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ARE VASPIN AND OMENTIN-1 RELATED TO INSULIN RESISTANCE, BLOOD PRESSURE AND INFLAMMATION IN NAFLD PATIENTS?

DA LI SU VASPIN I OMETIN-1 POVEZANI SA INSULINSKOM REZISTENCIJOM, KRVNIM PRITISKOM I INFLAMACIJOM KOD NAFLD PACIJENATA?

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Summary

Background: Non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of insulin resistance, is the most common cause of chronic liver. The present study aimed to investigate the roles of vaspin and omentin-1 in the NAFLD-related pathology including IR, inflammation and elevated blood pressure.
Methods: This cross-sectional study was conducted among 83 NAFLD patients in Jahrom, Iran. Plasma levels of omentin-1, vaspin, hs-CRP and IL-6 were measured. Anthropometric indices, lipid profiles, liver enzymes as well as abdominal ultrasonography were assessed.
Results: Partial correlations controlling for age and sex showed significant positive correlation between vaspin and fasting blood sugar (FBS), insulin, HOMA-IR, and hs-CRP. It has been observed that omentin negatively correlated with glucose levels. Moreover, a marginally significant association has been found between omentin levels and systolic blood pressure (SBP).
Conclusions: This study shows that vaspin and omentin-1 are associated with inflammation, insulin resistance and serum glucose levels in patients with NAFLD.

Keywords: insulin resistance, NAFLS, adipokines, lipid profiles, inflammation

Kratak sadržaj

Uvod: Oboljenje ne-alkoholna masna jetra (NAFLD) je posledica promene na jetri usled insulinske rezistencije je najčešći uzrok hroničnog oboljenja jetre. Ovaj rad ima za cilj ispitivanje uloge vaspina i ometina-1 u NAFLD-patologiji, inflamaciji i povećanom krvnom pritisku.
Metode: Ispitivanja su izvedena na 83 NAFLD pacijenta u Jahrom-u, Iran. Mereni su nivoi ometina-1, vaspina, hs-CRP i IL-6. Ispitivani su antropometrijski parametri, profil lipida, jetreni enzimi i abdominalna ultrasonografija.
Rezultati: Delimičnom korelacijom između pola i starosti ukazala su na pozitivnu korelaciju između vaspina i nivoa glukoze u krvi (FBS), insulina, HOMA-IR i hs-CRP. Nađeno je da je ometin u negativnoj korelaciji sa nivoima glukoze. Međutim, marginalno značajna veza je nađena između nivoa ometina i sistolnog krvnog pritiska (SBP).
Zaključak: Rezultati su pokazali da vaspin i ometion-1 su praćeni inflamacijom, insulinskom rezistencijom u nivoima glukoze u serumu kod pacijenata sa NAFLD.

Ključne reči: insulinska rezistencija, NAFLD, adipokini, lipidni profil, inflamacija

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Introduction

The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing due to the growing epidemics of obesity (1). NAFLD is considered as one of the leading causes of chronic liver disease and encompasses a wide spectrum of liver diseases, ranging from a simple fatty liver (steatosis) to steatohepatitis, fibrosis, or cirrhosis (1). Given the widespread increasing rates of NAFLD, a better understanding of its pathophysiology is of significant importance. NAFLD is considered to be the hepatic component of metabolic syndrome (MS) and is associated with visceral obesity, with insulin resistance (IR) playing a key role (2), however, the pathogenesis remains unclear.

On the basis of the National Cholesterol Education Program Adult Treatment Panel III, in the presence of three out of five criteria which include a high waist circumference, high TG or reduced high-density lipoprotein (HDL)-cholesterol levels, elevated blood pressure, and high fasting glucose levels or a diagnosis of T2DM, MS can be diagnosed (3). Approximately 90% of the NAFLD patients present more than one component of the MS, and about 33% of the patients meet the criteria for the MS (4). Additionally, in both cross-sectional and prospective studies, NAFLD has been associated with an increased prevalence of hypertension (5).

The ability of insulin to inhibit glucose production is impaired in patients with metabolic syndrome or NAFLD, which results in mild hyperglycemia, which in turn stimulates insulin secretion and leads to hyperinsulinemia. Thus fasting hyperglycemia and hyperinsulinemia are consequences of hepatic insulin resistance and correlate positively with liver fat, even independent of BMI (6).

