

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 April 14; 23(14): 2453-2634



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NAME OF JOURNAL  
*World Journal of Gastroenterology*

ISSN  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

LAUNCH DATE  
October 1, 1995

FREQUENCY  
Weekly

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Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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Pleasanton, CA 94588, USA  
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Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE  
April 14, 2017

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## Observational Study

# Serum omentin and vaspin levels in cirrhotic patients with and without portal vein thrombosis

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Supported by Medical University of Silesia- Contract, No. KNW1-090/N/6/0.

**Institutional review board statement:** The study was reviewed and approved by Department of Science of Medical University of Silesia in Katowice.

**Informed consent statement:** All study participants provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Invited manuscript

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Telephone: +48-327894401  
Fax: +48-327894402

**Received:** September 11, 2016

**Peer-review started:** September 12, 2016

**First decision:** November 21, 2016

**Revised:** February 24, 2017

**Accepted:** March 15, 2017

**Article in press:** March 15, 2017

**Published online:** April 14, 2017



## Abstract

### AIM

To investigate serum omentin and vaspin levels in cirrhotic patients; and to assess the relationship of these levels with hemostatic parameters, metabolic abnormalities, cirrhosis severity and etiology.

### METHODS

Fifty-one cirrhotic patients (17 with portal vein thrombosis) were analyzed. Serum omentin and vaspin levels were measured with commercially available direct enzyme-linked immunosorbent assays (ELISAs). To assess platelet activity, the following tests were performed using a MULTIPLATE<sup>®</sup> PLATELET FUNCTION ANALYZER: (1) an ADP-induced platelet activation test; (2) a cyclooxygenase dependent aggregation test (ASPI test); (3) a von Willebrand factor and glycoprotein Ib-dependent aggregation (using ristocetin) test (RISTO test); and (4) a test for thrombin receptor-activating peptide-6 induced activation of the thrombin receptor, which is sensitive to II b/IIIa receptor antagonists.

### RESULTS

Omentin, but not vaspin, serum concentrations were significantly decreased in patients with portal vein thrombosis (PVT) ( $P = 0.01$ ). Prothrombin levels were significantly increased in patients with PVT ( $P = 0.01$ ). The thrombin receptor activating peptide (TRAP) test results were significantly lower in the PVT group ( $P = 0.03$ ). No significant differences in adipokines serum levels were found regarding the etiology or severity of liver cirrhosis assessed according to the Child-Pugh or Model of End-Stage Liver Disease (MELD) scores. There was a significant increase in the TRAP ( $P = 0.03$ ), ASPI ( $P = 0.001$ ) and RISTO high-test ( $P = 0.02$ ) results in patients with lower MELD scores. Serum omentin and vaspin levels were significantly down-regulated in patients without insulin resistance ( $P = 0.03$ ,  $P = 0.02$ , respectively). A positive relationship between omentin and vaspin levels were found both when all of the patients were analyzed ( $r = 0.41$ ,  $P = 0.01$ ) and among those with PVT ( $r = 0.94$ ,  $P < 0.001$ ).

### CONCLUSION

Serum omentin levels are increased in patients without PVT. Cirrhosis origin and grade do not affect omentin and vaspin levels. The analyzed adipokines do not influence platelet activity.

**Key words:** Omentin; Vaspin; Cirrhosis; Adipokine; Portal vein thrombosis; Portal hypertension

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**Core tip:** Accumulating data suggest that obesity and insulin resistance are related to a more rapid progression of chronic liver diseases, the development of cirrhosis and its complications. Some adipokines have been suggested to contribute to the complicated

pathophysiology of hepatic injury and repair. Ongoing research has revealed alterations in the levels and expression of various adipokines in cirrhosis. Portal vein thrombosis (PVT) has been considered to be a complication of more advanced liver cirrhosis. The data regarding novel adipokines in liver cirrhosis is scarce and ambiguous. The current study evaluated the serum concentrations of omentin and vaspin in patients with liver cirrhosis of different origins and stages with and without PVT. The relationships of these measures with disease severity and etiology, platelet activity, hemostatic parameters and potential complications were also assessed. The study included 51 patients with cirrhosis of different etiologies (alcohol in 30 patients, hepatitis C virus infection in 15, autoimmune hepatitis in 6). Seventeen these patients manifested portal vein thrombosis confirmed by contrast-enhanced computed tomography.

Kukla M, Waluga M, Żorniak M, Berdowska A, Wosiewicz P, Sawczyn T, Bułdak RJ, Ochman M, Ziora K, Krzemiński T, Hartleb M. Serum omentin and vaspin levels in cirrhotic patients with and without portal vein thrombosis. *World J Gastroenterol* 2017; 23(14): 2613-2624 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i14/2613.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i14.2613>

## INTRODUCTION

Liver cirrhosis is associated with progressive liver impairment, leading to the development of numerous complications, including portal hypertension and portal vein thrombosis (PVT)<sup>[1]</sup>. PVT is generally recognized as rare in the general population, being primarily a consequence of myeloproliferative diseases, genetic or acquired thrombophilia or inflammation in the abdominal cavity<sup>[2]</sup>. However, PVT is a relatively common complication of liver cirrhosis, with an estimated frequency of 5%-28%<sup>[3,4]</sup>. Excessive hepatic deposition of fibrotic tissue contributes to intra-hepatic resistance, an up-regulation of portal blood pressure and a reduction in portal blood flow into the liver<sup>[5]</sup>.

Adipokines are polypeptide hormones that are primarily produced by adipocytes. Apart from fat cells, adipose tissue is composed of stromal cells, including macrophages, fibroblasts and infiltrating monocytes, all of which may serve as an additional source of adipokines<sup>[6]</sup>. Accumulating data reveal disturbances in the secretion of some adipokines in chronic liver diseases (CLDs) and cirrhosis, leading to the complex pathophysiology of hepatic injury and healing<sup>[7]</sup>. Some adipokines are also recognized to be active as pro-fibrotic and pro-thrombotic agents. The best of these is known leptin, receptors for which have been identified in hepatic stellate cells and many types of vascular cells, including sinusoidal endothelial cells (SECs), macrophages (Kupffer cells) and platelets<sup>[8-10]</sup>. Another

adipokine, adiponectin, exerts opposite anti-fibrotic and anti-inflammatory effects<sup>[11]</sup>. Novel adipokines and hepatokines were recently described, and their role in liver diseases are now being intensively investigated<sup>[7]</sup>.

