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Authors

Li, Jiabei

Song, Mingbao

Qian, Dehui

et al.

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ORIGINAL RESEARCH

Decreased plasma apolipoprotein A-IV levels in patients with acute coronary syndrome

Jiabei Li PhD[1]
Mingbao Song PhD[1]
Dehui Qian PhD[1]
Wei Lu PhD[1]
Juan Wang PhD[2]
Guoyan Jiang MSc[3]
Jun Jin PhD[1]
Xiaojing Wu PhD[1]
Lan Huang PhD[1]

[1] Institute of Cardiovascular Medicine, Xinqiao Hospital, Third Military Medical University, Chongqing, China
[2] Department of Laboratory Medicine, Southwest Hospital, Third Military Medical University, Chongqing, China
[3] Department of Oncology, the Second Affiliated Hospital, Chongqing Medical University, Chongqing, China

Abstract

Purpose: The purpose of this study was to evaluate the relationship between apolipoprotein A-IV (apoA-IV) plasma concentrations and acute coronary syndrome (ACS).

Methods: Plasma apoA-IV concentrations were measured in 115 patients with different types of ACS and in 68 gender- and age-matched control subjects using Enzyme-Linked Immunosorbent Assay (ELISA) kits. The clinical data were collected by an internist, who was blinded to plasma apoA-IV concentrations.

Results: Plasma apoA-IV levels in ACS patients were significantly decreased compared to the levels in control subjects (437.0 ± 157.5 μg/mL *vs.* 590.2 ± 183.7 μg/mL, $P<0.001$). An statistically significant decreasing trend of plasma apoA-IV levels from the control subjects, to patients with unstable angina pectoris (UAP) (457.3 ± 152.9 μg/mL), to patients with acute myocardial infarction (AMI) (311.7 ± 127.8 μg/mL), was observed. Moreover, plasma apoA-IV level was negatively associated with New York Heart Association (NYHA) functional class. NYHA class II (467.2 ± 142.1 μg/mL, $P<0.001$) and class III/IV (368.1 ± 170.8 μg/mL, $P<0.001$) patients had statistically decreased levels of plasma apoA-IV when compared to the control subjects. A stepwise multivariate regression analysis identified types of ACS, NYHA classes, and plasma fibrinogen levels as the most important determinants of plasma apoA-IV levels in ACS patients.

Conclusions: Low plasma apoA-IV levels are associated with ACS, and plasma apoA-IV levels may be a potential treatment target for ACS patients.

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Correspondence to:
Lan Huang, Ph.D.
Institute of Cardiovascular Medicine
Xinqiao Hospital
183 Xinqiao Street, Chongqing 400037, China
E-mail: lhuang260@163.com

Human apolipoprotein A-IV (apoA-IV), discovered in 1970s, is a 46 kD glycoprotein exclusively synthesized and secreted by intestinal enterocytes [1]. The stimulated production of apoA-IV in response to lipid absorption is achieved by increased transcription of apoA-IV in the enterocytes [2]. Physiologically, apoA-IV circulates in both blood and lymph in a free form; a structural protein of chylomicron or a high-density lipoprotein (HDL) [3]. It is well recognized that apoA-IV is a satiety factor suppressing food intake [4-6], and is involved in lipid metabolism [7-10]. Recently, accumulating evidence has shown that apoA-IV has an endogenous anti-inflammatory effect [11,12] and is a potent endogenous antioxidant that protects against copper-induced oxidation of low-density lipoprotein (LDL) [13] and macrophage-mediated oxidation [14]. Over-expression of either human or mouse apoA-IV in transgenic mice confers significant protection against diet-induced atherosclerosis in cholesterol-fed animals and apoE-deficient mice have been shown previously [13,15,16]. There is, however, little evidence to date that patients with coronary artery disease (CAD) have low serum apoA-IV levels [17-19].

Acute coronary syndrome (ACS), acute cardiac events resulting from atherosclerosis, is related to rupture of coronary artery atherosclerotic plaques and subsequent thrombus formation [20,21]. Inflammation and oxidative stress also participate in the pathogenesis of ACS [22-24]. Clinically ACS spans a broad classification, including unstable angina pectoris (UAP) and acute myocardial infarction (AMI), and the latter refers to non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) [25]. Despite receiving appropriate treatments, ACS patients still have a high risk of death and disability [26-28]. This study was undertaken to assess the relation between apoA-IV plasma concentrations and ACS, to explore a potential and novel treatment target for ACS patients.

