Association between α1-antitrypsin and acute coronary syndrome

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Abstract. α1-antitrypsin (AAT) is a protein released as part of the anti-inflammatory response. It regulates the activity of serine proteinases and has a crucial role in the pathogenesis of acute coronary syndrome (ACS). The present study aimed to examine its role in patients with ACS. The plasma samples of 117 patients were collected at the Cardiology Department of the Affiliated Hospital of Youjiang Medical University (Baise, China). These included 46 cases of ACS (who met the diagnostic criteria for ACS and had ≥50% luminal stenosis of any coronary vessel), 35 cases of stable angina (SA; with ≥50% luminal stenosis of any coronary vessel but in a stable condition) and 36 normal healthy controls (subjects with no luminal stenosis in their coronary arteries). Plasma AAT protein concentrations were measured by ELISA and clinical data were collected. The plasma levels of AAT protein in patients with ACS were lower than those in controls and cases of SA (P<0.05), and the levels tended to decrease with the number of coronary artery lesions involved. There were no significant associations of the expression of plasma AAT protein and the number of diseased vessels in patients or the degree of stenosis. There was no correlation between the plasma protein levels of AAT and Gensini scores of patients with ACS. In conclusion, the plasma AAT protein levels in patients with ACS may contribute to the occurrence and development of coronary artery disease.

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Abbreviations: AAT, α1-antitrypsin; CAD, coronary artery disease; ACS, acute coronary syndrome; hs-CRP, high sensitivity C-reactive protein; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; AST, aspartate transferase; ALT, alanine transferase; GGT, γ-glutamyl transferase; CAG, coronary angiography

Introduction

Acute coronary syndrome (ACS) presents a major cause of mortality and economic burden in the world and accounts for >2.5 million hospitalizations annually worldwide (1,2). Approximately 15% of patients with ACS experience recurrent cardiovascular events within one year (3). The etiology and pathogenesis of this disease are complex and the morbidity increases with age as well as with the presence of risk factors such as hypertension and smoking (4,5). Numerous studies suggested that innate immunity and inflammatory responses have important roles in the occurrence and development of ACS (6-8).

α1-antitrypsin (AAT) deficiency was first identified by paper electrophoresis in 1963 by Laurel and Eriksson (9). AAT is an acute-phase protein that is mainly produced in the liver and it is expressed in neutrophils, monocytes, macrophages, alveolar macrophages, intestinal epithelial cells, cancer cells and corneal cells (9). It is also a serine protease inhibitor which circulates in healthy individuals and is usually increased in most inflammatory diseases such as ACS (10). The normal AAT plasma level is 1.04 g/l or ~20 μM (11) and this may increase by 3-5-fold when an inflammatory reaction occurs (12).

An increase in AAT expression may also contribute to activation of signaling events that initiate the production and release of pro-inflammatory cytokines and adhesion molecules, such as lipopolysaccharides, TNF-α, IL-1 and IL-6, which are released by neutrophils, monocytes, macrophages and alveolar macrophages that may in turn activate innate immunity and inflammatory responses (13-15). A number of studies have suggested that AAT is associated with the development of chronic hepatitis, liver cirrhosis (16), chronic obstructive pulmonary disease (17), atherosclerotic diseases (18), tumors (19) and autoimmune diseases (20).

Plasma AAT levels have been demonstrated to correlate with both the presence and severity of coronary stenosis in patients with stable angina pectoris (SA) (21). However, at present, available studies on the association between plasma AAT concentrations and the severity of ACS are sparse and insufficient (21). Thus, it remains elusive whether plasma AAT

is correlated with ACS. The AAT concentration is likely to be different in patients with ACS as they can express differing pathological features. It remains elusive whether an increase or a decrease in plasma AAT is an independent predictor for the severity of coronary atherosclerosis in patients with ACS. Accordingly, it was hypothesized in the present study that decreases in plasma AAT levels in patients with ACS may be a predictor for the risk and severity of the disease. In order to test this hypothesis, plasma AAT levels were first compared between patients with SA and controls. It was further investigated whether there was a correlation between AAT levels and Gensini scores in patients with ACS.

Patients and methods

Study population. A total of 117 cases (36 control subjects, 35 patients with SA and 46 ACS patients) who underwent coronary angiography between March 2017 and April 2018 at the Affiliated Hospital of Youjiang Medical University for Nationalities (Baise, China) were enrolled.

Exclusion criteria. The exclusion criteria were as follows: rheumatic heart disease, dilated cardiomyopathy, congenital heart disease, patients undergoing intravenous thrombolysis, coronary stenting and coronary artery bypass grafting, systemic or local severe infection, auto-immunologic and blood system diseases, severe kidney or liver disease and malignancies.