Omentin-1 (intelectin-1, also known as an active endothelial factor) is a newly identified adipokine that is highly and selectively expressed in visceral adipose tissue<sup>[12,13]</sup>. The data regarding hepatic omentin expression is equivocal. Our previous study confirmed omentin expression in the liver tissue from chronic hepatitis C (CHC) patients<sup>[14]</sup>. However, an earlier study by Yang *et al.*<sup>[15]</sup> found higher omentin expression in the stroma-vascular cells of omental fat and lower expression in the intestine and lung; no expression was observed in the liver, kidney and pancreas. Omentin has been suggested to be a "good adipokine" because its serum concentration were negatively associated with a multiplicity of metabolic risk factors in metabolic syndrome (MS)<sup>[16]</sup>. A previous study by Pan *et al.*<sup>[17]</sup> revealed significantly lower serum omentin levels in patients with diabetes mellitus (DM). However, the role of omentin in CLD is unclear. A small number of studies have shown that omentin serum are levels increased in CHC, NAFLD and cirrhosis<sup>[14,18,19]</sup>.

Vaspin (visceral adipose tissue-derived serine protease inhibitor) is a novel adipokine that was isolated from both the visceral and subcutaneous white adipose tissues of subjects with obesity and impaired glucose tolerance<sup>[20]</sup>. Vaspin has also been confirmed to down-regulate the expression of profibrogenic and proinflammatory agents, such as leptin, tumor necrosis factor (TNF)-alpha and resistin<sup>[7]</sup>. Some studies have indicated that the induction of vaspin mRNA expression in human adipose tissue might be a compensatory mechanism associated with obesity and increasing insulin resistance (IR)<sup>[7]</sup>. Serum levels of vaspin in CHC patients without fibrosis or with less advanced fibrosis were significantly lower than in healthy controls. However, in patients with bridging fibrosis or cirrhosis, the levels were almost as high as in the control group<sup>[21,22]</sup>. In NAFLD patients, vaspin serum levels seemed to be higher in patients with definite NASH and more advanced fibrosis<sup>[23,24]</sup>.

In light of the aforementioned studies, we decided to investigate serum concentrations of two novel adipokines, omentin and vaspin, in cirrhotic patients with and without PVT. These analyses were performed to assess their prothrombotic action. We then analyzed the association between the serum levels of these adipokines and hemostatic parameters, platelet counts and platelet-aggregation activity markers. We also elucidated the relationship between omentin and vaspin serum levels and cirrhosis severity, etiology and metabolic abnormalities.

## MATERIALS AND METHODS

### Study population

A total of 51 patients (16 females) with cirrhosis of

different etiologies [alcohol in 30 patients (51%), hepatitis C virus (HCV) infection (genotype 1b) in 15 (29%), and autoimmune hepatitis in 6 (12%)] were enrolled. After meeting the qualification criteria, the presence of portal vein thrombosis in 17 was confirmed using contrast-enhanced computed tomography. Data on complications of the liver disease, present and past co-morbidities and current medication use were collected. Patients were excluded for the following reasons: infection with HCV genotypes other than 1b; hepatitis B virus infection; human immunodeficiency virus (HIV) co-infection; drug abuse; the presence of neoplastic, thyroid or psychiatric diseases; or renal or heart failure. Contrast-enhanced spiral computed-tomography was performed on each patient to confirm the presence of PVT. Computed tomography was independently evaluated by two experienced radiologists. The severity of cirrhosis was evaluated by the Model of End-Stage Liver Disease (MELD) and the Child-Pugh score. For further analysis, the patients were divided according to their Child-Pugh score (from A to C) or divided in two subgroups according to MELD scores > 18 and ≤ 18. This cut-off was determined based on studies that assessed MELD predictive values in patients with end-stage liver disease<sup>[25]</sup>. The baseline clinical and laboratory characteristics of the patients are presented in Table 1.

### Ethics statement

The study protocol was approved by the Local Bioethical Committee of the Medical University of Silesia (Approval of Committee NoKNW/0022/KB1/45/II/15, Nov<sup>17</sup>2015). All of the clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All of the study participants provided informed written consent prior to study enrollment.

### Biochemical and serological assays

Biochemical parameters were measured using routine methods. The upper limit of ALT activity was set at 38 IU/L, that of AST at 40 IU/L and that of gamma-glutamyltransferase (GGT) activity at 50 IU/L. The upper total serum bilirubin concentration was set at 17 μmol/L. Insulin concentrations were measured with a DiaMetra Insulin EIA Kit, Cat. No DK0076 (DiaMetra, Italy). For IR estimation, the homeostatic model assessment (HOMA-IR) was calculated using the following formula: fasting insulin level (mUI/L) × fasting glucose level (mg/dL)/405. With respect to the HOMA-IR value, the patients were divided into two subgroups - below and equal or greater than 3.0. The cut-off was determined on the basis of reviewed recent literature<sup>[26]</sup>.

The blood samples were drawn from the antebrachial vein after 16 h of fasting and were the centrifuged. The serum was frozen and stored for further analysis at a temperature of -70 °C. Commercially available direct enzyme-linked immunosorbent assays (ELISA)

**Table 1** General characteristics and basic laboratory tests of cirrhotic patients with and without portal vein thrombosis