In addition, pro-inflammatory cytokines play important roles in fatty liver diseases (7). In this regard, several studies suggested an important role for IL-6 in NAFLD (8, 9).

Derived from adipose tissue, multiple regulating proteins, so-called adipokines, are secreted molecules with diverse local, peripheral and central functions.

A growing body of evidence reported that an impaired pattern in adipokine secretion could play a pivotal role in the development of metabolic syndrome, including NAFLD and the progression to NASH (1).

Omentin-1 is a circulating adipokine and has been identi ed as an adipokine that may improve insulin sensitivity. Decreased omentin expression was shown to be implicated in a variety of chronic in ammatory diseases (10).

Visceral adipose tissue-derived serine protease inhibitor (vaspin) is a member of the serine protease inhibitor family (serpin) and is a recently discovered adipokine (11). Serum vaspin concentration is reported to be increased in patients with NAFLD and has been found to be positively associated with liver fibrosis scores and C-reactive protein (12). Regarding its recent discovery, there are inconsistent reports of the role of vaspin in hepatic fibrosis.

In this study, we provide insights into the roles of vaspin and omentin-1 in the NAFLD-related pathology including IR, inflammation and elevated blood pressure.

Materials and Methods

Study Setting and Design and Subjects

This cross-sectional study surveyed the association of inflammatory markers including omentin 1 and vaspin as well as Insulin resistance and blood pressure in NAFLD patients. An overall of 83 patients from Jahrom University of medical science in Iran participated in this study. Age group between 20 and 50 years with the history of NAFLD regarded as Inclusion criteria. Exclusion criteria included chronic diseases including kidney diseases, diabetes and malignancy, smoking, menopause and pregnancy and lactation. The aim of the study was explained and the written consent was obtained from all patients. Furthermore, the ethical committee of Jahrom University of Medical Sciences approved this study.

Anthropometric measurements

Weight and height were measured by seca scale (Hamburg Germany) and a stadiometer attached to the scale respectively. Body mass index (BMI) was calculated from measurement height in meters and weight in kilograms. Waist circumference measurements made at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference measurements have been taken around the widest portion of the buttocks and waist-to-hip ratio (WHR) was determined.

Sample collection and laboratory assessment

Approximately 10 mL of venous blood samples were taken from all patients after a 12-h overnight fasting to evaluate serum concentration of adipokines and lipid profiles, liver enzymes. All the samples centrifuged at 4 °C for 10 min at 2500 r.p.m to separate serum and plasma and were frozen at − 80 °C.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as serum vaspin and omentin-1, hs-CRP, IL-6 were analyzed by Commercial ELISA kit. Total cholesterol, HDL cholesterol (high-density lipoprotein-cholesterol) and triglyceride levels were analyzed by enzymatic procedures. If triglyceride concentration was <4.5 mmol/L, LDL cholesterol levels

was calculated by the Friedewald equation. HDL and TG levels reported in molar concentration.

All the abdominal ultrasonography was taken through an East Medical sonographic scanner equipped with a convex 3.5 MHz browser by a radiology specialist.

After a 12 h fasting, FBS and Insulin level was evaluated by the hexokinase/glucose-6-phosphate dehydrogenase method; HbA1c Insulin resistance (homeostasis model assessment insulin resistance, HOMA-IR) were calculated according to Mathews et al. (13). HOMA-IR values higher than 2.70 showed insulin resistance, as identified in the Brazilian Metabolic Syndrome Study (14). The blood pressure was measured in standard conditions.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS, Chicago, USA) software, version 21.0 for Windows. Data are presented as frequencies for nominal variables and as means ± standard deviation (SD) for ordinal variables.

Associations between adipokines and inflammatory biomarkers, SBP AND DBP, and parameters of glycemic status were analyzed using Partial correlation controlling for age and sex. A P value of <0.05 was considered statistically significant.

Table I Demographic and anthropometric characteristics in NAFLD patients.

Characteristics	Patients (n=83)
Gender (n,%) Male Female	 42 (50.6 %%) 41 (49.4%)
Grade of fatty liver (n, %) Grade I Grade I Grade III	 49 (59.0%) 25 (30.1%) 9 (10.8%)
Physical activity Light (%) Moderate (%) Severe (%)	 35 (42.2%) 35 (42.2%) 13 (15.7%)
Age (years)	36.71± 7.21
Weight (kg)	83.07±12.83
BMI (kg/m^2)	29.41±4.18
WC (cm)	99.07±10.43
HC (cm)	104.85 ± 7.03
WHR	0.94±0.08
Fat percentage	32.70 ± 7.70

Mean ± standard deviation is reported for age, weight, BMI, WC and WHR. BMI: body mass index, WC: waist circumference, WHR: waist to hip ratio.

