

Original Article

Association of serum omentin-1 levels with coronary artery disease

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Aim: Omentin-1, a novel adipokine expressed in visceral adipose tissue, is negatively correlated with insulin resistance and obesity. Decreased omentin-1 expression has been found in many chronic inflammatory diseases. However, the role of omentin-1 in coronary artery disease (CAD) has not been elucidated. The aim of the present study was to determine whether serum concentration of omentin-1 was independently associated with CAD.

Methods: One hundred and fifty five patients with CAD were divided into two groups: acute coronary syndrome (ACS) and stable angina pectoris (SAP). A total of 52 healthy participants served as controls. Serum concentrations of omentin-1 and interleukin-6 (IL-6) were measured using ELISA. The association of omentin-1 with CAD and cardiovascular disease risk factors was evaluated.

Results: Serum omentin-1 levels were lower in patients with ACS or SAP compared with controls (ACS, 113.08 ± 61.43 ng/mL; SAP, 155.41 ± 66.89 ng/mL; control, 254.00 ± 72.9 ng/mL; $P < 0.01$). Patients with ACS also had lower serum concentrations of omentin-1 compared with patients with SAP ($P < 0.01$). Serum concentration of omentin-1 was negatively correlated with body mass index ($r = -0.17$, $P < 0.05$) and serum IL-6 concentration ($r = -0.19$, $P < 0.05$). Furthermore, multiple logistic regression analysis showed that serum omentin-1 concentrations were independently correlated with CAD.

Conclusion: The findings suggest that serum concentrations of omentin-1 are related to CAD.

Keywords: coronary artery disease; acute coronary syndrome; adipokines; omentin-1; interleukin-6

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Introduction

Adipose tissue secretes many adipokines including adiponectin, chemerin, leptin, resistin, retinol binding protein 4, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6)^[1]. These adipokines play important roles in carbohydrate and lipid metabolism, homeostasis, insulin resistance, diabetes, atherosclerosis, vascular endothelial dysfunction, inflammation, and cardiovascular function^[2–6].

Omentin, a recently identified fat deposition-specific adipokine codified by two genes (1 and 2), is highly and selectively expressed in visceral omental adipose tissue^[7]. While its biological activity is not well understood, omentin-1 has been shown to be the major circulating isoform in human plasma with reportedly lower levels in overweight or obese subjects and those with impaired glucose regulation (IGR) or type 2

diabetes mellitus (T2DM)^[8–10]. Recent studies have shown that omentin-1 levels are negatively correlated with body mass index (BMI), leptin, waist circumference, fasting insulin, and homeostasis model assessment (HOMA) index, and omentin-1 levels are positively associated with adiponectin and high density lipoprotein cholesterol (HDL-C)^[8, 11]. Several reports indicated that omentin-1 was implicated in many chronic inflammatory diseases^[12, 13]. In addition, Yamawaki *et al* demonstrated a vasodilating effect of omentin on isolated blood vessels, suggesting omentin involvement in endothelial function^[14].

There have been several reports showing that other adipokines, such as adiponectin^[15–17], resistin^[17–20], leptin^[19], visfatin^[21–23], TNF- α ^[24], and IL-6^[25], are related to inflammation and coronary artery disease (CAD). We hypothesized that omentin-1 might be implicated in CAD due to a possible association with inflammation and endothelial function. To test the hypothesis, we measured serum omentin-1 levels in patients with CAD and evaluated possible correlations with other cardiovascular risk factors such as age, sex, smoking, CAD family history, lipid levels, fasting glucose (FG), and blood pressure.

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We investigated whether serum omentin-1 levels were independently related to the incidence of CAD.

Materials and methods

Subjects

The protocol was authorized by the Ethical Committee of Shandong Provincial Hospital. Prior written informed consent was obtained from all participants. The study group consisted of 155 patients undergoing coronary angiography primarily for chest pain or dyspnea on exertion in Shandong Provincial Hospital between June 2009 and September 2010. Patients with valvular heart disease, coronary artery bypass graft surgery, malignant disease, infectious disease, inflammatory disease such as collagen disease, neoplasm, hematological disorders, advanced renal disease (defined as either creatinine >220 $\mu\text{mol/L}$ or glomerular filtration rate <60 mL/min per 1.73 m^2 according to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines^[26], and liver disease (aspartate transaminase and alanine transaminase >2 times the upper limit of normal) were excluded. Patients with CAD were divided into two groups: 1) acute coronary syndrome (ACS), including acute myocardial infarction (AMI) or unstable angina pectoris (UAP); and 2) stable angina pectoris (SAP).