Materials and Methods

Study population

A total of 115 ACS patients (61 males and 54 females, aged 63.3 ± 10.7 years) admitted to the Institute of Cardiovascular Medicine, Xinqiao Hospital, which is affiliated with the Third Military Medical University, were eligible for inclusion in this study. Exclusion criteria included the use of lipid-lowering medicine, a history of gastrointestinal surgery and renal impairment (serum creatinine > 105 μmol/L). An age- and gender-matched group of 68 control subjects (43 males and 25 females, aged 61.0 ± 7.0 years) from the Senior Health-Checking Centre, Southwest Hospital, which is also affiliated to the Third Military Medical University, was studied. These subjects had no history of either renal impairment or use of lipid-lowering medicine. The Local Ethics Committee of the Third Military Medical University approved the study protocol and the informed consent form. This study was conducted in accordance with the Declaration of Helsinki, and written consent was obtained from all participants.

Definition of ACS

Following the ACC/AHA 2007 Guidelines, UAP was defined as manifesting at least one of the following presentations, without any rise of cardiac troponin I or elevated ST-segment on electrocardiograph: (1) angina at rest, (2) new-onset severe angina and (3) increasing angina (more frequent and longer in duration). NSTEMI was defined as chest pain longer than 20 min with documented transient ST-segment depression (≥1 mm) or T-wave inversion (≥1 mm) in at least two contiguous leads and positive cardiac troponin I (cTnI) (>0.5 μg/mL). STEMI was defined as chest pain longer than 20 min with ST-segment elevation (≥1 mm) in at least two contiguous leads or new left bundle branch block, and elevated cTnI (>0.5 μg/mL).

Questionnaires

Information on cardiovascular risk factors, including history of current smoking, hypertension, diabetes, hypercuricemia and dyslipidemia, was obtained through review of medical records. Smoking was defined as either "yes" (current smoker) or "no" (non-smoker). Hypertension was defined as self-reported use of antihypertensive medicines or a diastolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg in the sitting position on at least three different occasions. Subjects with fasting blood glucose levels ≥7 mmol/L or on treatment with plasma glucose-lowering medications were classified as diabetics. Hyperuricemia was defined as serum uric acid levels >420 mmol/L in males and >360 mmol/L in females. Dyslipidemia was defined as follows: total cholesterol >5.69 mmol/L, triglycerides >1.68 mmol/L, LDL-cholesterol >3.1 mmol/L, or HDL-cholesterol <0.9 mmol/L. The New York Heart Association Class (NYHA class) was used to evaluate patients' functional status.

Blood collection and biochemical analysis

Blood samples were drawn for the purpose of diagnosis and treatment, and necessary biochemical parameters were measured by standard automated techniques in our hospital. Additionally, to prepare plasma samples for measuring apoA-IV, fasting whole blood was collected the following morning in

TABLE 1. Clinical characteristics of ACS patients and control subjects

	ACS patients (N =115)	Control subjects (N = 68)	*P* value
Gender: Male	61 (53.0%)	43 (63.2%)	0.217
Age (years)	63.3 ± 10.7	61.0 ± 7.0	0.115
Current smoking	29 (25.2%)	13 (19.1%)	0.369
Types of ACS			
UA	99 (86.1%)	—	—
USTEMI/STEMI	16 (13.9%)	—	—
NYHA functional class			
Class II	80 (69.6%)	—	—
Class III/IV	35 (30.4%)	—	—
Hypertension	61 (53.0%)	19 (27.9%)	0.001*
Diabetes	17 (14.8%)	5 (7.4%)	0.163
Hyperuricemia	5 (4.5%)	2 (2.9%)	0.713
Dyslipidemia	41 (35.7%)	11 (16.2%)	0.006*
Platelet count ($\times 10^9$/L)	166 ± 55	172 ± 53	0.471
Lipid profile			
Total cholesterol (mmol/L)	4.30 ± 0.94	3.84 ± 1.15	0.006*
Triglyceride (mmol/L)	1.62 ± 1.12	1.28 ± 1.09	0.047*
Apolipoprotein A-I (g/L)	1.15 ± 0.20	1.19 ± 0.18	0.177
Apoliprotein A-IV (μg/mL)	437.0 ± 157.5	590.2 ± 183.7	0.000*
Apolipoprotein B (g/L)	0.78 ± 0.21	0.82± 0.20	0.207
HDL cholesterol (mmol/L)	1.17 ± 0.33	1.24 ± 0.39	0.217
LDL cholesterol (mmol/L)	2.46 ±0.70	2.25 ± 0.58	0.038*
Coagulation profile			
Prothrombin time (s)	11.4 ± 2.0	11.9 ± 1.7	0.086
Fibrinogen (g/L)	2.68 ± 0.71	2.74 ± 0.82	0.616
Activated partial thromboplastin time (s)	30.4 ± 5.8	32.1 ± 5.7	0.055
Thrombin time (s)	17.9 ± 1.7	16.8 ± 2.0	0.000*