Coronary angiography (CAG). Coronary artery disease (CAD) was defined as patients with ≥50% of luminal stenosis in at least one major coronary vessel and major branches (the left main, left anterior descending, left circumflex and right coronary arteries) based on the result of CAG, which was determined as agreed by two experienced cardiologists. According to the number of diseased vessels based on the results of the CAG, patients were classified into 1-vessel, 2-vessel and multiple-vessel disease groups. If the left main coronary artery was affected by 2-vessel disease and it was combined with the right coronary artery, this was referred to as multiple-vessel disease.

The severity of coronary lesions was assessed by determining the Gensini score (GS) (22), which was calculated according to the severity of stenosis as follows: 1 point for <25% stenosis, 2 points for 26-50% stenosis, 4 points for 51-75% stenosis, 8 points for 76-90% stenosis and 32 points for complete occlusion. The scores were then multiplied by a coefficient representing the importance of the lesion's position in the coronary artery system. Control subjects also underwent a CAG and were confirmed to be free of coronary artery stenosis. In addition, these patients did not exhibit any clinical or electrocardiographic evidence of myocardial infarction or CAD.

Clinical data and laboratory tests. Clinical data, including age, sex, body mass index (BMI), smoking status (smokers were defined as smoking at least one cigarette per day for >1 year), drinking status (drinkers were defined as consuming at least one alcoholic drink per day for a minimal period of six months), hypertension, diabetes, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol

(HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1, apolipoprotein B, lipoprotein a, homocysteine, hemoglobin A1C (HbA1C), uric acid (UA), platelets (PLT), high-sensitivity C-reactive protein (hs-CRP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and γ-glutamyl transferase (GGT) were obtained from all participants.

AAT protein assay. Blood was collected aseptically from the caudal vein by venipuncture into one of three vacutainer tubes containing either sodium heparin, sodium citrate or EDTA. These tubes were immediately centrifuged at 375 x g for 15 min at 4°C and samples were prepared or analyzed within 45 min of collection. Aliquots were frozen at -80°C for determination of AAT by ELISA using a commercially available kit purchased from Enzyme-linked Biotechnology Co., Ltd. (cat. no. ml057793). The intra- and inter-assay coefficient of variation for the ELISA kit for AAT was determined to be <10 and <15%, respectively. The detection range of the ELISA was 125-4,000 μg/ml. AAT levels in the plasma were determined according to the manufacturer's protocol.

Statistical analysis. All data were analyzed with SPSS 22.0 (IBM Corp.) and GraphPad Prism 5.0 (GraphPad Software, Inc.). The data were first tested for normality using the Kolmogorov-Smirnov test and if they were normally distributed, the variables were expressed as the mean ± standard deviation and were compared by t-test or one-way ANOVA. For ANOVA, Fisher's least significant difference method was used as the post hoc test. Otherwise, the data with a non-normal distribution were expressed as the medians (interquartile range) and were compared by the Kruskal-Wallis test. Categorical variables were expressed as n (%) and were compared with the χ^2 test. A two-tailed P<0.05 was considered to indicate statistical significance.

Results

Characteristics of the study participants. The basic biochemical parameters and clinical characteristics of all subjects are summarized in Table I. A total of 36 patients with SA, 46 patients with ACS and 35 healthy controls were enrolled in the present study.

As for the SA patients, 11 (31.4%) were females and 24 (68.6%) were males, with a mean age of 62.57±6.20 years (range, 44-75 years). Among the ACS patients, 14 (30.4%) were females and 32 (69.6%) were males, with a mean age of 59.43±9.47 years (range, 31-79 years). With respect to the healthy controls, 14 (38.9%) were females and 22 (61.1%) were males, with a mean age of 57.17±9.49 years (range, 28-79 years). There were no statistically significant differences between the controls and patient groups in terms of sex, smoking, BMI, TC, TG, HDL-C, VLDL-C, apolipoprotein A1, apolipoprotein B, lipoprotein a, PLT and HbA1c. Compared with the SA group, the ACS group had a larger proportion of individuals with hypertension, but less cases of diabetes. Significantly higher values for systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, homocysteine, admission glucose, postprandial blood glucose and hs-CRP were

Table I. Characteristics of the participants enrolled in the study.