	All patients <i>n</i> = 51	PVT (+) <i>n</i> = 17	PVT (-) <i>n</i> = 34	<i>P</i> value
Sex (M/F), <i>n</i> (%)	35/16 (68.6/31.4)	12/5 (70.6/29.4)	23/11 (67.6/32.4)	<i>P</i> > 0.05
Age (yr)	52 (26-80)	56 (26-80)	54 (27-68)	<i>P</i> > 0.05
BMI (kg/m <sup>2</sup> )	27 (17-40)	27 (20-40)	27 (17-36)	<i>P</i> > 0.05
Child-Pugh (points)	7.7 (5-12)	7.3 (5-11)	7.9 (5-12)	<i>P</i> > 0.05
MELD score (points)	13.9 (6-26)	12.8 (9-22)	14.5 (6-26)	<i>P</i> > 0.05
Bilirubin (mg/dL)	3.4 (0.6-14.3)	2.3 (1.1-4.8)	3.9 (0.6-14.3)	<i>P</i> > 0.05
Hemoglobin (g/dL)	7.5-15.3	11.9 (8.4-15)	12.2 (7.5-15.3)	<i>P</i> > 0.05
Platelets (× 10 <sup>3</sup> /mm <sup>3</sup> )	96 (18-330)	83 (32-149)	103 (18-330)	<i>P</i> > 0.05
WBC (× 10 <sup>3</sup> /mm <sup>3</sup> )	5.1 (1.3-15.3)	4.3 (1.9-11.2)	5.5 (1.3-15.3)	<i>P</i> > 0.05
Albumin (g/dL)	3.2 (1.7-5.1)	3.2 (2.4-4.3)	3.2 (1.7-5.1)	<i>P</i> > 0.05
ALT (U/L)	39 (15-130)	41.6 (15-130)	38.1 (15-115)	<i>P</i> > 0.05
AST (U/L)	71.2 (18-216)	69 (18-164)	72.1 (20-216)	<i>P</i> > 0.05
GGTP (U/L)	122 (25-489)	180.3 (25-489) <sup>1</sup>	91.2 (13-236)	<i>P</i> = 0.02
Cholesterol (mg/dL)	176 (45-409)	147.8 (45-284)	187 (87-409)	<i>P</i> > 0.05
HDL-Ch (mg/dL)	46.2 (13-78)	33.6 (17-45)	49.6 (13-78)	<i>P</i> > 0.05
LDL-Ch (mg/dL)	97.5 (19-203)	83 (19-171)	102.4 (43-203)	<i>P</i> > 0.05
TG (mg/dL)	127 (47-407)	133.3 (47-341)	125.3 (48-407)	<i>P</i> > 0.05
Ascites	19/51 (42%)	8/17 (47%)	15/34 (44%)	<i>P</i> > 0.05

<sup>1</sup>GGTP level was significantly higher in PVT (+) patients. *P* value < 0.05 was considered statistically significant. The data are shown as the mean and range or percentage where applicable. BMI: Body mass index; TG: Triglycerides.

were used for measurement of the serum omentin and vaspin levels (BioVendor; Brno, Czech Republic).

Blood platelets play a pivotal role in physiological hemostasis but also in the development of thrombosis. In addition to increased circulating prothrombotic agents, such as von Willebrand factor (vWf), changes in platelet biology and function may underlie up-regulated thrombotic risk in cirrhosis. These changes include an increase in mean platelet volume, enhanced platelet aggregatory response to agonists and a resistance to the anti-aggregatory effects of nitric oxide and prostacyclin I<sub>2</sub>.

Platelet function testing is used to analyze inherited and acquired platelet function disorders. In our study, platelet activity was examined with the MULTIPLATE<sup>®</sup> PLATELET FUNCTION ANALYZER (Roche; Basel, Switzerland) using multiple electrode aggregometry (MEA). The Multiplate<sup>®</sup> analyzer is an easy-to-use instrument that standardizes platelet function testing in small quantities of whole blood.

Platelet activity was examined using a MULTIPATE<sup>®</sup> PLATELET FUNCTION ANALYZER (Roche; Basel, Switzerland) and MEA. This method is recommended for conducting studies on platelets by the Clinical and Laboratory Standards Institute (document H58-A, 2008). The following tests were performed: ADP-induced platelet activation - ADP test; Cyclooxygenase dependent aggregation - ASPI test; vWf and glycoprotein Ib-dependent aggregation (using ristocetin) - RISTO test; Thrombin receptor activating peptide 6 (TRAP6)-induced activation of thrombin receptor (TRAP test), which is sensitive to II b/IIIa receptor antagonists

All of the platelet-activity tests were performed 30-180 min after blood collection, as suggested by the

manufacturer.

### Statistical analysis

The Shapiro-Wilk test was used to evaluate the distribution. Because of the non-Gaussian distribution, non-parametric tests were used. Differences in studied variables between groups were tested using the Mann-Whitney *U*-test and ANOVA range Kruskal-Wallis tests for independent groups. The correlations were analyzed with the Spearman rank correlation coefficient of *P* < 0.05 was considered statistically significant. The statistical analysis was performed with STATISTICA 7.0 (StatSoft Polska Sp z o.o., Krakow, Poland). The statistical review of the study was performed by a biomedical statistician.

## RESULTS

### Comparison of cirrhotic patients with and without PVT

A detailed comparison of analyzed groups regarding anthropometric, demographical and basic laboratory parameters is shown in Table 1.

When compared cirrhotic patients with and without PVT, there were significantly increased prothrombin levels in patients with PVT (*P* = 0.01). The TRAP test results were significantly lower in the PVT group (*P* = 0.03). No other differences in coagulation parameters or other platelet activity tests were found the groups. The comparison of analyzed coagulation factors and the results of the platelet activity tests are shown in Table 2.

Omentin serum concentrations were significantly decreased in patients with PVT (*P* = 0.01). There were no significant differences in vaspin levels between the groups. No significant differences were found in terms



**Table 2** Coagulation parameters and platelet activity tests in cirrhotic patients with and without portal vein thrombosis

	PVT (+) n = 17	PVT (-) n = 34	P value
PT (s)	15.5 (12.5-21.9)	16.8 (11.3-44)	$P > 0.05$
Prothrombin activity (%)	67.8 (41-92)	66.5 (36-106)	$P > 0.05$
INR	1.37 (1.11-1.9)	1.36 (1-2.19)	$P > 0.05$
APTT	35.5 (29.1-57)	34.4 (23.6-49.4)	$P > 0.05$
TRAP test	37.2 (12-113)	55.6 (16-156)	$P = 0.03$
ASPI test	29.1 (5-108)	40.5 (5-130)	$P > 0.05$
ADP test	25.8 (1-94)	34.5 (5-99.9)	$P > 0.05$
RISTO low test	9.5 (1-35)	11.6 (0-33)	$P > 0.05$
RISTO high test	46.4 (5-162)	61.5 (4-156)	$P > 0.05$
D-dimer (mg/L)	4434 (663-9455)	3134 (563-11026)	$P > 0.05$
Protein C (%)	56.9 (38.1-90.3)	65.1 (20.9-177.5)	$P > 0.05$
Prothrombin ( $\mu$ g/mL)	175.6 (71-390)	117.4 (36-422)	$P = 0.01$
von Willebrand factor (mU/mL)	1872 (1328-2339)	1906 (981-2372)	$P > 0.05$
von Willebrand factor activity (IU/mL)	3.75 (1.72-6.61)	4.01 (1.01-7.71)	$P > 0.05$

$P$  value  $< 0.05$  was considered statistically significant. The data are shown as the mean and range or percentage where applicable. PT: Prothrombin time; INR: International normalized ratio.