* $P < 0.05$

one 2 mL tube containing K_3EDTA to achieve a final concentration of 1.735 mg/mL. These samples were centrifuged (2,000 g for 15 min) immediately after collection, and stored at -70°C for further analysis. Human plasma apoA-IV concentrations were determined in duplicate using commercial sandwich enzyme-linked immunosorbent assay (ELISA) kits (Millipore, Billerica, MA, USA) in a blinded fashion. All plasma samples were measured within three months of collection. The dose-response curve of this assay was established by a sigmoidal five-parameter logistic equation. The standard curve for human plasma apoA-IV concentration was created by using serial dilutions (1:64-1:2) of 4.3 ug/mL purified recombinant human apoA-IV from the ELISA kit according to the instructions. The intra- and inter-assay coefficients of variation (CV) were 4.6% and 12.3%, respectively.

Statistics

Continuous variables were presented as mean ± standard deviation (mean ± SD). Categorical variables were expressed as percentage or frequency. The independent-samples t-test or one-way ANOVA were used to compare continuous variables, and categorical variables were compared by nonparametric chi-square test. The Kolmogorov-Smirnov test was applied for identifying normally distributed variables. The relationship

TABLE 2. Comparison of plasma apolipoprotein A-IV levels in ACS patients (N=115) grouped according to cardiovascular risk factors.

	N	ApoA-IV (μg/mL)	*P* value
Gender (male/female)	61/54	412.2/465.1	0.071
Smoking (yes/no)	29/85	426.4/441.7	0.655
Hypertension (yes/no)	61/54	444.2/428.9	0.604
Diabetes (yes/no)	17/99	462.5/432.6	0.473
Hyperurecemia (yes/no)	5/110	443.5/436.7	0.926
Dyslipidemia (yes/no)	41/74	458.7/425.1	0.275

between plasma apoA-IV concentration and other variables was evaluated by stepwise multivariate regression analysis. Statistical analysis was performed using PASW statistics version 18 (SPSS, Chicago, IL, USA). For all tests, $P<0.05$ was considered to be statistically significant.

Results

Table 1 shows the clinical characteristics of ACS patients and control subjects. The patients with ACS (N = 115) had statistically significant reduction in plasma apoA-IV levels when compared to gender- and age-matched control subjects (N = 68) (437.0 ± 157.5 μg/mL *vs.* 590.2 ± 183.7 μg/mL, $P<0.001$). The ACS group had higher percentages of the patients with hypertension and dyslipidemia. Concentrations of plasma HDL cholesterol, triglyceride and LDL cholesterol were significantly lower and thrombin time longer in controls than they were in the patients. ACS patients were further grouped according to cardiovascular risk factors (gender, smoking, hypertension, diabetes, hyperuricemia and dyslipidemia), and there was no significant difference among subgroups (Table 2).

These patients were classified by types of ACS, i.e., the UAP group (N = 99, 86.1%) and the AMI group (N = 16, 13.9%). Fig. 1 shows the differences in plasma apoA-IV concentrations between control subjects and two types of ACS patients. There seemed to be an obvious decreasing trend from the control subjects to patients with unstable angina pectoris (UAP) to acute myocardial infarction (AMI) patients. Two types of ACS patients had a markedly lower apoA-IV level compared to the control subjects (UAP *vs.* control, 457.3 ± 152.9 μg/mL *vs.* 590.2 ± 183.7μg/mL, $P<0.001$; AMI *vs.* control, 311.7 ± 127.8 μg/mL *vs.* 590.2 ± 183.7μg/mL, $P<0.001$). Moreover, the plasma apoA-IV concentration was significantly decreased in the AMI group compared with the UAP group (311.7 ± 127.8 μg/mL *vs.* 457.3 ± 152.9 μg/mL, $P<0.01$).