Characteristics	Controls (n=36)	SA (n=35)	ACS (n=46)	χ^2 (F)	P-value
Male sex	22 (61.1)	24 (68.6)	32 (69.6)	0.731	0.694
Smoking	7 (19.4)	5 (14.3)	14 (30.4)	3.231	0.199
Drinking	19 (52.8)	25 (71.4)	36 (78.3)[a]	6.280	0.043
Hypertension	2 (5.6)	17 (48.6)[a]	27 (58.7)[a]	25.696	<0.001
Diabetes	0 (0)	10 (28.6)[a]	5 (10.9)[b]	13.220	0.001
Smoking (n)[c]	1.72±0.74	2.17±0.95	3.13±1.07	0.595	0.553
Age (years)	57.17±9.49	62.57±6.20	59.43±9.47	3.170	0.046
SBP (mmHg)	126.72±1.44	133.69±3.22	142.54±2.90[a,b]	9.058	<0.001
DBP (mmHg)	78.78±1.41	82.20±1.76	85.48±1.75[a]	4.118	0.019
MAP (mmHg)	94.76±1.17	99.36±2.07	104.5±1.97[a,b]	7.421	0.001
BMI (kg/m^2)	23.14±0.44	23.47±0.45	24.61±0.63	2.179	0.118
AG (mmol/l)	4.96±0.11	7.21±0.40[a]	7.03±0.40[a]	12.443	<0.001
PG (mmol/l)	6.98±0.23	10.50±0.67[a]	9.50±0.64[a]	9.363	<0.001
HbA1C (%)	5.21±0.16	5.71±0.28	5.80±0.13[a]	2.749	0.068
UA (μmol/l)	308.33±13.81	379.23±16.77[a]	319.69±14.30[b]	6.164	0.003
TC (mmol/l)	4.63±0.19	4.24±0.25	4.11±0.15	1.959	0.146
TG (mmol/l)	1.94±0.18	2.04±0.38	1.47±0.09	1.973	0.144
LDL-C (mmol/l)	2.63±0.15	2.40±0.16	2.66±0.15	0.814	0.446
HLDL-C (mmol/l)	1.21±0.07	1.22±0.04	1.17±0.04	0.224	0.800
VLDL-C (mmol/l)	0.63±0.04	0.61±0.04	0.68±0.04	0.779	0.461
Apolipoprotein A1 (g/l)	1.49±0.15	1.42±0.05	1.37±0.04	0.584	0.560
Apolipoprotein B (g/l)	0.94±0.09	0.83±0.04	0.81±0.04	0.516	0.599
Lipoprotein a (nmol/l)	47.28±18.58	225.56±44.82	341.80±51.00	2.614	0.079
Homocysteine (μmol/l)	12.14±0.48	14.60±0.61[a]	15.23±0.77[a]	5.980	0.003
hs-CRP (mg/l)	2.85±0.91	5.20±1.64	8.12±1.62[a]	3.356	0.038
PLT (x10^9/l)	203.39±12.42	202.23±11.08	228.93±9.14	2.116	0.125
AST (U/l)	29.01±6.91	27.89±7.21	28.91±10.38	0.203	0.816
ALT (U/l)	28.94±6.54	29.03±7.04	26.8±8.37	1.197	0.306
GGT (U/l)	30.72±6.39	31.29±7.37	32.87±10.97	0.677	0.510
Gensini score	0	30.97±5.45[a]	32.74±2.73[a]	19.295	<0.001

[a]P<0.05 when compared to the control group; [b]P<0.05 when compared to the SA group; [c]Smoking refers to the average number of cigarettes smoked per day for each group. Data were tested for normality using the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± standard deviation and were compared by ANOVA using Fisher's least significant difference as the post hoc test. Categorical variables are indicated as n (%) and were compared with the χ^2 test. SA, stable angina; ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; BMI, body mass index; AG, admission glucose; PG, postprandial blood glucose; HbA1C, haemoglobin A1C; UA, uric acid; TC, total cholesterol; TG, triglycerides; HLDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; PLT, platelets; AST, aspartate transferase; ALT, alanine transferase; GGT, γ-glutamyl transferase.

observed in the ACS group when compared to the controls. There were significant differences between the SA and ACS groups with respect to systolic blood pressure, mean arterial blood pressure and UA. No significant differences in AST, ALT and GGT levels were present between the groups.

Associations between plasma AAT protein levels and different types of CAD. A comparison of the plasma levels of AAT protein between the different types of CAD and the control group was performed. AAT was determined by ELISA of the plasma of all 117 patients. The results indicated that the plasma concentrations of AAT in the SA group were significantly higher than those in the ACS group [867.34 (588.48-1,156.53) vs. 491.33 (242.02-827.93) ng/ml; P<0.05; Table II]. These results show that the levels of AAT were higher in the control group, indicating that the levels of this metabolite decreased with the severity of the pathology of CHD.