**Table 3** Adipokine serum levels, insulin resistance profile and diabetes occurrence in cirrhotic patients with and without portal vein thrombosis

	PVT (+) n = 17	PVT (-) n = 34	P value
Diabetes, n (%)	5/17 (29%)	10/34 (29%)	$P > 0.05$
Glucose (mg/dL) (N:75-115 mg/dL)	128.4 (86-309)	122.8 (82-430)	$P > 0.05$
Insulin ( $\mu$ U/mL)	19.5 (8.7-41.7)	17.8 (6.1-47.6)	$P > 0.05$
HOMA-IR	6.6 (2.5-14.1)	5.3 (0.9-13.4)	$P > 0.05$
Omentin (ng/mL)	855 (579-1205)	1105 (619-2208)	$P = 0.01$
Vaspin (ng/mL)	0.31 (0.09-0.84)	0.27 (0.09-0.78)	$P > 0.05$

$P$  values  $< 0.05$  were considered statistically significant.

of diabetes mellitus occurrence, fasting glucose, fasting insulin levels, or HOMA-IR. The details are described in Table 3.

### Results according to Child-Pugh score

Data comparing patients with various Child-Pugh (C-P) scores are presented in Table 4.

We observed that the APTT was significantly longer in C-P B patients than in the C-P A group. Moreover, D-dimer levels were increased slightly with more severe cases of liver disease. There was a significant decrease in prothrombin activity in more advanced liver disease cases. Von Willebrand factor levels and activity were significantly higher in C-P C group compared to the C-P A group.

No significant differences in platelet activity or adipokines serum levels were found with respect to liver disease severity as assessed with the C-P score.

### Results according to MELD score

The patients were also divided into two groups based

on MELD score ( $\text{MELD} \leq 18$  and  $> 18$ ). A significantly shorter prothrombin time, activity and INR were confirmed in patients with MELD scores  $> 18$ . In contrast to the Child-Pugh score, there was a significant increase in the results of the TRAP-, ASPI- and RISTO tests in patients with lower MELD scores. The TRAP test values were higher in patients with less severe liver disease (56.2 vs 42.1,  $P = 0.03$ ). The ASPI test (45.9 vs 26.4,  $P = 0.001$ ) and RISTO-high test results were also higher in this group (68.5 vs 43,  $P = 0.02$ ). On the other hand, von Willebrand factor levels were significantly higher in the MELD  $> 18$  group (Table 5).

There were no significant differences with respect to omentin levels, vaspin levels, or metabolic parameters in the groups of patients with different MELD score.

### Comparison of cirrhotic patients with viral vs non-viral and alcoholic vs non-alcoholic etiology

No significant differences were found between patients with viral and non-viral cirrhosis with respect to the analyzed adipokines and metabolic and coagulation factors (Table 6).

When compared to patients with alcoholic and non-alcoholic cirrhosis, prothrombin levels appeared to be higher in the latter. There was no difference in terms of omentin, vaspin, metabolic factors or other coagulation parameters between these two groups (Table 7).

### Comparison of adipokine concentrations in cirrhotic patients with and without diabetes and different HOMA-IR levels

There was no significant difference in serum omentin or vaspin levels between cirrhotic patients with and without diabetes ( $991.0 \pm 352.7$  ng/mL vs  $1035 \pm 330.6$  ng/mL,  $0.20 \pm 0.10$  ng/mL vs  $0.32 \pm 0.23$  ng/mL, respectively).

When compared cirrhotic patients with HOMA-IR  $> 3$  vs  $\geq 3$ , both serum omentin and vaspin levels were significantly down-regulated in patients with better insulin sensitivity ( $858.2 \pm 196.0$  ng/mL vs  $1100.0 \pm 355.1$  ng/mL,  $P = 0.03$ ;  $0.17 \pm 0.09$  ng/mL vs  $0.32 \pm 0.19$  ng/mL,  $P = 0.02$ , respectively).

### Correlations between coagulation factors, platelet activity tests, metabolic factors, adipokines and clinical outcomes

A positive relationship between serum omentin and vaspin levels were found both when all of the patients were analyzed ( $r = 0.41$ ,  $P = 0.01$ ) and among those with PVT ( $r = 0.94$ ,  $P < 0.001$ ). In patients without PVT, the results were on the threshold of statistical significance ( $P = 0.05$ ).

We found a positive correlation between insulin and omentin levels in PVT (+) patients ( $r = 0.47$ ,  $P = 0.04$ ). There was significant negative correlation between the presence of diabetes and the results of the platelet activity tests: ADP ( $r = [-0.29]$ ,  $P = 0.04$ ) and RISTO-low ( $r = [-0.32]$ ,  $P = 0.02$ ).

**Table 4** Coagulation factors and platelet activity test results with regards to the severity of cirrhosis, as assessed according to the Child-Pugh score