There were 61 patients diagnosed with AMI based on clinical symptoms; electrocardiogram evidence (ST elevation in two or more leads); coronary angiography findings (occlusion of a main coronary artery branch) with thrombolysis in myocardial infarction (TIMI) grade flow of 0, 1, or 2; and significantly increased serum creatine kinase (CK)-MB and troponin-I levels (more than twice the upper limit of normal). All AMI patients were catheterized within 12 h of onset of chest pain. Sixty-six patients were diagnosed with UAP using the following criteria: new onset chest pain or unexplained changes in the pattern of stable angina (such as increased frequency, intensity or duration or decreased response to nitrates); angiographic evidence (documented stenosis of >50% in one or more principal coronary arteries); and no increase in serum CK-MB and troponin-I concentrations in the previous 2 months. Twenty-eight patients were diagnosed with SAP based on symptoms, specifically typical precordial chest pain during exercise and no episodes of angina at rest and documented stenosis of >50% in one or more principal coronary arteries upon coronary angiography.

The reference (control) group consisted of 52 healthy participants matched by age and BMI. Among the reference group, 36 participants underwent coronary angiography; of those, 16 participants were examined by coronary CT angiography. None of the controls was diagnosed with CAD.

Measurement of serum concentrations of omentin-1 and other parameters

Each blood sample was obtained between 7 and 8 h after an overnight fast and was collected in chilled polypropylene tubes. Serum was separated by centrifugation at 750 \times g for 15 min and stored at -80 $^{\circ}\text{C}$ until being assayed.

Routine lab tests including FG, low density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol (TC), triglycerides (TG), uric acid, and creatinine were assayed by an automatic analyzer (Olympus, Irish Branch) in the hospital clinical laboratories. Serum omentin-1 and IL-6 concentrations were measured using Human Enzyme-linked immunosorbent assay (ELISA) kits (Cusabio Biotech Corporation, USA). Serum samples were diluted and assayed according to manufacturer instructions.

Statistical analysis

Continuous variables with normal distributions were expressed as mean \pm SD. Differences in the mean values between groups were compared by One-Way Analysis of Variance (ANOVA). Continuous variables with skewed distributions were summarized as median and quartile ranges and compared using the Kruskal-Wallis test. The χ^2 test was used to test categorical variables. Correlations between serum concentrations of omentin-1 and other parameters were studied by Pearson correlation analysis. We first used simple logistic regression and then multivariate analysis to analyze correlations between CAD and all other parameters. SPSS 12.0 software was used for statistical analysis. $P < 0.05$ was considered statistically significant.

Results

Study group characteristics

The clinical characteristics and laboratory data of the study groups are shown in Table 1. There were no differences in age, BMI, sex, smoking, family history of CAD, TG, uric acid, and creatinine between patients and controls. Compared to the control group, those in the ACS or SAP groups had higher systolic blood pressure (SBP), serum concentrations of FG, LDL-C, TC, and IL-6 and lower serum omentin-1 and HDL-C levels. Compared with patients with SAP, patients with ACS also had lower serum concentrations of omentin-1 and SBP and higher serum IL-6 concentrations.

Correlation between serum concentrations of omentin-1 and other parameters

As Figure 1 showed, there was a negative correlation between serum concentrations of omentin-1 and BMI ($r = -0.17$, $P < 0.05$) in patients with CAD. Notably, as presented in Figure 2, serum omentin-1 levels were also negatively associated with serum IL-6 levels ($r = -0.19$, $P < 0.05$). However, we did not find any association between serum omentin-1 levels and other variables such as lipid parameters, blood pressure, age, smoking, sex, and family history of CAD.