Plasma apoA-IV level was negatively associated with NYHA functional class (Fig. 2). In the current study, there were no class I patients among the ACS group. Compared to the control subjects, NYHA class II (N = 80, 69.6%) and class III/IV (N = 35, 27.8%) patients had decreased levels of plasma apoA-IV (class II *vs.* control, 467.2 ± 142.1 μg/mL *vs.* 590.2 ± 183.7 μg/mL, $P<0.001$; class III/IV vs. control, 368.1 ± 170.8 μg/mL *vs.* 590.2 ± 183.7 μg/mL, $P<0.001$). And there was a significant difference between class III/IV and class II patients (368.1 ± 170.8 μg/mL *vs.* 467.2 ± 142.1 μg/mL, $P<0.05$).

A stepwise multivariate regression analysis was used to determine the factors related to plasma apoA-IV levels in ACS patients with a model that included all variables listed in Table 1. The plasma apoA-IV concentrations were independently associated with different types of ACS ($P = 0.022$), NYHA functional classes ($P = 0.027$) and plasma fibrinogen levels ($P = 0.040$). The standardized coefficients were -0.214, -0.201 and -0.186, respectively, in the regression equation. This was consistent with the results from one-way ANOVA (Fig. 1 and Fig. 2) in subgroup analyses according to ACS types and NYHA functional classes. Besides, fibrinogen levels were also independently relative to plasma apoA-IV concentrations in a stepwise multivariate regression model. Thus, a scatter dot plot with fitting curve was used for further quantifying their relationship (Fig. 3), and revealed a weak negative, but statistically significant, correlation between plasma apoA-IV levels and fibrinogen concentrations in ACS patients (Pearson correlation coefficient, r = -0.276; $P = 0.003$).

Discussion

In this study, compelling evidence of a relationship between low plasma apoA-IV concentrations and ACS is presented. Patients with ACS had a 26% lower apoA-IV concentrations when compared with the gender- and age-matched control subjects. This is the first study suggesting an obvious decreasing trend of plasma apoA-IV levels from control subjects to patients with unstable angina pectoris (UAP) to acute myocardial infarction (AMI) patients, and demonstrating the negative association of plasma apoA-IV concentrations with NYHA functional classes.

ACS is related to rupture of coronary artery atherosclerotic plaques and subsequent thrombus formation [20,21]. Thrombolytics may be administered or urgent primary coronary angioplasty may be performed if the ECG confirms changes suggestive of STEMI. For those who are diagnosed as having NSTEMI/UAP, antiplatelet agents and nitrates are cornerstones of medical treatment. If troponin is positive, coronary angiography is typically performed on an urgent ba-