Results

Demographic and anthropometric characteristics of patients are shown in *Table I*. The biochemical parameters of patients including lipid profile, liver enzymes, inflammatory biomarkers and adipokines are shown in *Table II* and *III*, respectively. Partial correlations controlling for age and sex showed that vaspin is significantly associated with FBS, insulin, HOMA-IR, and inversely associated with QUICKI (*Table IV*). As it is observed, omentin levels correlated negatively with glucose levels. Similarly, partial correlations controlling for age and sex showed that vaspin is significantly associated with hs-CRP. Additionally, omentin levels showed a marginally significant association with SBP (*Table IV*).

Table II The values of biochemical parameters of patients are presented in Table II.

Variables	Patients (n=83)
Triglyceride (mmol/L)	10.85 ± 3.08
Total cholesterol (mmol/L)	11.64 ± 2.01
High-density lipoprotein (HDL) (mmol/L)	2.15 ± 0.48
Low-density lipoprotein (LDL) (mmol/L)	8.29 ± 1.55
Aspartate aminotransferase (AST) (U/L)	41.99 ± 8.84
Alanine transaminase (ALT) (U/L)	40.85 ± 8.76

Mean ± standard deviation is reported.

Table III The values of glycemic parameters, blood pressure and inflammatory biomarkers of patients.

Variables	Patients (n=83)
FBS (mmol/L)	5.3 ± 0.4
Insulin (μIU/mL)	15.44 ± 2.89
HOMA-IR	3.64 ± 0.73
HOMA-B	178.13 ± 47.37
QUICKI	0.317 ± 0.009
SBP (mmHg)	12.57 ± 0.91
DBP (mmHg)	7.70 ± 0.87
IL6 (pg/mL)	72.11 ± 76.29
hs-CRP (mg/L)	2.75 ± 1.27
Omentin (ng/mL)	263.45±110.70
Vaspin (ng/mL)	6.83±2.37

Mean± SD is reported.

Table IV Evaluation of correlations between serum adipokines, and insulin resistance in the subjects.

	Vaspin		Omentin-1 (ng/mL)	
	r	p	r	p
FBS	0.216	0.53	-0.213	0.05
Insulin	0.290	0.009	NS	
HOMA-IR	0.324	0.003	NS	
HOMA-B	NS		NS	
QUICKI	-0.330	0.003	NS	
SBP	NS		-0.210	0.06
DBP	NS		NS	
IL6	0.395	< 0.001	NS	
Hs-CRP	0.296	0.007	NS	

Spearman's correlation coefficients were used, $P<0.05$ is statistically significant; NS: non-significant.

Discussion

NAFLD is a spectrum of metabolic abnormalities disturbance including obesity, insulin resistance, hypertension, and impaired plasma glucose and lipid profile, so it can be regarded as a hepatic manifestation of metabolic syndrome (15, 16). One of the most prominent features of this syndrome is obesity-related insulin resistance and inflammation that identified by raised inflammatory cytokines level and pro-inflammatory pathway activation (17). Numerous studies have suggested adipokines as a Link between metabolic disturbances such as insulin resistance and inflammation that involved in the pathogenesis or progression of NAFLD (1, 18, 19). In this study, we detected a significant correlation between vaspin and insulin resistance, hs-CRP and IL-6 in patients with NAFLD. Omentin showed a marginally significant correlation with glucose homeostasis, but no association was found for inflammatory cytokines. In addition, a significant association between omentin and SBP observed in patients with NAFLD.