Omentin-1 and CAD

Initially, a simple logistic regression analysis was performed. As shown in Table 2, the incidence of CAD was correlated with SBP, DBP, serum concentrations of TC, LDL-C, HDL-C, FG, omentin-1, and IL-6 ($P < 0.05$). In multiple stepwise logistic regression analysis, serum concentrations of TC, omentin-1 and IL-6 were independently associated with the development

Table 1. Clinical characteristics and laboratory data of the study group. ^b*P*<0.05, ^c*P*<0.01 vs control; ^e*P*<0.05, ^f*P*<0.01 for ACS vs SAP.

Variable	ACS (n=127)	SAP (n=28)	Control (n=52)	P value
Age (year)	61.85±12.05 ⁽¹⁾	60.61±15.02 ⁽¹⁾	59.81±9.88 ⁽¹⁾	0.5663
Men (%)	90 (70.87) ⁽²⁾	15 (53.57) ⁽²⁾	38 (73.08) ⁽²⁾	0.1548
BMI (kg/m ²)	25.52±3.35 ⁽¹⁾	24.71±3.74 ⁽¹⁾	25.73±3.14 ⁽¹⁾	0.4171
Smoking (%)	54 (42.52) ⁽²⁾	9 (32.14) ⁽²⁾	14 (26.92) ⁽²⁾	0.1227
Family history (%)	25 (19.69) ⁽²⁾	7 (25.00) ⁽²⁾	9 (17.31) ⁽²⁾	0.7114
SBP (mmHg)	135.00 (33.00) ^{(3)ce}	145.36±24.52 ^{(1)c}	119.35±13.83 ⁽¹⁾	<0.0001
DBP (mmHg)	78.00 (19.00) ^{(3)b}	80.82±15.51 ⁽¹⁾	73.85±10.39 ⁽¹⁾	0.0915
FG (mmol/L)	5.74 (2.22) ^{(3)c}	6.37±1.53 ^{(1)c}	5.05±1.03 ⁽¹⁾	<0.0001
TC (mmol/L)	4.78 (1.63) ^{(3)c}	4.91±0.95 ^{(1)c}	3.94±1.07 ⁽¹⁾	<0.0001
LDL-C (mmol/L)	2.91 (1.19) ^{(3)c}	2.80±0.72 ^{(1)c}	2.29±0.80 ⁽¹⁾	<0.0001
HDL-C (mmol/L)	1.24 (0.36) ^{(3)c}	1.27 (0.45) ^{(3)c}	1.27 (0.46) ⁽³⁾	<0.0001
TG (mmol/L)	1.33 (1.19) ⁽³⁾	1.30 (1.00) ⁽³⁾	1.66 (1.03) ⁽³⁾	0.1317
Uric acid (μmol/L)	321.00 (118.00) ⁽³⁾	318.64±98.14 ⁽¹⁾	328.94±86.81 ⁽¹⁾	0.6953
Creatinine (μmol/L)	85.30 (29.40) ⁽³⁾	89.65 (34.60) ⁽³⁾	93.54±12.33 ⁽¹⁾	0.1019
Omentin-1 (ng/mL)	113.08±61.43 ^{(1)cf}	155.41±66.89 ^{(1)c}	254.00 (72.98) ⁽³⁾	<0.0001
IL-6 (pg/mL)	108.11±69.77 ^{(1)cf}	55.98 (35.77) ^{(3)c}	16.12±7.62 ⁽¹⁾	<0.0001

⁽¹⁾ mean±SD ; ⁽²⁾ n (%); ⁽³⁾ median (quartile range).

ACS, acute coronary syndrome; SAP, stable angina pectoris; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; IL-6, interleukin-6.

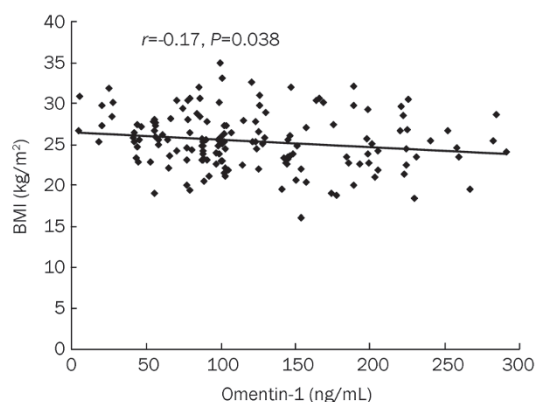


Figure 1. Correlation of serum concentrations of omentin-1 with body mass index (BMI). There was a negative correlation between serum omentin-1 levels and BMI in patients with coronary artery disease.

