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Original Article

Cystatin C is associated with coronary artery disease and coronary atherosclerotic plaque morphology in patients with normal glomerular filtration rate

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Abstract: Objective: To explore whether cystatin C was associated with coronary artery disease and coronary atherosclerotic plaque morphology in patients with normal glomerular filtration rate. Methods: Two hundred and forty-three patients who underwent elective coronary angiography were enrolled in the study. Patients with abnormal creatinine-derived glomerular filtration rate (<90 ml/min/1.73 m^2) were excluded. All subjects were divided into four groups: control group, single-vessel group, dual-vessel group and multivessel-vessel group. Demographic characteristics, coronary angiography and laboratory assay information were collected. Serum cystatin C level was measured and its association with the severity of coronary artery disease and coronary atherosclerotic plaque morphology were analyzed. Results: Cystatin C levels were significantly higher in coronary lesion group than those of control group, whereas it was lower in non-calcified plaques compared with calcified plaques. Moreover, cystatin C levels were associated with the severity of coronary artery disease, stenosis score and extent score. Multivariable analysis showed that the elevated cystatin C was a risk factor for coronary artery disease, while it was an inhibiting factor for noncalcified plaque. Conclusion: Cystatin C is associated with coronary artery disease and coronary atherosclerotic plaque morphology in patients with normal glomerular filtration rate.

Keywords: Cystatin C, coronary artery disease, coronary angiography, calcified plaque, noncalcified plaque, risk factor

Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. A series of previous studies have demonstrated that the presence of metabolic syndrome was associated with an increased risk of developing CAD [1, 2]. However, the pathophysiology of CAD remains not well defined. CAD was a disease characterized by chronic inflammation and lipid infiltration [3, 4]. The extracellular matrix (ECM) remodeling (formation and degradation) in vascular wall was an important feature in the pathogenesis of CAD [5]. Cystatin C (Cys C) is a key factor in the process of ECM remodeling, it is a member of the cystatin superfamily of endogenous cysteine protease inhibitors that inhibits the protease of cathepsin and is produced by all nucleated cells, which has emerged as a highly sensitive marker of even mildly impaired glomerular filtration rates (GFR) in the past few years [6, 7]. Interestingly, many recent studies have consistently reported that a graded association exists between the serum Cystatin C and the cardiovascular disease (CVD) in patients without established chronic kidney disease [8, 9], more notably, experimental studies suggest that its inhibitory effects on cysteine protease might inhibit the degradation of ECM and help preventing plaque destabilization [10]. However, the reasons of this association are incompletely understood and whether the serum Cys C is associated with CAD and coronary atherosclerotic plaque morphology among patients without established kidney dysfunction have not been fully elucidated. Therefore, in this study, we investigated the association of serum Cys C concentration with CAD and coronary atherosclerotic plaque morphology among patients without established

kidney dysfunction, in order to provide evidences for the prevention of serious cardiovascular events.

Materials and methods

Patients

During December 2013 and June 2014, a total of 156 patients with CAD as case group: 65 patients with single-vessel stenosis > 50% as single-vessel group (48 male, 17 female, mean age 61.37±9.33 years); 43 patients with dual-vessel stenosis > 50% as dual-vessel group (26 male, 17 female, mean age 61.37±10.48 years); 48 patients with three and more vessel stenosis > 50% as multivessel-vessel group (34 male, 14 female, mean age 61.85±9.01 years) and 87 patients with no significant coronary artery disease (<50% stenosis) and normal coronary arteries (37 male, 50 female; mean age 61.59±8.24 years) were enrolled as control group. A total of 243 patients who met inclusion criteria in the Cardiovascular Center at the First People's Hospital in Ma'an Shan, China, were enrolled in this study. The inclusion criteria were: (1) age from 40 to 75; (2) without the history of cardiovascular disease; (3) GFR ≥ 90 ml/min/1.73 m^2 [11]; (4) without stroke; (5) without the history of coronary stenting. (6) without the history of tumor; (7) without the history of infection. Informed consents were obtained from all participants (The medical ethics committee of Ma'an Shan People's Hospital, 2014001).

