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RESEARCH ARTICLE

Serum omentin-1 levels are inversely associated with the presence and severity of coronary artery disease in patients with metabolic syndrome

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Abstract

Context: Omentin-1, an adipokine secreted from visceral adipose tissue, has been reported to be associated with coronary artery disease (CAD) and metabolic disorders.

Objective: To clarify the relationship between serum omentin-1 levels and the presence and severity of CAD in patients with metabolic syndrome (MetS).

Methods: We measured serum omentin-1 levels in 175 consecutive patients with MetS and in 46 controls.

Results: Serum omentin-1 levels are inversely associated with the presence and angiographic severity of CAD in MetS patients.

Conclusions: Serum omentin-1 might be a potential biomarker to predict the development and progression of CAD in MetS patients.

Keywords: Adipokines, biomarker, cardiometabolic syndrome, coronary atherosclerosis index

Introduction

Metabolic syndrome (MetS), a cluster of cardiovascular risk factors, is associated with a 2-fold increased risk of coronary artery disease (CAD) (Lakka et al., 2002). As CAD is the leading cause of death worldwide, early and accurate diagnosis of CAD in patients with MetS is very important.

Today it is known that visceral adipose tissue functions as an important endocrine organ rather than only a fat storage depot (Ouchi et al., 2011). Adipokines, the secretory products of adipose tissue, are among the critical mediators of the pathophysiologic processes implicated in metabolic disorders (Deng et al., 2010). Omentin is a newly identified adipokine predominantly expressed and secreted by visceral adipose tissue (Schäffler et al., 2005). There are two highly homologous isoforms of omentin, omentin-1 and omentin-2; the former is the major circulating form in human plasma (Souza Batista et al., 2007). Serum omentin-1 levels have been shown to correlate negatively with body mass index (BMI), waist circumference, fasting insulin and homeostasis model assessment (HOMA) index and positively with high-density lipoprotein cholesterol (HDL-c) levels in a previous study (Souza Batista et al., 2007). Navarrete et al. recently reported that weight loss can increase circulating omentin-1 levels in obese volunteers (Moreno-Navarrete et al., 2010). The above findings demonstrated the association of omentin-1 with clinical features of the MetS.

In addition to its metabolic actions, recent studies raised the possible role of omentin-1 in the pathogenesis of atherosclerosis. Liu et al. revealed that serum omentin-1 levels were negatively correlated with carotid atherosclerosis in Mets patients (Liu et al.,

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2011). However, the link between omentin-1 and CAD in MetS patients has not been adequately investigated. Therefore, the current study was designed to clarify the relationship between serum omentin-1 levels and the presence and angiographic severity of CAD in patients with MetS.

Materials and methods

Study subjects

A total of 175 consecutive patients with MetS underwent coronary angiography in our hospital from March 2009 to April 2011 were enrolled in this study. All the MetS patients included were referred for coronary angiography because of the occurrence of cardiac symptoms or positive stress test. The MetS was defined using the Chinese Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidaemia in adults as having ≥3 of the following components: waist circumference ≥90 cm for men or ≥85 cm for women; triglycerides (TG) ≥1.70 mmol/L; HDL cholesterol <1.04 mmol/L for men or <1.7 mmol/L for women; blood pressure ≥130/85 mmHg or anti-hypertensive medications; or fasting blood glucose (FBG) ≥6.1 mmol/l and/or 2-h post-challenge glycaemia ≥7.8 mmol/l or on hypoglycaemic therapy for treatment of diabetes (Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults, 2007). Patients were excluded on the basis of having acute coronary syndromes (ACS), previously documented CAD, suspected myocarditis or pericarditis, known malignant disease, advanced renal disease and systemic inflammatory or autoimmune disorders. ACS included unstable angina (UA) and acute myocardial infarction (AMI). UA was defined as having ischemic chest pain at rest within the preceding 48 h or within the past month, with transient ST-T segment depression or T wave inversion and normal serum level of cTnT. AMI was defined as typical chest pain with (STEMI) or without ST-segment (NSTEMI) elevation on the electrocardiogram and an increase in the serum level of cardiac troponin T (cTnT) to greater than twice the upper limit of the normal range. The description of previously documented CAD is on the basis of patients' previous medical records. The determination of exclusion was made by the investigators. Forty-six age and sex matched volunteers undergoing routine physical examination in our hospital were recruited as controls during the same period. The controls were excluded CAD and MetS by means of medical history, physical examination and laboratory studies. Informed consent was obtained from all participants. This study was approved by the ethics committee of our hospital and conducted in conformity with the Declaration of Helsinki.