Adipokines, in adipose tissues, based on their effects on inflammatory responses are classified into two groups: pro- and anti-inflammatory adipokines (20). Recent studies indicated anti-inflammatory effects of vaspin and omentin in obesity and insulin resistance conditions (20–22). Vaspin, a member of the serine protease inhibitor family, is an insulin-sensitizing adipokine which upregulated in metabolic diseases to compensate insulin resistance and inflammatory complication and furthermore may play an inhibition role in brosis development and progression (23, 24). This observation suggested the possible contribution of vaspin in liver brogenesis (25). In our study, vaspin correlated positively with insulin resistance which provides support to the mentioned compensatory mechanism of vaspin overexpression in human adipose tissue in IR condition (23, 25–27). Although the exact mechanisms by which vaspin improved insulin sensitivity is unclear, studies suggested that vaspin may antagonize the effect of proteases that are up-regulated in IR states (23, 26). Vaspin also decreased the expression of leptin, TNF-α, and resistin, so ameliorate in ammatory process that may effectively improve IR (10). In the present study, Keeping with previous research, vaspin associated significantly with hs-CRP and IL-6 in study participants (12, 28–31). Inflammatory process amelioration may aid in impaired insulin sensitivity (25, 29). In contrast, a series of previous studies revealed a negative association between hs-CRP and vaspin levels (32, 33). These controversies in reported results may in part be due to the different influences of various chronic inflammatory diseases on vaspin concentrations. Thus, further studies with larger participants are needed to investigated vaspin and inflammatory cytokines associations (34, 35).

Clinical studies demonstrated the close relationship between plasma vaspin levels and atherosclerosis, so, vaspin might be involved in the coronary artery disease (CAD) process (35–37). Experiments also indicated that vaspin could inhibit the release of key inflammatory markers in vascular smooth muscle cells and prevent FFA-induced apoptosis in endothelial cells, also vaspin could inhibit proliferation of vascular smooth muscle cells which induced by chemokinesis inactivation of ROS and MAPK, PI3K/Akt, and NF-kB signaling (12, 36). In Kameshima et all study, it was indicated that vaspin prevents elevation of blood pressure through peripheral arterial hypertrophy inhibition that may induce via antioxidative and anti-inflammatory mechanisms (38). In addition, vaspin augments acetylcholine-induced endothelium-dependent relaxation through the inhibition of acetylcholinesterase activity (AChE) activity (39).

However, in the present study, we did not find any significant association between vaspin level and blood pressure. This could be explained by the fact that the blood pressure of the participants was in normal range, thus there is no association between adipokines and blood pressure.

Plasma omentin levels are significantly lower in obese subjects, diabetic patients, and in people with chronic inflammatory diseases compared to healthy ones (20, 26, 27, 30, 31, 35, 40). A negative correlation has been reported between plasma omentin levels and anthropometric indices including BMI and waist circumference and, fasting insulin, and HOMA. Similarly, we have found an inverse association between omentin concentration and FBS. The association between omentin and these metabolic indices suggests that omentin may be a protective factor

against the obesity-related complications (41). Although these findings suggest that omentin levels may reduced in NAFLD, there is evidence of increased levels of omentin in patients with NAFLD (42). More studies are needed to understand the exact roles of omentin in obesity and its related disorder. More studies are needed to identify reasons for these paradoxical findings.

Omentin could reduce the activation of nuclear factor kappa-light-chain- enhancer of activated B cell (NF-κB), and decreases the inflammatory cytokines such as CRP, IL- 6, and TNF-α (34). In the present study, we did not find any significant association between omentin levels and inflammatory cytokines, even though a negative correlation observed between serum omentin and systolic blood pressure. Previous animal studies indicated that omentin improves endothelial functions and prevented blood pressure elevation in rats through endothelium-dependent relaxation. It has been determined that omentin increases the phosphorylation of eNOS and consequently induced relaxation in endothelium (35, 39). As mentioned, obese subjects have significantly reduced omentin levels, so omentin low level may play at least in part a key role in accompanied hypertension in obese patients (40). Although we did not observe a significant correlation between omentin levels and inflammatory cytokines, previous studies indicated positive associations. Taken together, further studies are needed to investigate whether omentin level elevation in NAFLD patients is a compensatory mechanism to insulin resistance and inflammatory states of disease (42).

In conclusion, the present study indicated raised serum levels of omentin and vaspin in patients with NAFLD. Both these adipokines seem to play a major role in the development and progression of NAFLD. Omentin and vaspin may have a potential role in glucose metabolism, inflammation process, and blood pressure as well. Altogether, the present study adds to a growing literature supporting that novel adipokines may contribute to the clinical expression of NAFLD. Future studies may continue to explore a new area to assess the possible role of these novel adipokines in the pathogens of NAFLD.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

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