	All patients ( <i>n</i> = 51)	Child-Pugh A ( <i>n</i> = 16)	Child-Pugh B ( <i>n</i> = 25)	Child-Pugh C ( <i>n</i> = 10)
Thrombosis	17/51 (33%)	6/16 (37.5%)	9/25 (24%)	2/10 (20%)
PT (s)	13.8 (11.3-44)	13.8 (11.3-16.9)	16.7 (11.3-44) <sup>1,3</sup>	19.2 (14.1-24.4) <sup>1,2</sup>
Prothrombin activity (%)	67 (36-106)	79.2 (58-106)	65.4 (43-95) <sup>1,3</sup>	51.4 (36-73) <sup>1,2</sup>
INR	1.3 (1-2.2)	1.2 (1-1.5)	1.4 (1.1-2) <sup>1,3</sup>	1.7 (1.2-2.2) <sup>1,2</sup>
APTT	34.7 (23.6-57)	32.3 (23.6-47.4)	36.2 (29.1-57) <sup>1</sup>	35.6 (28.2-44)
TRAP test	49.6 (12-156)	54.5 (15-156)	43.5 (12-98)	53.3 (16-113)
ASPI test	36.8 (5-130)	45.6 (10-130)	32.3 (5-110)	34.2 (5-108)
ADP test	31.6 (1-99.9)	36.3 (13-99.9)	25.8 (1-77)	38.4 (9-94)
RISTO low test	10.9 (0-35)	10.5 (1-25)	8.9 (0-26)	16.4 (2-35)
RISTO high test	56.5 (4-162)	65.5 (7-152)	41 (4-156)	60.49 (17-162)
D-dimer (mg/L)	3568 (563-11026)	2521 (563-9455)	3243 (795-8790) <sup>3</sup>	6053 (724-11026) <sup>1,2</sup>
Protein C (%)	56.5 (20.9-177.5)	60.9 (49.1-105.1)	60.8 (20.9-177.5)	58.3 (29.4-121.1)
Prothrombin (μg/mL)	136.8 (36-422)	128.9 (43.1-390)	152.1 (36-422)	110.2 (60.4-194)
vWf (mU/mL)	1941 (981-2372)	1789 (986-2372)	1941 (981-2339)	2062 (1450-2311) <sup>1</sup>
vWf activity (IU/mL)	3.8 (1-7.7)	3.3 (1.5-7.6)	3.8 (1-7.7)	4.8 (2.6-6.6) <sup>1</sup>
Omentin (ng/mL)	1023 (579-2208)	942 (635-1432)	964 (579-2208)	1102 (657-1571)
Vaspin (ng/mL)	0.29 (0.1-0.8)	0.2 (0.1-0.6)	0.3 (0.1-0.8)	0.4 (0.1-0.7)

<sup>1</sup>Significantly different *vs* Child-Pugh A group; <sup>2</sup>Significantly different *vs* Child-Pugh B group; <sup>3</sup>Significantly different *vs* Child-Pugh C group. *P* value < 0.05 was considered statistically significant. The data are shown as the mean and range or percentage where applicable. PT: Prothrombin time; INR: International normalized ratio; vWf: von Willebrand factor.

**Table 5** Coagulation factors and platelet activity test with regards to the severity of cirrhosis, as evaluated according to the model of end-stage liver disease score

	All patients ( <i>n</i> = 51)	MELD ≤ 18 ( <i>n</i> = 28)	MELD > 18 ( <i>n</i> = 23)
Thrombosis	17/51 (33%)	11/28 (39.2%)	7/23 (30.4%)
PT (s)	13.8 (11.3-44)	14.1 (11.3-21)	19.1 (13.4-44) <sup>1</sup>
Prothrombin activity (%)	67 (36-106)	76.4 (43-106)	55.6 (36-86) <sup>1</sup>
INR	1.3 (1-2.2)	1.3 (1-1.5)	1.6 (1.2-2.2) <sup>1</sup>
APTT	34.7 (23.6-57)	35.1 (23.6-57)	34.4 (28.2-44.9)
TRAP test	49.6 (12-156)	56.2 (15-156)	42.1 (12-113) <sup>1</sup>
ASPI test	36.8 (5-130)	45.9 (10-130)	26.4 (5-108) <sup>1</sup>
ADP test	31.6 (1-99.9)	36.2 (7-99.9)	26.5 (1-94)
RISTO low test	10.9 (0-35)	10.6 (1-25)	11.3 (0-35)
RISTO high test	56.5 (4-162)	68.5 (7-156)	43 (4-162) <sup>1</sup>
D-dimer (mg/L)	3568 (563-11026)	3094 (563-9455)	4144 (724-11026)
Protein C (%)	56.5 (20.9-177.5)	58.7 (20.9-105.1)	66.7 (29.4-177.5)
Prothrombin (μg/mL)	136.8 (36-422)	143.6 (36-390)	128.5 (59-422)
vWf (mU/mL)	1941 (981-2372)	1841 (986-2372)	2006 (981-2311) <sup>1</sup>
vWf (IU/mL)	3.8 (1-7.7)	3.7 (1.5-7.6)	4.2 (1-7.7)
Omentin (ng/mL)	1023 (579-2208)	948 (579-1432)	1110 (619-2208)
Vaspin (ng/mL)	0.29 (0.1-0.8)	0.25 (0.1-0.8)	0.32 (0.1-0.8)

<sup>1</sup>*P* value < 0.05 was considered statistically significant. MELD ≤ 18 *vs* MELD > 18. The data are shown as the mean and range or percentage where applicable. PT: Prothrombin time; INR: International normalized ratio; vWf: von Willebrand factor.

Vaspin serum levels were negatively associated with diabetes occurrence ( $r = [-0.64]$ ,  $P = 0.04$ ) and protein C concentration ( $r = [-0.63]$ ,  $P = 0.04$ ). Vaspin levels were positively associated with von Willebrand factor levels ( $r = 0.36$ ,  $P = 0.02$ ). Omentin serum concentrations were positively related to von Willebrand factor levels ( $r = 0.40$ ,  $P = 0.008$ ).

There was no relationship between the grade of esophageal varices and serum vaspin or omentin levels.

## DISCUSSION

Adipokines, adipose tissue-derived hormones, have

been shown to have a variety of local, peripheral and central effects<sup>[6]</sup>. A growing number of studies show a particularly important role of adipokines in the development of liver damage in a variety of diseases<sup>[6,7,27,28]</sup>. However, relatively little research has been done concerning the influence of adipokines on the natural history of liver cirrhosis. To the best of our knowledge, this is the first study to assess omentin and vaspin levels in cirrhotic patients with PVT, the diagnosis of which remains challenging. It has been demonstrated that PVT generally coexists with a more severe course of cirrhosis. It is therefore essential to identify patients who are at risk for this complication.