Questionnaire scale

The questionnaire was designed by the clinical experts and epidemiologist. It was consists of the demographic characteristics, behaviors and body examination. The demographic characteristics include age, sex, height, weight. Behavior characteristics includes smoking (smoking ≥ 1 cigarette/day, time of smoking duration ≥ 6 months), drinking (current drinker *vs* occasional or never drinker), and physical exercise. The body examination includes blood pressure, fasting blood glucose, Body mass index (BMI) was calculated as: weight (kg)/square of height (m^2). Hypertension was defined as SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg and/or treated hypertension, patients with fasting blood glucose > 7.1 mmol/L or treated diabetes was defined as diabetes.

Laboratory assay

5-7 ml venous blood was collected after overnight fasting before coronary artery angiography and then centrifuged. Aliquots of serum were stored at -70°C until assayed. Serum Cys C was determined by immunoturbidimetric assay, C-reactive protein (CRP) was determined by latex Immunoturbidimetry assay, fasting plasma glucose (FPG) was determined by glucose oxidase method, serum total cholesterol (TC) and triglyceride (TG) were determined by CHOD-PAP, high-density lipoprotein (HDL) was determined by phosphotungstic acid-magnesium precipitation, low-density lipoprotein (LDL) was determined by selective removal method, and the serum creatinine (Cr) was determined by Jaffe reaction. Estimated GFR was calculated by Modification of diet in renal disease (MDRD) formula as follows: eGFR (ml/min/1.73 m^2)=186 × serum creatinine (mg/dl)$^{-1.154}$ × Age (years)$^{-0.203}$ (× 0.742 if female) [12]. All biochemistry assays were performed by the automatic biochemical analyzer (DPP-800, Roche, Germany) and were performed by professional laboratory technician in hospital.

Coronary angiography

Coronary artery angiography was performed using standard Judkins techniques. Angiographic analysis was conducted by two expert investigators who were blinded to the study protocol. At least one main coronary artery vessels stenosis > 50% defined as CAD (mainly refers to the left anterior descending coronary artery, the left circumflex artery and the right coronary artery) [13]. The extent of CAD was described as 0-, 1-, 2- or 3 and more-vessel disease based on the number of coronary vessels with > 50% luminal narrowing. Any plaque with higher CT attenuation values than the contrast-enhanced coronary lumen or high-density CT attenuation values > 130 HU at precontrast scan was defined as calcified. Any plaque that could be assigned to the coronary artery wall with CT attenuation values below the contrast-enhanced coronary lumen was defined as non-calcified [14]. The severity of CAD was scored based on stenosis score and extent score [11].

Statistical analysis

To evaluate the association of serum Cys C and CAD and coronary atherosclerotic plaque morphology, we initially transformed serum Cr, TC,