Coronary angiography analysis

Coronary angiography was performed according to standard protocols. Angiographic analysis was carried out by two interventional cardiologists blinded to the study protocol. Angiographic CAD was defined as ≥50% luminal diameter stenosis of at least one major epicardial coronary artery. Severity of CAD was estimated by coronary atherosclerosis index (CAI). CAI was defined as the sum of the following scores by assigning points to each lesion as follows: a score of 1, 1–24% narrowing; 2, 25–49% narrowing; 3, 50–74% narrowing; and 4, 75–100% narrowing (Tatami et al., 1981).

Blood chemistry analysis

Peripheral venous blood samples were collected after a 12-h fasting from all the subjects. After clotting, the samples were centrifuged at 3000*g* for 10 min and frozen at–80°C until analysis. Serum FBG, TG, total cholesterol (TC), low density lipoprotein cholesterol (LDL-c) and HDL-c levels were measured with standard laboratory techniques on a Hitachi 7600 Automatic Biochemical Analyzer (Hitachi Co., Japan). Serum omentin-1 levels were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit with high sensitivity and excellent specificity for detection of human omentin-1 (BlueGene Biotech Co., Shanghai, China).

Statistical analysis

Kolmogorov–Smirnov test was used to analyze data normality. Normally distributed continuous variables were expressed as the mean value ± SD, and non-normally distributed continuous variables were expressed as the median value (interquartile range). Differences between the two groups were analyzed using unpaired *t*-test, Mann–Whitney *U* test or χ^2-test when appropriate. Univariate logistic analysis was performed and the variables with a $p < 0.20$ were then entered into a backward stepwise multivariate logistic regression model to assess the independent predictors for the presence of CAD. Receiver operating characteristic (ROC) analysis was employed to determine sensitivity, specificity, and positive and negative predictive values of plasma omentin-1 levels in detecting CAD. Pearson rank correlation coefficient was employed to determine the correlation between serum omentin-1 levels and CAI scores. As the serum omentin-1 levels and CAI score were not normally distributed, log transformations values were performed. Multivariate linear regression analysis was performed to assess the independent predictors of CAI scores. Statistical significance was considered as $p < 0.05$ (two-tailed). The power of the study *post hoc* was 0.999. All Statistical analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL).

Results

Baseline clinical characteristics

The baseline clinical characteristics of the subjects are shown in Table 1. Compared with control group, MetS group had significantly higher waist circumference, BMI, SBP/DPB (systolic/ diastolic blood pressure), FBG, TC

Table 1. Baseline clinical characteristics.