**Table 6** Coagulation factors, platelet activity tests and adipokines levels with regards to the presence of chronic hepatitis C

	All patients (n = 51)	HCV (+) (n = 15)	HCV (-) (n = 36)
Thrombosis	17/51 (33%)	3/11 (27.3%)	14/40 (35%)
PT (s)	13.8 (11.3-44)	14.5 (11.3-19.9)	16.8 (11.3-44)
Prothrombin activity (%)	67 (36-106)	72.1 (47-94)	65.6 (36-106)
INR	1.3 (1-2.2)	1.3 (1-1.8)	1.4 (1.2-2.2)
APTT	34.7 (23.6-57)	36.6 (28.2-57)	34.8 (23.6-49.4)
TRAP test	49.6 (12-156)	53.3 (15-156)	47.5 (12-113)
ASPI test	36.8 (5-130)	37.9 (10-130)	36.5 (5-110)
ADP test	31.6 (1-99.9)	33.4 (13-99.9)	31.2 (1-94)
RISTO low test	10.9 (0-35)	13.5 (4-25)	10.2 (0-35)
RISTO high test	56.5 (4-162)	44.5 (7-115)	60.1 (4-162)
D-dimer (mg/L)	3568 (563-11026)	3317 (595-10043)	3637 (563-11026)
Protein C (%)	56.5 (20.9-177.5)	65.1 (41.4-105.1)	61.6 (20.9-177.5)
Prothrombin (μg/mL)	136.8 (36-422)	149.2 (59.7-390)	133.4 (36-422)
vWf (mU/mL)	1941 (981-2372)	1912 (986-2311)	1890 (981-2372)
vWf activity (IU/mL)	3.8 (1-7.7)	4.2 (1.5-6.4)	3.9 (1-7.7)
Omentin (ng/mL)	1023 (579-2208)	991 (731-1432)	1028 (579-2208)
Vaspin (ng/mL)	0.29 (0.1-0.84)	0.43 (0.1-0.77)	0.26 (0.1-0.84)

<sup>1</sup>P value < 0.05 was considered statistically significant. The data are shown as the mean and range or percentage where applicable. PT: Prothrombin time; INR: International normalized ratio; vWf: von Willebrand factor; HCV: Hepatitis C virus.

**Table 7** Coagulation factors, platelet activity tests and adipokines levels with regards to the etiology of alcoholic liver cirrhosis

	All patients (n = 51)	Alcoholic cirrhosis (n = 30)	Non-alcoholic cirrhosis (n = 21)
Thrombosis	17/51 (33%)	9/30 (30%)	8/21 (38%)
PT (s)	13.8 (11.3-44)	17 (11.3-44)	15.3 (11.3-21)
Prothrombin activity (%)	67 (36-106)	65.7 (36-106)	68.8 (43-94)
INR	1.3 (1-2.2)	1.5 (1-2.2)	1.4 (1.1-2)
APTT	34.7 (23.6-57)	34.6 (23.6-47.4)	34.8 (28.2-57)
TRAP test	49.6 (12-156)	51.2 (16-113)	47.2 (12-156)
ASPI test	36.8 (5-130)	39.1 (5-110)	33.4 (5-130)
ADP test	31.6 (1-99.9)	32.8 (5-94)	29.9 (1-99.9)
RISTO low test	10.9 (0-35)	11.4 (0-35)	10.15 (1-25)
RISTO high test	56.5 (4-162)	68.4 (10-162)	39.5 (4-115)
D-dimer (mg/L)	3568 (563-11026)	3635 (563-11026)	3471 (595-10043)
Protein C (%)	56.5 (20.9-177.5)	59.2 (20.9-121.2)	66.8 (33.4-177.5)
Prothrombin (μg/mL)	136.8 (36-422)	116.6 (36-382)	165.8 (59-422) <sup>1</sup>
vWf (mU/mL)	1941 (981-2372)	1937 (1209-2372)	1834 (981-2311)
vWf (IU/mL)	3.8 (1-7.7)	4.1 (1.5-7.7)	3.7 (1-6.4)
Omentin (ng/mL)	1023 (579-2208)	1072 (579-2208)	923 (635-1432)
Vaspin (ng/mL)	0.29 (0.1-0.84)	0.29 (0.1-0.84)	0.26 (0.1-0.72)

<sup>1</sup>P value < 0.05 was considered statistically significant. The data are shown as the mean and range or percentage where applicable. PT: Prothrombin time; INR: International normalized ratio; vWf: von Willebrand factor.

Our study for the first time showed significantly lower levels of serum omentin in cirrhotic patients with PVT. However, omentin serum levels were not associated with the severity of cirrhosis according to either the Child-Pugh or MELD scales. There was also no relationship between omentin and the grade of esophageal varices. Patients with PVT had significantly higher prothrombin concentrations. Prothrombin is a key factor in clot formation, and elevated levels appear to promote venous thrombosis. In the study by Eisinger *et al*<sup>[19]</sup>, omentin levels were significantly higher in the portal vein. In addition, these levels tended to be higher in the hepatic vein and systemic blood of patients with liver cirrhosis compared with the respective blood compartments of control patients with healthy livers. Similar to our results, no association

with complications resulting from portal hypertension was observed.

As mentioned above, there are conflicting results regarding omentin synthesis in the liver<sup>[14,15]</sup>. Our previous study of non-obese CHC patients, 16% of whom were cirrhotic, showed significantly higher omentin serum levels compared to healthy controls. However, omentin serum levels were not associated with any histopathological findings<sup>[14]</sup>. Similar results were found by Nassif *et al*<sup>[18]</sup>'s study, which showed significantly higher serum omentin levels in CHC subjects; however, no information was provided regarding histopathological examination.

In patients with obesity and metabolic syndrome, circulating omentin levels were negatively associated with a multiplicity of metabolic risk factors, suggesting

that omentin acts as a biomarker of metabolic disorders<sup>[16]</sup>. IR, which is considered to be negatively associated with serum omentin in patients with metabolic diseases, is commonly present in patients with liver cirrhosis. Therefore, higher serum omentin levels in cirrhotic patients with increased IR is an unexpected finding. However, our results are in accordance with results obtained by Eisinger *et al.*<sup>[19]</sup>, who found omentin serum levels to be significantly decreased in cirrhotic patients with better insulin sensitivity.

Nassif *et al.*<sup>[18]</sup> analyzed CHC patients and found a negative correlation between serum omentin and HOMA-IR and fasting glucose, with lower serum omentin levels in subjects with T2DM. However, in those patients, serum omentin concentration was still significantly higher than in diabetic patients without CHC. We must still bear in mind the strong influence of DM and obesity on serum omentin levels<sup>[29,30]</sup>. An additional factor is the direct impact of HCV on inflammatory, metabolic and intracellular insulin pathways<sup>[31]</sup>. In the present study, there was no difference in serum omentin levels in cirrhotic patients with and without DM. This is an unexpected result considering the negative correlation between serum omentin and metabolic abnormalities in DM and MS. However, the result must be analyzed with caution due to a small number of patients with DM in our group. Nevertheless, in the study by Yilmaz *et al.*<sup>[32]</sup>, serum levels of omentin were significantly lower in normal controls compared to non-cirrhotic patients with biopsy-proven NAFLD, 40% of whom were diabetic and over 60% of whom had metabolic syndrome. Moreover, serum omentin appeared to be a predictor of hepatocyte ballooning, independent of potential confounders, including metabolic parameters. This last observation points to a pivotal role omentin in the development and progression of NAFLD.

