06	0.75	0.04	0.85

** $p < 0.05$. GDM: gestational diabetes mellitus; HDL: high-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low- density lipoprotein cholesterol; NGT: normal glucose tolerance; NC: non-pregnant women with normal glucose tolerance.*

Results

The clinical and biochemical characteristics of all groups studied are presented in Table I. In the present study, the demographic features (median age, gestational age, and pre-pregnancy BMI) of subjects in all groups were similar. Fasting serum vaspin, IL-6, insulin, TC, TG, LDL, and HDL values in the GDM and NGT groups were significantly higher than those in the NC group ($p < 0.01$). Furthermore, serum vaspin, IL-6, insulin, TC, TG, LDL, and HDL levels in the GDM and NGT groups were similar ($p > 0.05$). Fasting serum glucose and serum glucose levels at one and two hours after OGTT in the GDM group were higher than in the NGT group ($p < 0.01$). Subjects in the NGT group had lower fasting serum glucose levels compared to subjects in the NC group ($p < 0.01$).

The correlations between serum vaspin, IL-6 and other measured parameters in these three groups are shown in Tables 2 and 3, respectively. Circulating vaspin did not significantly correlate with markers of adiposity (BMI) and IR (FPG and HOMA-IR) in the GDM and NGT groups. However, vaspin was positively correlated to TC and TG levels in the GDM and NGT groups ($r = 0.42$ and $p = 0.02$, $r = 0.51$ and $p < 0.01$; $r = 0.74$ and $p < 0.01$, $r = 0.38$ and $p = 0.046$), but not in the NC group (Table 2). Circulating IL-6 was significantly positively correlated with FPG ($r = 0.54$ and $p < 0.01$), pre-pregnancy BMI ($r = 0.44$ and $p = 0.02$) and the present BMI ($r = 0.45$ and $p = 0.01$) in the GDM group (Table 3). Moreover, circulating vaspin levels were significantly negatively correlated with circulating IL-6 levels in the GDM group ($r = -0.47$ and $p=0.01$).

Discussion

The present study involved the investigation of circulating levels of vaspin and IL-6 in women who were in their second trimester of pregnancy, and the relationships between serum vaspin and the measured parameters were compared. These results revealed that vaspin levels were higher in the GDM and NGT groups than in the NC group. However, vaspin levels in the GDM and NGT groups were similar. Patients with GDM had significantly higher FPG and HOMA-IR levels than in subjects with NGT, whereas women in the NGT group had markedly lower FPG levels, compared to the NC group, which was expected. In contrast to these findings, Giomisi *et al.* [11] found that serum vaspin levels were lower in pregnant women when compared with non-pregnant controls. The reports of Gkiomisi *et al.* [12] and Stepan *et al.* [19] revealed that there was no significant difference in circulating vaspin levels between the GDM and non-GDM groups at both the second and third trimesters, which was in good agreement with the results of the present study. However, Jia *et al.* found that vaspin levels in the GDM group were higher than in the NGT group, which may be correlated with that the weight that grew were more in the GDM group, compared to that in the NGT group.

Previous studies on vaspin levels in T2DM and obesities are also contentious. Some studies have reported increased serum vaspin levels in T2DM patients compared with control subjects [17, 20]; however, one study found that vaspin levels were lower in female subjects with T2DM compared with those who have NGT. However, the difference was not statistically significant [6]. Furthermore, another study revealed unchanged serum levels between NGT, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or T3DM [21, 22].

Vaspin is a newly discovered adipocytokine mainly secreted by visceral adipose tissues. Vaspin expression and its serum levels increased at the peak of obesity and insulin resistance, and decreased with the worsening of diabetes [5]. Caminos *et al.* [10] found that vaspin expression in the placenta gradually increased during pregnancy, and reaching its highest levels at the end of gestation. This may be the mechanism by which circulating vaspin levels are increased in pregnant women. Furthermore, non-pregnant women can

store more fat, and thereby have higher levels of vaspin in serum. In addition, placental vaspin mRNA levels were significantly elevated in pregnant rats with intrauterine growth restriction, compared to control pregnant rats [10]. Finally, a previous study reported that cord vaspin levels were significantly higher in small-for-gestational age neonates than in neonates appropriate for gestational age or large for gestational age [23]. Consequently, it has been postulated that vaspin may have a catabolic function during pregnancy, and that its levels are modulated by placental energy status. This can be explained by the larger fetuses in subjects with GDM, in which the placenta is rich in local nutrition. Thus, the decreased secretion of vaspin in serum was not different from that in the NGT group. However, the mechanism controlling vaspin secretion in humans also remains unclear. Bluher [22] postulated that vaspin inhibited a protease that played a role in the degradation of a hormone or molecule with direct or indirect glucose lowering effects. The administration of recombinant vaspin to obese mice has been found to improve glucose tolerance and insulin sensitivity [5].

Previous studies have demonstrated negative, positive, or no relationship [24-26] between vaspin and IR in humans. In the present study, no association was found between vaspin and insulin sensitivity in pregnant women, as previously reported [11, 19]. However, vaspin was positively correlated to lipid parameters (TC and TG) in the GDM group and in normal pregnant women. This is agreement with the authors' earlier studies that serum vaspin level was positively correlated to TC in the NGT group during later pregnancy [27]. In contrast to the findings of the present study, Giomisi *et al.* [11] revealed a negative correlation between vaspin and TG in normal pregnancy. In all the relationships found between these markers, it was revealed that vaspin may be mainly involved in lipid metabolism. Thus, the relationship between vaspin and lipid metabolism requires further investigation.

Maternal serum vaspin levels slightly decreased in the GDM group, compared with the NGT group, while IL-6 levels slightly increased in the GDM group. However, there was no significantly difference between these two groups. As previously reported [28], circulating IL-6 was positively correlated with FPG, pre-pregnancy BMI and the present BMI. However, serum vaspin was significantly negatively correlated with serum IL-6 levels in the GDM group. Similar to the study conducted by El-Mesallamy *et al.* [17] on T2DM, serum vaspin may be related to serum IL-6. This observation raises the suggestion of the possible association between vaspin and IL-6 in GDM, which requires further studies.

The present study had its limitations. Only the vaspin levels at the second trimester pregnancy were studied. As the number of subjects was small, a definitive conclusion could not be drawn from the study. Furthermore, the data in the present study should be considered as preliminary findings, and further studies are required to validate these findings.

In conclusion, the results of the present study suggest that serum vaspin levels are higher in pregnant women than in non-pregnant healthy controls. This elevated level was not found to be correlated to the state of glucose tolerance. The elevation of circulating vaspin during pregnancy may be caused by its additional secretion from the placenta or some other sources. Vaspin may be a marker of lipid metabolism in pregnancy, and affected by proinflammatory cytokines such as IL-6. Further research is required to explore the exact role of vaspin in pregnancy and GDM.

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