Variables	Controls ($n=46$)	MetS patients	
		Without CAD ($n=68$)	With CAD ($n=107$)
Age (years)	62.56 ± 9.35	62.51 ± 8.66	64.41 ± 8.14
Male *n* (%)	26 (56.5%)	35 (51.47%)	65 (60.75%)
Smoking *n* (%)	19 (41.3%)	25 (36.76%)	48 (44.86%)
Waist circumference (cm)	83.73 ± 8.30*	88.78 ± 9.95	89.89 ± 8.13
BMI (kg/mm^2)	23.36 ± 2.59*	24.55 ± 2.79	25.11 ± 2.52
SBP (mm/Hg)	123.78 ± 12.80*	135.62 ± 19.88	136.63 ± 14.48
DBP (mmHg)	81.91 ± 11.11*	82.16 ± 12.48	82.26 ± 11.47
FBG (mmol/L)	5.25 ± 0.61*	5.67 ± 0.61	5.82 ± 0.69
(mg/dl)	94.54 ± 11.01*	102.07 ± 10.90	104.79 ± 12.44
TC (mmol/L)	4.10 ± 0.92*	4.67 ± 1.10	4.78 ± 1.00
(mg/dl)	159.71 ± 36.03*	182.14 ± 43.27	186.49 ± 39.08
TG (mmol/L)	1.20 (0.85–1.53)*	1.69 (1.27–2.36)	1.85 (1.34–2.53)
(mg/dl)	106.80 (75.65–136.17)*	150.41 (113.03–210.04)	164.65 (119.26–225.17)
LDL-c (mmol/L)	2.53 ± 0.77	2.70 ± 0.79	2.83 ± 0.91
(mg/dl)	98.75 ± 29.96	105.19 ± 30.88	110.27 ± 35.37
HDL-c (mmol/L)	1.08 ± 0.22	1.07 ± 0.21	0.99 ± 0.22**
(mg/dl)	42.43 ± 8.76	41.75 ± 8.07	38.47 ± 8.62**
Cardiovascular medication			
Statins *n* (%)	3 (6.5%)*	19 (27.94%)	34 (31.77%)
ACEI/ARB *n* (%)	4 (8.7%)*	22 (32.35%)	36 (33.64%)

All values are mean ± SD, median value (interquartile range) or *n* (%).
CAD, coronary artery disease; MetS, metabolic syndrome; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting glucose; TC, total cholesterol; TG, triglycerides; LDL-c, low density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
*$p<0.05$ compared with MetS patients; **$p<0.05$ compared with patients without CAD.

and TG ($p<0.01$). In MetS group, there were no significant differences in baseline clinical characteristics except for HDL-c levels ($p=0.013$) between patients with CAD and those without CAD.

Serum omentin-1 levels

MetS patients had significantly lower serum omentin-1 levels compared with controls (15.46 [range 11.46–22.26] ng/mL vs. 31.31 [range 22.84–42.26] ng/mL, $p<0.01$; Figure 1A). In patients with MetS, those with CAD had significantly lower serum omentin-1 levels than those without CAD (12.88 [range 10.26–16.20] ng/mL vs. 22.07 [range 16.25–26.89] ng/mL, $p<0.01$; Figure 1B).

Association of serum omentin-1 levels with CAD

In MetS patients, simple logistic regression analysis revealed that age, BMI, FBG, TG, HDL-c and serum omentin-1 levels showed a trend ($p<0.20$) toward an association with the presence of angiographic CAD (Table 2). All these variables were then entered into a backward stepwise multivariate logistic regression model. Multivariate logistic regression demonstrated that serum omentin-1 and HDL-c were independent predictors for predicting the presence of angiographic CAD (Table 2). The ability of serum omentin-1 levels to differentiate patients with CAD from those without CAD was assessed by ROC curve analysis. ROC curves for the diagnosis of CAD had an area under curve of 0.801 (95% CI: 0733–0.869, $p<0.001$). A serum omentin-1 level of ≤16.34 ng/mL predicted the presence of CAD with a sensitivity of 75.0%, specificity of 78.0%, and positive and negative predictive values of 84.3 and 83.3%, respectively (Figure 2).

Correlation of serum omentin-1 levels with the CAI

In MetS patients with CAD, a significant and negative correlation was found between log (serum omentin-1 levels) and the log (CAI) ($p=-0.316$, $p=0.001$; Figure 3). Multivariate regression model showed that serum omentin-1 was the independent contribution to log (CAI) after controlling for potential confounders ($\beta=-0.394$, 95% CI:–0.742 to–0.257; $p<0.01$).