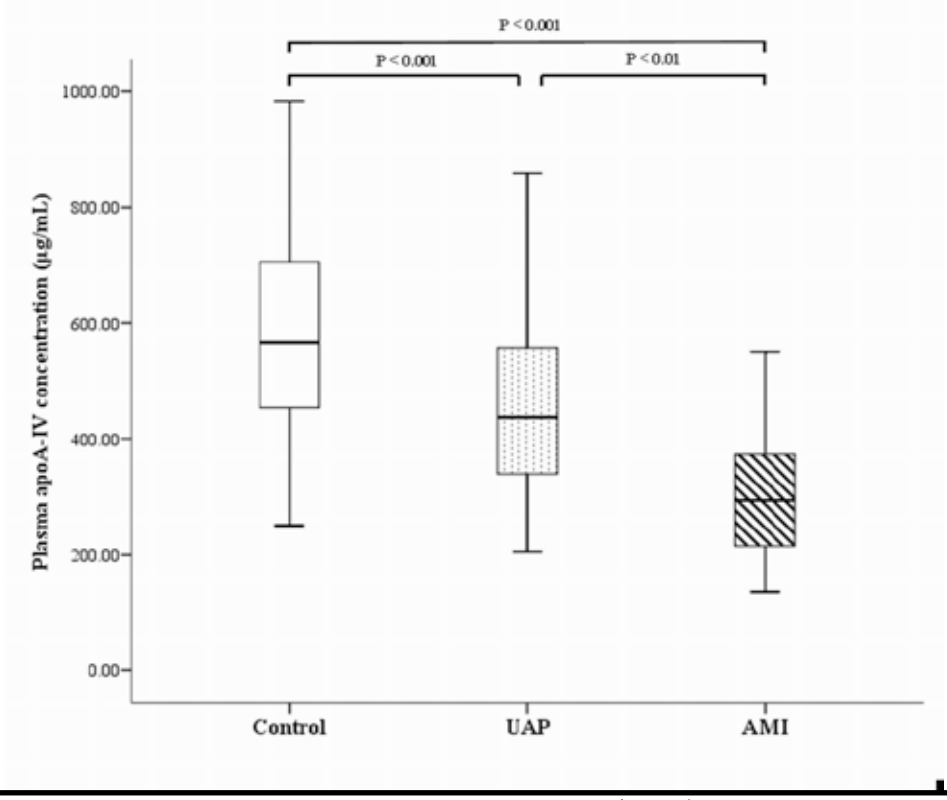

FIGURE 1. Comparison of plasma apoA-IV concentrations between control subjects (N=68) and the two types of ACS patients (N=115).

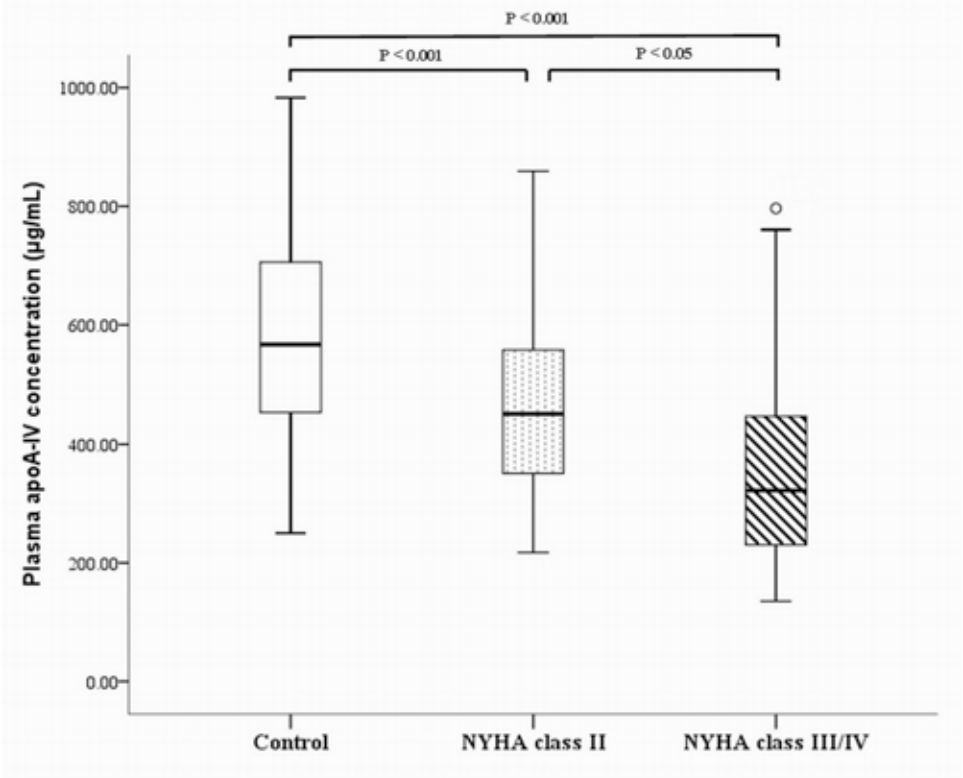

FIGURE 2. Plasma apoA-IV concentrations in control subjects (N=68) and ACS patients with different NYHA classes (N=115).
(○ represents a suspected outlier larger than the third quartile by at least 1.5 times the inter-quartile range)