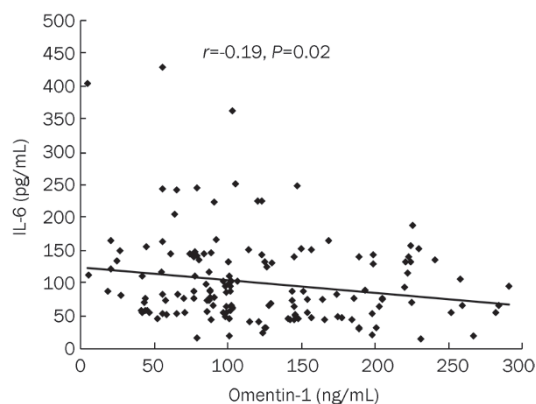


Figure 2. Correlation of serum concentrations of omentin-1 with interleukin-6 (IL-6). Serum concentrations of omentin-1 correlated negatively with serum IL-6 levels in patients with coronary artery disease.

of CAD (*P*<0.05, Table 3).

Discussion

Our present study showed that serum omentin-1 levels were lower in patients with CAD than in control participants. Patients with ACS also had lower serum concentrations of omentin-1 and higher serum concentrations of IL-6 compared with patients with SAP. In addition, serum omentin-1 levels were negatively correlated with BMI and IL-6 in patients. More importantly, we found that serum omentin-1 levels were independently associated with CAD prevalence.

Association of serum concentrations of omentin-1 with CAD

In the present study, mechanisms of the association of omentin-1 with CAD have not been elucidated; however, one could consider several possibilities. First, omentin induces endothelium-dependent relaxation via endothelium-derived NO through phosphorylation of eNOS in rat isolated aorta^[14]. CAD may also be associated with impaired endothelium-dependent coronary dilatation^[27]. Therefore, omentin may participate in CAD development at least in part through regulation of coronary contractility. Second, omentin has been shown to increase insulin sensitivity^[28]. Rodrigues *et al*^[29]

Table 2. Simple logistic regression analysis with CAD.

Variable	β	Standard error	Wald χ^2	P value	OR	95% CI
Age	0.0128	0.0135	0.8985	0.3432	1.013	0.986–1.040
Sex	0.2566	0.3567	0.5173	0.4720	1.292	0.642–2.601
BMI	-0.0319	0.0479	0.4436	0.5054	0.969	0.882–1.064
Smoking	-0.6199	0.3528	3.0866	0.0789	0.538	0.269–1.074
Family history	0.2175	0.4168	0.2723	0.6018	1.243	0.549–2.814
SBP ^c	0.0419	0.0096	19.1519	<0.0001	1.043	1.023–1.063
DBP ^b	0.0317	0.0131	5.8495	0.0156	1.032	1.006–1.059
FG ^c	0.9294	0.2077	20.0243	<0.0001	2.533	1.686–3.806
TC ^c	0.8003	0.1780	20.2149	<0.0001	2.226	1.571–3.156
LDL-C ^c	0.9918	0.2350	17.8124	<0.0001	2.696	1.701–4.274
HDL-C ^c	-3.6301	0.6545	30.7629	<0.0001	0.027	0.007–0.096
TG	-0.0172	0.0841	0.0418	0.8380	0.983	0.834–1.159
Uric acid	0.0007	0.0015	0.2319	0.6301	1.001	0.998–1.004
Creatinine	0.0017	0.0044	0.1514	0.6972	1.002	0.993–1.010
Omentin-1 ^c	-0.0330	0.0051	41.7697	<0.0001	0.968	0.958–0.977
IL-6 ^c	0.2088	0.0437	22.8128	<0.0001	1.232	1.131–1.342

^bP<0.05, ^cP<0.01 with logistic regression analysis.

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FG, fasting glucose; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; IL-6, interleukin-6.

Table 3. Multivariable logistic regression analysis with CAD.

