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Circulating omentin is associated with coronary artery disease in men

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ABSTRACT

Objective: Obesity is closely associated with an increased risk for cardiovascular morbidity and mortality. Omentin is a fat-derived secreted factor that is downregulated in obesity. We investigated whether circulating omentin associates with the prevalence of coronary artery disease (CAD).
Methods: The consecutive 78 male subjects were enrolled from patients who underwent coronary angiography. Sixty one age-matched male subjects served as controls. Plasma omentin concentration was measured by enzyme-linked immunosorbent assay.
Results: Plasma levels of omentin correlated negatively with body mass index (BMI), systolic blood pressure, hemoglobin A1c and total cholesterol levels, and positively with HDL cholesterol and adiponectin levels. Circulating omentin was independently associated with hemoglobin A1c and HDL cholesterol in a multiple regression analysis. Plasma levels of omentin were markedly lower in CAD patients than in control subjects (CAD: 102.8 ± 69.0 ng/ml, control: 454.7 ± 128.6 ng/ml, $P < 0.001$). Multiple logistic regression analysis with BMI, systolic blood pressure, glucose, hemoglobin A1c, HDL cholesterol, adiponectin and omentin revealed that plasma omentin levels were independently correlated with CAD.
Conclusion: These data indicate that low levels of omentin are closely linked with the presence of CAD and that omentin serves as a novel biomarker for CAD.

1. Introduction

Cardiovascular disease is one of the leading causes of mortality in western countries [1,2]. Obesity, in particular, visceral fat accumulation, causes a cluster of hypertension, type 2 diabetes and dyslipidemia, also referred to as metabolic syndrome, ultimately leading to the development of atherosclerotic cardiovascular disease [3–8]. Adipose tissue secretes various bioactive molecules, which are known as adipocytokines or adipokines [9–11]. A large number of adipocytokines including tumor necrosis factor-α, interleukin-6 and plasminogen activator inhibitor type 1 are upregulated in the obese state, and these molecules usually function to promote obesity-inducible cardiovascular or metabolic diseases [9–11]. Adipose tissues also secrete a small number of factors such as adiponectin and Sfrp5, which are protective against obesity-linked complications [9,12,13]. Thus, the dysregulated production of adipocytokines is linked to the pathogenesis of cardiovascular disorders [9,11,14].

Omentin, also referred to as intelectin-1, has been newly identified as an adipocytokine that is expressed abundantly in human visceral fat tissue [15–17]. Omentin is present in blood stream in humans, and plasma omentin levels are decreased in obese individuals [18]. Conversely, circulating omentin concentrations are increased in obese subjects after weight reduction [19]. Furthermore, circulating omentin levels are reduced in patients with impaired glucose tolerance and type 2 diabetes [20]. Reduced levels of plasma omentin were also observed in overweight insulin-resistant women with polycystic ovary syndrome [21]. Recently, circulating omentin concentrations are reported to associate with endothelium-dependent vasodilation in patients with impaired glucose tolerance [22]. A more recent report showed the negative correlation between circulating omentin and carotid atherosclerosis in patients with metabolic syndrome [23]. These data suggest that omentin levels are associated with obesity-related metabolic and vascular complications. However, nothing is known about the relationship between omentin and coronary artery disease (CAD). Here we investigated whether plasma omentin levels associate with the presence of CAD. Our observations document

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that low omentin levels are independently associated with CAD prevalence even after adjustment for the known CAD risk factors.

2. Materials and methods

2.1. Study group

Consecutive 78 male patients were enrolled from inpatients who underwent coronary angiography at Nagoya University Hospital between 2009 and 2011. Cases included patients aged 40–79 years who had a 75% or greater organic stenosis of at least 1 major coronary artery as confirmed by coronary angiogram. We excluded patients with acute myocardial infarction, congestive heart failure, hemodialysis and malignant neoplasm. Age-matched control subjects were selected from apparently healthy subjects who visited Chunichi Hospital in Nagoya for an annual routine checkup. A total of 61 men with no history of cardiovascular disease who were not taking any medication served as control subjects. Diabetes was defined according to World Health Organization criteria. All patients and subjects enrolled in this study were Japanese and provided written informed consent. This study was approved by the ethics committee of the Nagoya University School of Medicine and the Chunichi Hospital.

2.2. Laboratory methods

Venous blood samples were obtained for chemical analysis after an overnight fast. Plasma omentin levels were determined with omentin enzyme-linked immunosorbent assay (ELISA) kit (Bio Vendor, NC, USA), and the intra-assay and inter-assay coefficients of variation were 4.1% and 4.8%, respectively (limit of detection: 0.5 ng/ml). Plasma adiponectin level was determined with the use of a latex turbidometric immunoassay (Otsuka Pharmaceutical Corporation, Tokushima, Japan). Standard assays were used to measure total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, hemoglobin A1c and creatinine levels. After an appropriate rest of 10 min, sitting blood pressure was measured. Body mass index (BMI) was calculated as the ratio of weight to squared height. Estimated glomerular filtration rates (eGFR) were calculated by the Simplified Modification of Diet in Renal Disease equation for Japanese.