To exclude a potential influence of HCV on IR and lipid profile, which may interfere with omentin serum levels, we compared cirrhotic patients with CHC to the rest of the study group. There were no significant differences between these two subgroups in terms of serum omentin, glucose and fasting insulin, HOMA-IR, cholesterol, coagulation factors or platelet activity.

The top three causes of cirrhosis in our study were alcoholic liver disease, CHC and autoimmune hepatitis. There were no differences in serum omentin levels in patients with viral or toxic cirrhosis compared to the rest of analyzed group. In the study by Eisinger *et al.*<sup>[19]</sup>, only three patients out of 34 had cirrhosis due to CHC. The comparison between our study and Nassif *et al.*<sup>[18]</sup>'s study is also difficult because no information was provided regarding the viral genotype and fibrosis stage in the analyzed patients. Therefore, the discrepancy in the obtained results regarding the relationship between serum omentin and insulin sensitivity may result from different study group characteristics.

In terms of to higher serum omentin levels in patients with CLDs, the question arises of whether these increased levels result from the impaired metabolism of this adipokine in the inflamed and fibrotic liver. However, our study did not show any difference in serum omentin concentrations in more advanced cirrhosis (*i.e.*, more impaired liver function), suggesting no significant influence of hepatic metabolism on the levels of this adipokine. Therefore, further questions remain as to whether omentin expression in the liver is an important source of the serum levels of this adipokine. Our previous study confirmed omentin liver expression. However, hepatic gene expression was not associated with its serum levels or any histopathological feature. Moreover, omentin was not up-regulated in cirrhosis<sup>[14]</sup>.

The dysfunction of SECs in cirrhotic liver is strictly associated with a low production of vasodilators, such as nitric oxide, which increases intrahepatic resistance and portal hypertension<sup>[33,34]</sup>. Nitric oxide is a central molecule in the regulation of vascular tone by regulating eNOS activity in blood vessels<sup>[35]</sup>. Omentin was found to mediate endothelium relaxation by up-regulating eNOS activity<sup>[12]</sup>. Omentin has also been described as a potent anti-inflammatory adipokine, inhibiting TNF alpha-mediated phosphorylation of p38 kinase and Jun kinase in vascular smooth muscle cells<sup>[36]</sup>. Therefore, higher omentin levels in patients with cirrhosis may be a compensatory mechanism against intrahepatic resistance.

Vaspin is another novel adipokine that is primarily produced by visceral and subcutaneous adipose tissue. The current study for the first time compared serum vaspin levels in cirrhotic patients with and without PVT and did not find any difference between these groups. Our previous study in CHC patients suggested serum vaspin to be a potential predictor of advanced liver fibrosis, with evident increases in subjects with advanced fibrosis<sup>[21]</sup>. However, in patients with insignificant fibrosis, serum vaspin level were significantly lower than in controls. Similarly, serum vaspin levels were lower in NAFLD patients with simple steatosis compared to healthy controls, with a subsequent increase in patients with NASH and ballooning degeneration<sup>[23]</sup>. The study by Aktas *et al.*<sup>[24]</sup> confirmed serum vaspin to be a predictor of liver fibrosis in NAFLD, independently of potential confounders, including metabolic parameters. Moreover, vaspin serum levels reflected the intensity of hepatic angiogenesis in CHC patients, a phenomenon that aggravates CLDs progression<sup>[22]</sup>. It is well established that active fibrogenesis and angiogenesis are connected with the progression of portal hypertension, an undisputed risk factor of PVT. In the present study, there was no difference in vaspin serum levels between patients with different stages of cirrhosis according to Child-Pugh and MELD scores. This is in accordance with previous results showing that there is no further increase in vaspin serum levels when advanced fibrosis



appears<sup>[21,22]</sup>.

Visceral vaspin expression significantly correlated with BMI, percentage of body fat and the levels of plasma glucose. As vaspin has been found to be a compensatory adipokine in IR, a common metabolic disorder in patients with cirrhosis, serum vaspin is expected to be higher in patients with worsen insulin sensitivity. As expected, the present study revealed significantly higher serum vaspin levels in patients with HOMA-IR  $\geq 3$ . The results with respect to vaspin levels are in accordance with our previous study in NAFLD patients, which showed HOMA-IR to be significantly higher in patients with fibrosis and to correlate with fibrosis stage<sup>[23]</sup>. In contrast, serum vaspin levels had no tendency to be increased in CHC patients with HOMA-IR  $\geq 3$ <sup>[37]</sup>. Bearing in mind a direct influence of HCV on insulin sensitivity, further analysis comparing serum vaspin levels in groups of patients with viral and non-viral cirrhosis was carried out. However, no significant differences were observed between these two subgroups of cirrhotic patients. Similarly, no difference was detected when comparing patients with toxic and non-toxic cirrhosis. These observation support the opinion that increased serum vaspin levels may be a compensatory mechanism to abolish IR.

Recently, vaspin has been found to exert anti-atherogenic actions. Vaspin decreased the levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of all types of nitric oxide synthases (NOSs), and activated dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that metabolizes ADMA to citrulline and dimethylamine. Elevated ADMA has been shown to attenuate endothelium-dependent vasodilation in humans<sup>[38]</sup> and, together with dysregulation of DDAH, is involved in endothelial dysfunction in hypercholesterolemia and diabetes. Some recent evidence has indicated that DDAH activity is impaired by oxidative stress, permitting ADMA to accumulate<sup>[39]</sup>. Considering the beneficial effect of vaspin on IR and oxidative stress, it may act as a compensatory and protective factor. Unfortunately, our study did not reveal any difference in vaspin serum levels between cirrhotic patients with and without PVT, and there was no relationship with the grade of esophageal varices. The evident limitation of our study is the lack of portal pressure measurement; therefore, the interpretation of the presented results should be performed with caution.