Variable	β	Standard error	Wald χ^2	P value	OR	95% CI
TC ^b	1.3313	0.5219	6.5082	0.0107	3.786	1.361–10.529
Omentin-1 ^b	-0.0371	0.0154	5.8039	0.0160	0.964	0.935–0.993
IL-6 ^b	0.2427	0.0976	6.1857	0.0129	1.275	1.053–1.543

^bP<0.05 with logistic regression analysis.

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; TC, total cholesterol; IL-6, interleukin-6.

recently named insulin resistance as one of the most important risk factors for subclinical atherosclerosis and reported an association with coronary artery calcification in patients with type 1 diabetes mellitus (T1DM). In one study, decreased insulin sensitivity was associated with increased incidence of myocardial infarction and death, even after adjusting cardiovascular risk for smoking and low physical activity. Bertoluci *et al* also indicated that increased HOMA of insulin resistance was positively associated with angiographic coronary artery disease^[30]. As a result, decreased omentin-1 levels may contribute to development of CAD by modulating insulin action. Third, consistent with other reports, our present data showed that decreased omentin expression is implicated in a variety of chronic inflammatory diseases. It was reported that plasma omentin-1 was decreased in T1DM subjects^[31]. Expression of the omentin gene was detected in omental adipose tissue of patients with Crohn's disease, suggesting that it may play an important role in chronic inflammatory diseases^[12]. Senolt *et al*^[13] also demonstrated significantly lower omentin levels in the synovial fluid of patients with rheumatoid arthritis than in

patients with osteoarthritis. In addition, synovial fluid levels of omentin were significantly correlated with serum levels of anticitrullinated peptide antibodies and IgM-rheumatoid factor. Based on these reports, omentin-1 might be involved in the development of CAD via dysfunction of endothelium-dependent coronary dilatation, insulin activity and inflammation.

Correlation between serum concentrations of omentin-1 and other factors

We reported that omentin-1 was related to IL-6 in patients with CAD. A large number of reports have shown that IL-6 is pathogenetically involved in CAD. Pan *et al*^[9] also reported a negative correlation between the level of serum omentin-1 and IL-6 in patients with newly diagnosed and untreated type 2 diabetes. Several groups have reported that IL-6 regulates the production of other adipokines, including leptin, adiponectin, and visfatin^[32–34]. IL-6 and omentin are primarily produced by stromal vascular fraction cells of adipose tissue with paracrine or endocrine effects directly on other cells locally and sys-

temically. Whether IL-6 profoundly influences the release of omentin from visceral tissue should be elucidated.

In our study, serum omentin-1 levels were negatively correlated with BMI in patients with CAD. Several reports have shown an association of omentin-1 with BMI^[8, 9]. Another report also indicated that baseline circulating omentin-1 concentrations were negatively correlated with BMI, increasing significantly after weight loss^[11]. These data suggest that obesity negatively regulates omentin expression. Further investigation is needed to determine the mechanism and pathogenesis.

We found no correlation between serum omentin-1 levels and lipid parameters. One report showed that plasma omentin-1 correlates positively with HDL^[8], whereas other reports have shown no correlation^[9, 11]. The majority of patients in our study had already received statin therapy; thus, the relationship between serum concentrations of omentin-1 and lipid variables may best be observed in newly diagnosed and untreated patients with CAD.

Serum omentin-1 levels negatively correlated with BMI and IL-6; however, the correlation coefficients are weak, likely because relatively small numbers of participants were investigated. Future research should observe a large sample of patients with CAD. Second, only patients with typical symptoms suggestive of angina were included in our study; we did not include CAD patients with no chest discomfort.

Conclusion

Serum omentin-1 concentrations may be associated with CAD. These findings may have important implications for the pathophysiology and therapy of CAD.

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Author contribution

Xia ZHONG, Fu-qin CHEN, and De-ya SHANG designed the research; Xia ZHONG and Hai-yang ZHANG performed the research; Hui TAN and Fu-li LIU contributed new analytical tools and reagents; Hui TAN, Fu-li LIU, and Xia ZHONG analyzed the data; Xia ZHONG, Hai-yang ZHANG, and Yi ZHOU wrote the manuscript.

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