2.3. Statistical analysis

Summary statistics are presented as mean ± standard error for continuous variables. The associations between omentin levels and the indicated parameters were examined by single or multiple logistic regression analyses. Single and multiple logistic regression analyses were also performed to analyze the associations of the indicated parameters with CAD. We estimated the odds ratios corresponding to a 1 standard deviation increase in each measure of the indicated parameters. A value of $P < 0.05$ was considered significant. All analyses were performed using JMP (version 6.03; SAS Institute Inc.).

3. Results

3.1. Patient characteristics

Clinical characteristics of male CAD patients and control subjects are displayed in Table 1. Patients with CAD had significantly higher levels of BMI, systolic blood pressure, fasting glucose, hemoglobin A1c, prevalence of diabetes, and the frequency of medication use, and lower levels of HDL cholesterol and adiponectin than control subjects. Frequency distributions of control and CAD subjects by concentrations of omentin are shown in Fig. 1. Plasma omentin levels in CAD patients were markedly lower than those in control subjects (102.8 ± 69.0 versus 454.7 ± 128.6 ng/ml, $P < 0.001$)(Table 1 and Fig. 1). There were no significant differences in age, the frequency of smokers, diastolic blood pressure, total cholesterol, LDL cholesterol, triglyceride, creatinine and eGFR between two groups.

Table 1
Patient characteristics.

Characteristic	Control ($n = 61$)	CAD ($n = 78$)	P value
Age (years)	61.3 ± 5.1	63.6 ± 8.2	0.057
BMI (kg/m^2)	22.9 ± 2.5	24.4 ± 3.8	0.008
Smoking (%)	42.6	30.7	0.148
Systolic BP (mmHg)	115.3 ± 16.3	123.9 ± 15.9	0.002
Diastolic BP (mmHg)	71.5 ± 10.9	70.4 ± 9.7	0.526
Glucose (mg/dl)	102.2 ± 11.1	108.9 ± 19.7	0.018
HbA1c (%)	5.02 ± 0.39	6.01 ± 0.93	<0.001
Diabetes (%)	8.2	41.0	<0.001
Total cholesterol (mg/dl)	183.9 ± 29.0	173.5 ± 32.8	0.053
LDL cholesterol (mg/dl)	103.4 ± 21.6	102.9 ± 28.5	0.908
HDL cholesterol (mg/dl)	57.6 ± 14.7	44.8 ± 12.0	<0.001
Triglyceride (mg/dl)	105.7 ± 66.3	126.2 ± 62.1	0.063
Creatinine (mg/dl)	0.88 ± 0.13	0.90 ± 0.39	0.700
eGFR (ml/min/1.73 m^2)	70.9 ± 12.7	72.8 ± 19.2	0.486
Adiponectin (μg/ml)	6.72 ± 0.52	5.41 ± 0.22	0.013
Omentin (ng/ml)	442.4 ± 131.2	102.8 ± 69.0	<0.001
Medication (%)			
Antihypertensive	0	66.7	<0.001
Antidiabetic	0	26.9	<0.001
Cholesterol lowering	0	67.9	<0.001

Data are presented as means ± SE. BP, blood pressure; HbA1c, hemoglobin A1c.

3.2. Relationship between omentin and clinical parameters

We next analyzed the correlation between plasma levels of omentin and clinical parameters in all subjects. Plasma omentin levels were negatively correlated with BMI consistent with a previous report (Table 2) [18]. Plasma levels of omentin correlated negatively with systolic blood pressure, hemoglobin A1c and total cholesterol levels, and positively with HDL cholesterol and adiponectin levels. Multiple logistic regression analysis with BMI, systolic blood pressure, hemoglobin A1c, total cholesterol, HDL cholesterol and adiponectin revealed that circulating omentin was independently associated with hemoglobin A1c and HDL cholesterol. Medication use included antihypertensive, antidiabetic and cholesterol lowering drugs in patients with CAD. The use of these drugs did not affect plasma omentin levels among CAD subjects (data not shown).

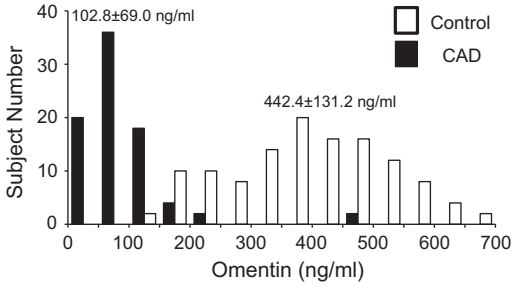

Fig. 1. The number of subjects according to omentin levels in patients with CAD and control subjects. Plasma omentin concentrations were determined by an ELISA system.