Discussion

In the present study, we investigated the possible role and clinical implications of omentin-1 in association with the presence and severity of CAD in patients with MetS. We demonstrated for the first time that MetS patients with CAD had significantly lower serum omentin-1 levels than those without CAD. Moreover, serum omentin-1 levels were independently and negatively associated with the presence and angiographic severity of CAD. These results indicated that omentin-1 deficiency in the setting of MetS may contribute to the development and progression of CAD.

MetS is fast becoming one of the leading public health problems around the world (Eckel et al., 2005). MetS is

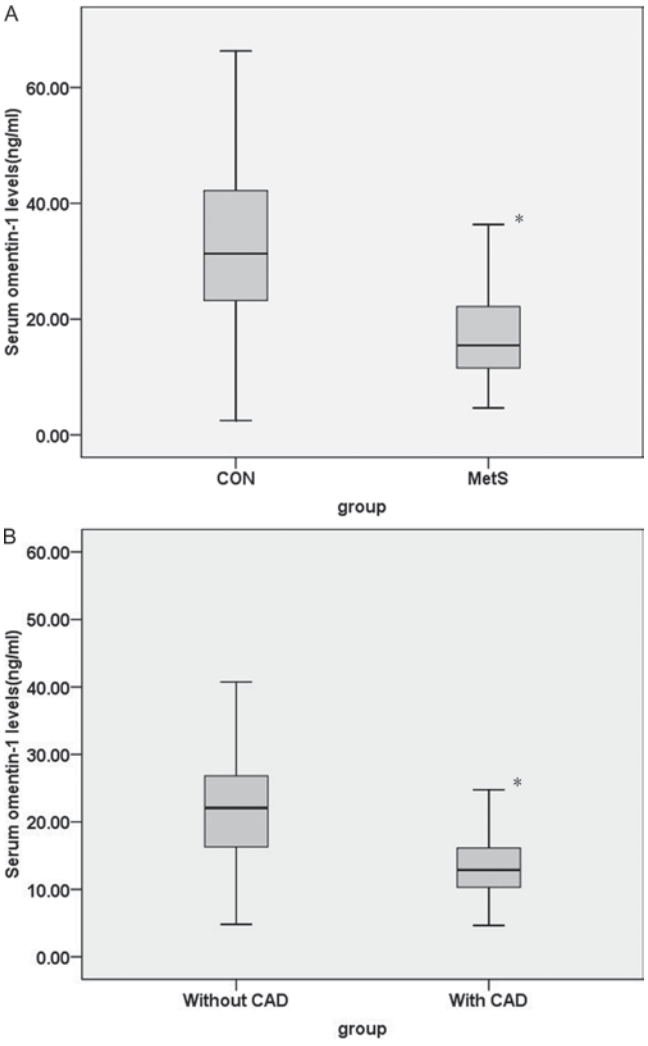

Figure 1. (A) Box-and-whisker plot showing serum omentin-1 levels between MetS patients and controls. CON = controls, MetS = metabolic syndrome, *$p < 0.01$ compared with controls. (B) Box-and-whisker plot showing serum omentin-1 levels between MetS patients with CAD and those without CAD. CAD, coronary artery disease; *$p < 0.01$ compared with patients with CAD.

associated with an increased mortality and morbidity of CAD (Hunt et al., 2004). The development of risk-reducing strategies and early-stage interventions for CAD is largely depend on better understanding of the molecular mechanisms and identification of reliable biomarkers that could reflect specific biological or pathological processes of cardiometabolic syndrome. In recent years, adipose tissues and adipokines have been considered to play a crucial role in the complex pathophysiological network between MetS and CAD, which opens the door for a new era of research that focused on the predictable value of adipokines for CAD in MetS patients.