Association between the levels of AAT and the number of diseased vessels. A comparison of the expression levels of AAT

Table II. Plasma levels of AAT protein in patients with different types of coronary artery disease.

Group	n	AAT (ng/ml)
Control	36	1,264.98 (1,033.88-1,711.67)
SA	35	867.34 (588.48-1,156.53)[a]
ACS	46	491.33 (242.02-827.93)[a,b]
Z	48.647	
P-value	<0.001	

[a]P<0.05 when compared to the control group; [b]P<0.05 when compared to the SA group. Normal AAT plasma levels are >1.04 g/l. Data were non-normally distributed when tested for normality using the Kolmogorov-Smirnov test; they are expressed as the median (interquartile range) and were compared by the Kruskal-Wallis test. SA, stable angina; ACS, acute coronary syndrome; AAT, α1-antitrypsin.

Table III. Association between plasma levels of AAT in patients with coronary heart disease and the number of diseased vessels.

Number of vessels	n	AAT (ng/ml)
1	20	784.19 (421.73-1,205.71)
2	26	776.97 (505.33-925.44)
>2	35	531.67 (258.85-984.59)
Z	2.347	
P-value	0.309	

Normal AAT plasma levels are >1.04 g/l. Data were non-normally distributed when tested for normality using the Kolmogorov-Smirnov test; they are expressed as the median (interquartile range) and were compared by the Kruskal-Wallis test. AAT, α1-antitrypsin.

Table IV. Association between the plasma levels of AAT in patients with coronary artery disease and the degree of coronary artery stenosis.

Severity of stenosis	n	AAT (ng/ml)
Mild	7	400.92 (217.47-990.27)
Moderate	23	789.79 (531.67-1,213.33)
Severe	51	599.09 (361.26-984.59)
Z	3.092	
P-value	0.213	

Normal AAT plasma levels are >1.04 g/l. Data were non-normally distributed when tested for normality using the Kolmogorov-Smirnov test; they are expressed as the median (interquartile range) and were compared by the Kruskal-Wallis test. AAT, α1-antitrypsin.
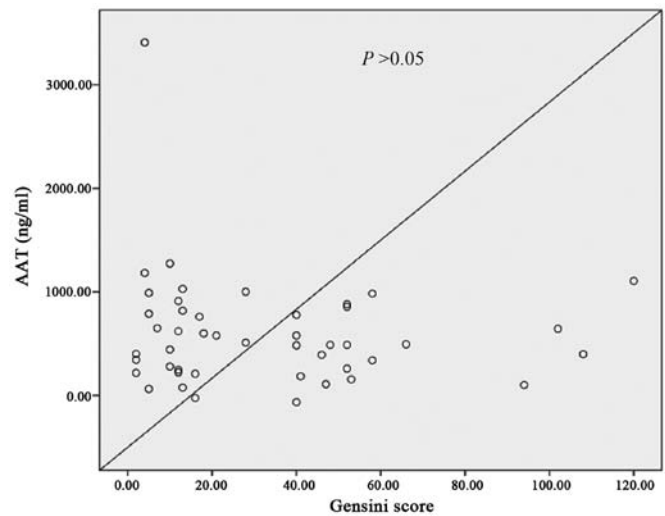

Figure 1. Correlation between the plasma levels of AAT and Gensini scores in patients with ACS. The line represents the best fit through the data points and shows no clear correlation between AAT levels and the coronary Gensini scores in ACS patients. AAT, α1-antitrypsin; ACS, acute coronary syndrome.

between different groups according to the number of coronary lesions was also made. The concentrations of AAT in the plasma were 784.19 (421.73-1,205.71), 776.97 (505.33-925.44) and 531.67 (258.85-984.59) ng/ml in the single, double and multi-lesion groups, respectively (P>0.05, Table III). The lowest expression of AAT was in the multi-vessel lesion group, followed by the double-vessel lesion group and the highest expression was in the single-vessel lesion group, but the inter-group differences did not reach statistical significance (P>0.05).

Association between AAT levels and the severity of coronary artery stenosis. A comparison of the expression levels of AAT between different groups according to the degree of coronary lesions was also made. The concentrations of AAT in the plasma were 400.92 (217.47-990.27), 789.79 (531.67-1,213.33) and 599.09 (361.26-984.59) ng/ml in the mild, moderate and severe stenosis group, respectively. Most of the patients had severe stenosis (62.96% of the total), but the highest AAT levels were in the moderate stenosis group. However, there were no statistically significant differences among these groups (Table IV).

Correlation between AAT levels and coronary Gensini scores in ACS patients. There was no clear correlation between AAT and the coronary Gensini scores in patients with ACS and this did not reach statistical significance (Fig. 1).