As mentioned above, PVT is more frequently observed in later stages of cirrhosis. However, the development of PVT is unpredictable, and its risk factors are not well characterized. According to Virchow's triad principle, a venous thrombosis results from the coexistence of blood flow abnormalities, endothelial injury and hypercoagulation. For these reasons, PVT in cirrhosis could be linked with endotoxemia, thrombophilia and portal hypertension. Alternatively, PVT it may have no definite association with any of these factors. Advanced cirrhosis is associated with profound and complex coagulation

defects, with concomitant defective fibrinolysis and impaired synthesis of thromboxane A2 and serotonin by platelets. The final result of all of these disturbances is a promotion of a prothrombotic state, likely related to up-regulated endothelial synthesis of von Willebrand factor (vWf) and increased levels of VIII factor. These effects occur in combination with low levels of hepatic anticoagulation agents, such as antithrombin III and proteins C and S<sup>[40,41]</sup>. vWf levels and the VIII factor-to-PC ratio are as predictive of mortality as MELD. Thrombogenic mechanisms that operate within the cirrhotic liver might underlie the progression of portal hypertension and adverse clinical outcomes in patients with cirrhosis<sup>[42]</sup>.

Our study revealed prothrombin concentration to be significantly higher in patients with PVT. Prothrombin is an essential agent that participates in clot formation. Elevated levels of this factor lead to thrombin formation, inhibit the activity of antithrombotic protein S, and promote venous thrombosis in the presence of endothelial injury<sup>[43,44]</sup>. On the other hand, in our study, protein C levels tended to be lower in PVT patients, although the difference did not reach statistical significance.

The loss of platelet inhibition by insulin has been suggested to be a major determinant of platelet hyperactivity during obesity. Low levels of HDL-cholesterol promote platelet activation and aggregation, possibly because HDL antagonizes the stimulating properties of LDL on platelets<sup>[45]</sup>. In agreement with these facts, we found that not HDL-cholesterol but also LDL-cholesterol and total blood cholesterol levels were markedly diminished in patients with PVT; however, the difference was not statistically significant. The roles of omentin and vaspin in decreasing IR and oxidative stress may exert a protective effect against platelet hyperreactivity. Unfortunately, serum omentin was not associated with platelet hyperactivity. On the other hand, both serum omentin and vaspin concentrations, in addition to fasting insulin, were positively related to vWF level and activity.

However, the tendency of patients with liver disease to bleed and to experience thrombus formation cannot be explained solely by alterations in hemostasis. A partial explanation of hemorrhagic and thrombotic events in patients with advanced CLDs or cirrhosis result from complex hemodynamic alterations, such as portal hypertension, endothelial dysfunction, kidney dysfunction, and the release of substances similar to heparin by bacterial<sup>[46]</sup>.

The last intriguing observation of the study, which has not been previously described, is a positive association between serum omentin and vaspin. As mentioned above, ADMA, an endogenous inhibitor of NOS, is increased in the serum of patients with liver cirrhosis compared with healthy controls and may antagonize peripheral vasodilatation. High intrahepatic ADMA levels may aggravate intrahepatic resistance<sup>[47,48]</sup>. The ability of vaspin and omentin to enhance eNOS

activity and to down-regulate ADMA production may be a compensatory and protective mechanism against portal hypertension. The positive mutual correlation between both adipokines may suggest a collaborative action of both adipokines, not only as compensatory agents in portal hypertension but also in insulin resistance, oxidative stress and inflammation.

There are some evident limitations of our study. First, the group of patients is relatively small and not homogenous. Second, no liver biopsy was carried out, and the measurement of collagen proportionate area, which may reflect the severity of cirrhosis and predict portal hypertension, was not applicable. Third, no measurement of portal pressure was made, so a direct assessment of how omentin and vaspin may influence vasodilatation or vasoconstriction was not possible. Fourth, the relationship between PVT and the levels of omentin is a simple association and not a cause-effect relationship. A follow-up study should have been designed to demonstrate that decreased omentin levels are related to a higher risk of developing PVT.

In conclusion, our study showed serum omentin but not vaspin levels to be significantly higher in cirrhotic patients without PVT. Moreover, omentin and vaspin concentrations were higher in cirrhotic patients with increased IR. Neither omentin nor vaspin were associated with other metabolic abnormalities, including DM. The origin of liver cirrhosis and grade of liver impairment as assessed by the Child-Pugh or MELD scores were not correlated with omentin or vaspin levels. There was no relationship between platelet hyperactivity and the serum levels of either analyzed adipokine. The positive mutual correlation between omentin and vaspin may suggest their collaborative action against IR, inflammation and portal hypertension. Our results indicate that although omentin and vaspin could be involved into the pathophysiology of the development of cirrhosis, they are not good indicators of its origin or severity and do not impact the thrombotic activity of platelets.

Additional studies must delineate whether the levels of omentin and vaspin play a pivotal, protective role in liver cirrhosis against PVT and portal hypertension.

## COMMENTS

### Background

Ongoing research has revealed alterations in the levels and expression of various adipokines in cirrhosis. Portal vein thrombosis (PVT) has been considered to be a complication of more advanced liver cirrhosis. The data regarding novel adipokines in liver cirrhosis is scarce and ambiguous. The current study evaluated the serum concentrations of omentin and vaspin in patients with liver cirrhosis of different origins and stages with and without PVT. The relationships of these measures with disease severity and etiology, platelet activity, hemostatic parameters and potential complications were also assessed.

### Research frontiers

Accumulating data suggest that obesity and insulin resistance are related to a more rapid progression of chronic liver diseases, the development of cirrhosis and its complications. Some adipokines have been suggested to contribute to

the complicated pathophysiology of hepatic injury and repair. Moreover, there is some data suggesting, that omentin plays role in regulating endothelial homeostasis.

### Innovations and breakthroughs

This study showed serum omentin levels to be significantly higher in cirrhotic patients without PVT. This finding confirms important role of this adipokine in vessel homeostasis. Serum levels of omentin and vaspin seem not to be associated with platelet hyperactivity.

### Applications

The presented study suggests that there is a need of further studies on the role of novel adipokines in liver cirrhosis and its complications as liver failure is strictly connected to metabolism disturbance.

### Peer-review

Interesting and certainly new topic describing two novel adipokines - omentin and vaspin in patients with liver cirrhosis with and without PVT. The study provides analysis of relationship between adipokines serum levels and disease severity and etiology, metabolic abnormalities and platelets activity.

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**P- Reviewer:** Khayyat YM, La Mura V, Strom SC    **S- Editor:** Yu J  
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ISSN 1007-9327