Omentin is a novel bioactive adipokine that has a predicted molecular weight of 33 kDa (Schäffler et al., 2005). Omentin has been shown to intimately link with the components of MetS such as diabetes and obesity (Souza Batista et al., 2007; Tan et al., 2008; Moreno-Navarrete et al., 2010; Pan et al., 2010). The components of MetS interact with each other and are associated with the development of atherosclerotic cardiovascular diseases (Grundy et al., 2005). The main finding of the present study was the demonstration of the inverse and independent relationship between serum omentin-1 levels and the presence of angiographically significant CAD. These results indicated that omentin-1 might serve as a cardiovascular protective role in patients with MetS. This cardiovascular protective role might be attributed to at least three reasons. First, omentin-1 could inhibit vascular endothelial inflammatory states and attenuate endothelial dysfunction (Yamawaki et al., 2011), which is regarded as an early stage of atherosclerosis. This hypothesis was confirmed by a recent study which revealed that circulating omentin was a novel biomarker of endothelial dysfunction (Moreno-Navarrete et al., 2011). Second, omentin-1 could induce endothelium-dependent relaxation and might have the effect on lowering blood pressure (Yamawaki et al., 2010). Third, omentin-1 could promote insulin sensitivity and optimize glucose metabolism, which will slow down the

Table 2. Logistic regression analysis for the presence of CAD in patients with MetS.

	Simple regression		Multiple regression	
Variables	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (per year)	1.028 (0.990–1.067)	0.145	1.044 (0.996–1.094)	0.073
Male (no/yes)	0.685 (0.371–1.266)	0.228		
Smoking (no/yes)	0.715 (0.383–1.332)	0.291		
Waist circumference (per cm)	1.014 (0.980–1.050)	0.420		
BMI (per kg/mm^2)	1.085 (0.964–1.220)	0.175	1.068 (0.921–1.238)	0.386
SBP (per mm/Hg)	1.004 (0.985–1.022)	0.697		
DBP (per mmHg)	1.001 (0.975–1.027)	0.956		
FBG (per mmol/L)	1.429 (0.887–2.302)	0.143	1.419 (0.818–2.464)	0.213
TC (per mmol/L)	1.109 (0.827–1.486)	0.489		
TG (per mmol/L)	1.286 (0.883–1.872)	0.189	1.196 (0.755–1.896)	0.445
LDL-c (per mmol/L)	1.194 (0.835–1.708)	0.331		
HDL-c (per mmol/L)	0.165 (0.039–0.696)	0.014	0.093 (0.016–0.533)	0.008
Statins (no/yes)	0.833 (0.427–1.624)	0.591		
ACEI/ARB (no/yes)	0.943 (0.494–1.802)	0.860		
Omentin-1 (per ng/mL)	0.851 (0.806–0.900)	<0.001	0.848 (0.800–0.899)	<0.001

CAD, coronary artery disease; MetS, metabolic syndrome; OR, odds ratio; CI, confidence interval; other abbreviations are shown in Table 1.

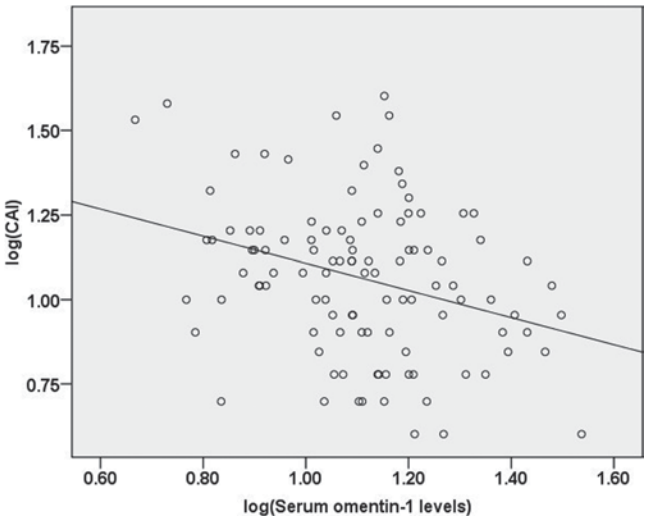

Figure 2. Correlations between serum omentin-1 levels and the severity of CAD evaluated by CAI score. CAD, coronary artery disease; CAI, coronary atherosclerosis index.