Discussion

CAD is considered to be a chronic inflammatory disease of the blood vessels, which is a disorder influenced by a combination of multiple factors (23,24). To date, several risk factors have been identified to be associated with CAD (25,26), including age, smoking, diabetes, hypertension, obesity and dyslipidemia as well as a high-fat or high-cholesterol diet. The results of the present study are consistent with those of other studies, suggesting that patients with CAD were older and had higher blood glucose, blood pressure, UA and homocysteine (P<0.05). However, these risk factors are only able to partially explain the occurrence and development of CAD. The molecular mechanisms of the pathogenesis of CAD remain to be fully elucidated. Studies have also indicated

that inflammatory factors have an important function in the molecular mechanisms associated with the pathogenesis of CAD, particularly in cases of ACS (27,28).

ACS is a syndrome of coronary atherosclerosis, erosion, thrombosis and other factors leading to obstruction and poor blood flow. ACS is commonly encountered at cardiology departments. Inflammatory factors cause atherosclerotic plaques to develop and become unstable, leading to thrombosis and resulting in obstruction of the coronary arteries (29). Studies have indicated that ACS is an inflammation-mediated atherosclerotic disease and that inflammation and immune responses have an important role at all stages of atherosclerosis (30).

Hs-CRP is an acute phase-reactive protein synthesized in the liver (31-33). Only a small amount of acute phase-reactive protein is present in the serum of healthy humans. However, during acute myocardial infarction, development of tumors and periods of infection, hepatocytes are stimulated to synthesize and secrete inflammatory factors, resulting in severe symptoms and increases in the serum concentration of hs-CRP (34). The present results indicated that hs-CRP levels in the ACS group were significantly higher than those in the SA and control groups (P<0.05). This further confirms that ACS is an inflammation-mediated disease.

AAT is produced mainly in the liver. It is a serine protease inhibitor synthesized by hepatocytes, which may also be synthesized by monocytes, alveolar macrophages and epithelial cells (35). Its molecular weight is 52 kDa and the concentration of AAT in the human body varies with the inhibition of protease phenotypes (36,37). AAT is able to inhibit >80-90% of protease activity in normal plasma (38,39). It is one of the most important members of a family of protease inhibitors in the human body. It is able to inhibit numerous serine-centered proteases, particularly neutrophil elastase, as well as trypsin, chymotrypsin, urokinase, renin, collagenase, fibrinolytic enzyme and thrombin-releasing enzyme (38).

AAT is able to inhibit protease-induced tissue damage during the inflammatory response. As AAT is an acute-phase reactive protein, an increase in plasma AAT levels in patients with ACS may be the result of the body being in an inflammatory state. In 1983, Gilutz et al (40) first confirmed a rise in plasma AAT levels in patients with acute myocardial infarction. Subsequently, Brunetti et al (41) detected elevated AAT levels in the plasma of patients with unstable angina pectoris. In 2015, Zhao et al (21) first indicated that the plasma concentrations of AAT in patients with stable angina pectoris were significantly higher than those in a healthy control population and positively correlated with the severity of coronary artery stenosis.

However, the results of the present study were opposite to these findings. The plasma AAT levels of patients with ACS were lower than those in the SA and healthy control groups (P<0.001). Furthermore, AAT levels were not correlated with the coronary Gensini score. In addition, there was no significant association between AAT levels and the number of diseased vessels or the disease severity. AAT is an acute phase-reactive protein and inflammation tends to increase its levels, but the plasma levels cannot always simultaneously reflect this. In addition, as an acute phase-reactive protein, AAT is able to inhibit serine proteases and endogenous inhibitors of neutrophil elastase, which may, in turn, inhibit protease-induced tissue damage during the inflammatory response. Thus, when it is deficient, its function will disappear.

The major limitation of the present study is the small sample size. This shortcoming will be remedied in the next study by our group; it is now possible to recruit more patients with ACS, as a Chest Center has been established at our hospital.

In conclusion, the plasma levels of AAT protein may contribute to the occurrence and development of CAD, particularly that of ACS. However, there were no significant associations the plasma levels of AAT protein and the number of coronary vessels affected or degree of stenosis.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL, DH and BL were involved in the acquisition, analysis and interpretation of the data. YL, DH, SRS and BL also contributed to the design and conception of the study. WL, ZH, JG and XP conceived the study and participated in its design and coordination. ZH, SRS and JG drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Affiliated Hospital of Youjiang Medical University for Nationalities (Baise, China), in accordance with the Declaration of Helsinki. All participants provided written informed consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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