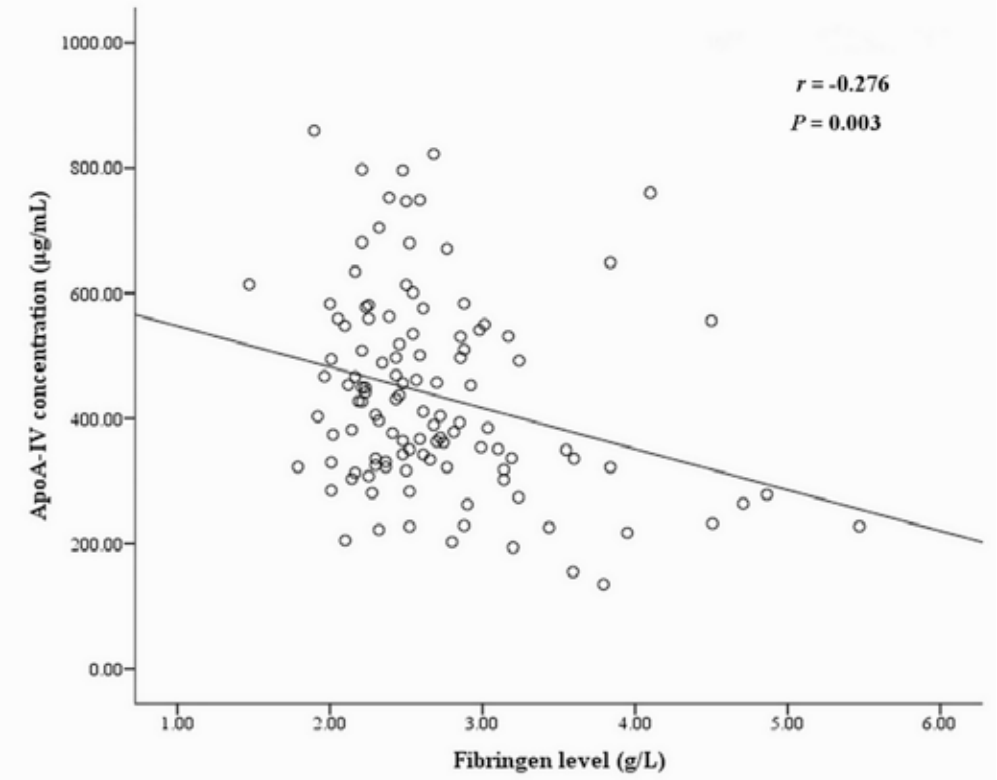

FIGURE 3. Correlation of plasma apoA-IV concentrations with fibrinogen levels in ACS patients (N=115); (Pearson correlation coefficient, r = -0.276; P = 0.003).

sis; however, despite receiving appropriate treatment, ACS patients still have a high risk of death and disability [20,25]. It is necessary to study further the pathogenic mechanisms of ACS and to identify novel therapeutic targets; therefore, the present study provided clinical significance to evaluate the relationship between apoA-IV plasma concentrations and ACS. This study further categorized ACS patients by type of ACS and NYHA class, and suggested a negative correlation between plasma apoA-IV concentrations and severity of ACS and NYHA classes based on reduced plasma apoA-IV levels in ACS patients compared with control subjects. These findings imply a role of apoA-IV involved in the pathogenesis of ACS and a potentially novel treatment target for ACS.

It has been confirmed that apoA-IV has positive roles in lipid metabolism [7-10], anti-inflammation [11,12], anti-oxidation [13,14] and anti-atherogenesis [15,16]. ApoA-IV binds to peripheral cells, promotes cholesterol efflux and the formation of HDL by stimulating lecithin-cholesterol acyltransferase (LCAT) activity [29], and transports cholesterol to the liver or steroidogenic organs where cholesterol could be metabolized, thus participating in reverse cholesterol transport pathways [8]. Moreover, it modulates cholesterol-ester transfer protein-mediated transfer of cholesteryl esters from HDL to LDL [9], and activates lipoprotein lipase [10], which hydrolyzes triglycerides in lipoprotein. It has been demonstrated that the expression of human apoA-IV in apoE-deficient mice decreases the secretion of pro-inflammatory cytokines and inhibits P-selectin expression that modulates leukocyte and platelet adhesive interactions [11,12]. In addition, Ostos *et al.* found that oxidation parameters were reduced in apoA-IV/E-deficient mice compared with apoE0 mice [13]. It has been also suggested that apoA-IV may serve as an antioxidant *in vivo*, where the oxidation of lipoproteins by macrophages in the subendothelial space may play a key role in the development of atherosclerosis [14] and attenuate oxidant-induced apoptosis [30]. Previous *in vitro* and *in vivo* animal studies have demonstrated that overexpression of either human or mouse apoA-IV in transgenic mice protects against diet-induced atherosclerosis in cholesterol-fed animals and apoE-deficient mice [15,16].; however, the value of apoA-IV in atherosclerotic patients is unclear. Only three previous clinical studies have reported its potential role as a risk protecting factor for coronary artery disease (CAD) [17-19]. Kronenberg *et al.* demonstrated an association between low apoA-IV concentrations and CAD in