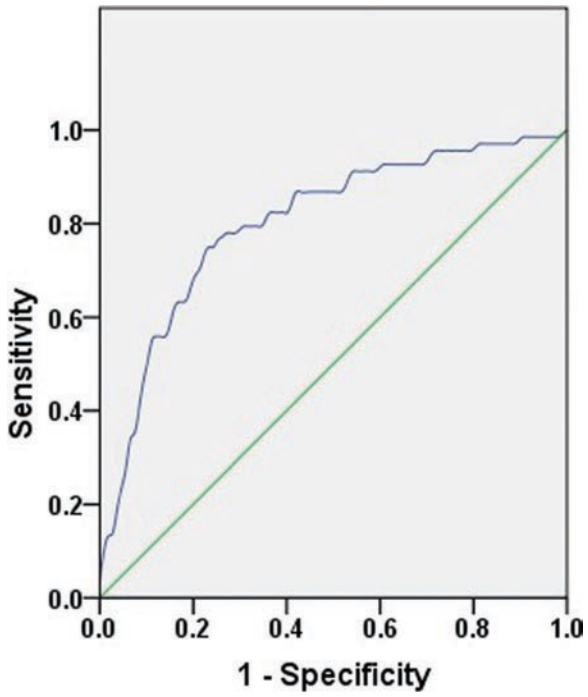

Figure 3. ROC analysis for determining sensitivity, specificity, and positive and negative predictive values of plasma omentin-1 levels in detecting CAD. ROC, receiver operating characteristic; CAD, coronary artery disease.

process of atherosclerosis (Yang et al., 2006; Pan et al., 2010). However, further studies are needed to define the clarified mechanisms whereby omentin-1 activation may have on the development of CAD in Mets patients. Besides, the present study also showed that the HDL-c levels were lower in MetS patients with CAD and the lower HDL-c levels could independently predict the presence of CAD in patients with MetS. These data are in accordance with many previous studies and fit into the notion that HDL particles could protect the coronary artery wall in patients with MetS (Mitsutake et al., 2009; Rein et al., 2010).

The CAI is an effective scoring system to assess the angiographic extent and severity of CAD (Tatami et al., 1981). Another notable observation of the present study was to demonstrate that serum omentin-1 levels were negatively correlated the CAI and this association remained significant after adjusting for other potential confounders. These results revealed that omentin-1 activation might also play a crucial role in the progression of CAD. This finding supports an additive role for serum omentin-1 to that of traditional risk factors in the risk stratification of CAD in MetS patients. However, the association between serum levels and the CAI was moderate and therefore these results should be interpreted cautiously.

The potential limitations of the present study should be noted. First, this study was cross-sectional with relatively small sample size, thereby allowing to detect associations, but not to determine the cause-effect relationship between omentin-1 and CAD. Prospective studies with larger sample size are necessary to validate our data and provide more information regarding the cause and effect relationship between omentin-1 and CAD in patients with MetS by using the marker to predict outcomes such as mortality or major adverse cardiac events. Second, this study only recruited MetS patients referred for coronary angiography in order to obtain accurate data about CAD severity. These might have resulted in increased prevalence of CAD in the study subjects than that in the general population. Third, we did not exclude other forms of atherothrombosis such as peripheral vascular, cerebrovascular, carotid, aortic disease in the present study, which might induce some bias.

In conclusion, our study demonstrated that serum omentin-1 levels were independently and negatively associated with the presence and angiographic severity of CAD in patients with MetS. Serum omentin-1 might be a potential biomarker to predict the development and progression of CAD in patients with MetS.

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Declaration of interest

The authors report no conflicts of interest.

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