humans [17], which was consistent with the result by Ezeh *et al.*, who suggested that lipid-free apoA-IV may play a key role for its antiatherogenic effect [18]. Wong *et al.* found that genetic variation in and around ApoA4, independent of the effects of triglyceride, is associated with risk of CAD [19]. Data has also been reported that show a correlation between apoA-IV levels and risk of CAD in type 2 diabetes [31] and hemodialysis patients [32].

In addition to the properties listed above, the cleavage of lipid-free apoA-IV by matrix metalloproteinase-7, which is known to be expressed primarily at the border between the fibrous cap and lipid core in atherosclerotic lesions, might be an important step leading to the disruption of normal lipid metabolism and the induction of atherosclerosis [33]. Atherosclerosis, inflammation and oxidative stress are essentially pathophysiological process in ACS; therefore, the beneficial effects of apoA-IV in ACS could be reasonably explained.

AMI is mostly caused by occlusion of a coronary artery following the rupture of a vulnerable atherosclerotic plaque [24]. Compared with UAP patients, AMI patients are at a higher risk for processes with severe life-threatening thrombotic events and, for the first time, our study provides evidence that patients with AMI have lower plasma apoA-IV levels. Vulnerability of the atherosclerotic plaque may be responsible for reduced plasma apoA-IV levels. As we all know, activation of platelets and white blood cells are involved in the rupture of vulnerable plaque [22,34]. Our observations may relate to modulation of platelet and white blood cell activation. In fact, it has been indicated that the neutrophil/lymphocyte ratio is associated with apoA-IV concentrations [32]; however, the roles of apoA-IV in platelet activation remains unknown.

Patients with heart failure often suffer from congestion of gastrointestinal organs [35] and apoA-IV originates from small intestine in humans. Small bowel dysfunction because of congestion may result in decreased production of apoA-IV from the enterocytes. This may be the reason why decreased apoA-IV levels were observed in NYHA class III/IV patients. Further studies are needed to clarify the physiological role of plasma apoA-IV in heart failure patients.

Our data also suggest a negative association between apoA-IV levels and fibrinogen concentrations. In a large individual participant meta-analysis, moderately strong associations were found between increased plasma fibrinogen levels and the risk of major adverse cardiovascular events (MACEs) [36]. This appeared to indirectly indicate the relationship between lower apoA-IV concentrations and risks of MACEs, including ACS. Fibrinogen participates in anticoagulation as an important part of fibrinolytic system. Whether human apoA-IV is involved in establishing a balance between coagulation, anticoagulation and fibrinolysis, thereby affecting atherothrombosis, needs to be further clarified.

Several limitations of this study should be considered: the study was an observational case-control design, only one center was involved and the sample size was relatively small. Whether the findings could be extrapolated to other populations and other disease conditions is yet to be determined. Another point to note is that the samples were drawn close (in time) to the diagnosis in the study. Furthermore, although these results suggest apoA-IV may be involved in the pathogenesis of ACS, we can not exclude the possibility that the change in plasma apoA-IV levels may be a consequence of the acute phase response, particularly since blood samples were collected at only one time point close to the diagnosis of ACS. Serial measurements of plasma apoA-IV drawn over time could potentially address this issue.

In conclusion, the present study revealed that plasma apoA-IV levels were 1) significantly decreased in ACS patients relative to controls, 2) were significantly lower in AMI patients compared with UAP patients, and 3) were negatively correlated with NYHA class. Our results support further large and multi-centered studies to demonstrate the role of apoA-IV in the field of cardiovascular medicine as a potential and novel treatment target for ACS.

Acknowledgments

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