Table 1. Baseline characteristics of study population

Baseline characteristics		Control (n=87, %)	Single-vessel (n=65, %)	Dual-vessel (n=43, %)	Multivessel-vessel (n=48, %)	*P values*
Age (years)	40-	10 (11.49)	9 (13.85)	10 (23.26)	5 (10.42)	0.28
	50-	21 (24.14)	15 (23.08)	6 (13.95)	16 (33.33)	
	60-75	56 (64.37)	41 (63.08)	27 (62.79)	27 (56.25)	
Gender	Male	37 (42.53)	48 (73.85)	26 (60.47)	34 (70.83)	<0.01
	Female	50 (57.47)	17 (26.15)	17 (39.53)	14 (29.17)	
Hypertension	Absence	35 (40.23)	19 (29.23)	10 (23.26)	17 (35.42)	0.22
	Presence	52 (59.77)	46 (70.77)	33 (76.74)	31 (64.58)	
Diabetes	Absence	64 (73.56)	50 (76.92)	35 (81.40)	36 (75.00)	0.79
	Presence	23 (26.44)	15 (23.08)	8 (18.60)	12 (25.00)	
Smoking	Absence	23 (26.44)	28 (43.08)	15 (34.88)	30 (62.50)	<0.01
	Presence	64 (73.56)	37 (56.92)	28 (65.12)	18 (37.50)	
Drinking	Absence	15 (17.24)	23 (35.38)	18 (41.86)	15 (31.25)	0.01
	Presence	72 (82.76)	42 (64.62)	25 (58.14)	33 (68.75)	
Physical exercise	Regularly	67 (77.01)	38 (58.46)	30 (69.77)	21 (43.75)	<0.01
	Occasionally	20 (22.99)	27 (41.54)	13 (30.23)	27 (56.25)	
BMI (Kg/m^2)	1st tertile <25	55 (63.22)	46 (70.77)	24 (55.81)	33 (68.75)	0.81
	2nd tertile 25-	24 (27.59)	14 (21.54)	14 (32.56)	11 (22.92)	
	3rd tertile ≥ 28	8 (9.20)	5 (7.69)	5 (11.63)	4 (8.33)	
TC	≥ 5.69 (mmol/L)	6 (6.90)	4 (6.15)	5 (11.63)	2 (6.90)	0.56
	<5.69 (mmol/L)	81 (93.10)	61 (93.85)	38 (88.37)	46 (95.83)	
TG	≥ 5.69 (mmol/L)	13 (14.94)	6 (9.23)	6 (13.95)	6 (12.50)	0.76
	<5.69 (mmol/L)	74 (85.06)	59 (90.77)	37 (86.05)	42 (87.50)	
HDL	≥ 1.04 (mmol/L)	57 (65.52)	48 (73.85)	27 (62.79)	26 (54.17)	0.19
	<1.04 (mmol/L)	30 (34.48)	17 (26.15)	16 (37.21)	22 (45.83)	
LDL	≥ 3.62 (mmol/L)	3 (3.45)	5 (7.69)	3 (6.98)	10 (20.83)	0.01
	<3.62 (mmol/L)	84 (96.55)	60 (92.31)	40 (93.02)	38 (79.17)	
Cys C (mg/L)	1st tertile <0.75	11 (12.64)	7 (10.77)	6 (13.95)	2 (4.17)	<0.01
	2nd tertile 0.75-	69 (79.31)	48 (73.85)	23 (53.49)	21 (43.75)	
	3rd tertile ≥ 1.15	7 (8.05)	10 (15.38)	14 (32.56)	25 (52.08)	
CRP (mg/L)	1st tertile <3	72 (82.76)	48 (73.85)	16 (37.21)	4 (8.33)	<0.01
	2nd tertile 3-	5 (5.75)	6 (9.23)	12 (27.91)	15 (31.25)	
	3rd tertile ≥ 5	10 (11.49)	11 (16.92)	15 (34.88)	29 (60.42)	
Coronary angiography	No plaque	57 (65.52)	0	0	0	<0.01
	Calcified plaque	18 (20.69)	53 (81.54)	29 (67.44)	26 (54.17)	
	Non-calcified plaque	12 (13.79)	12 (18.46)	14 (32.56)	22 (45.83)	
	Stenosis score	0.37±0.51	2.08±0.4[1]★	4.14±0.47★,▲	6.51±0.88★,▲,•	<0.01
	Extent score	7.37±10.17	41.08±9.04★	82.79±9.34★,▲	124.15±13.77★,▲,•	<0.01

Note: ★present *vs.* control group, *P*<0.01; ▲*vs.* single-vessel group, *P*<0.01; •*vs.* dual-vessel group, *P*<0.01.

TG, HDL, LDL demographic characteristics and behaviors into categorical variables. BMI was transformed into three tertiles (<25 as the first tertile and recode into "0", 25-27.9 as the second tertile and recode into "1", ≥ 28 as the third and recode into "2"). Serum Cys C and CRP was transformed into three tertiles (Cys C: <0.75 mg/L recode into "0", 0.75-1.14 mg/L recode into "1", ≥ 1.15 mg/L recode into "2"; CRP: <3 mg/L recode into "0", 3-4.99 mg/L recode into "1", ≥ 5 mg/L recode into "2"), and age was also transformed into ordered categorical variables by means of 40-49 recode into "1", 50-59 recode into "2", 60-75 recode into "3".

The statistical analysis was conducted with SPSS 13.0. Descriptive statistics were expressed as mean ± SD for continuous variables and percentage for categorical variables. The Chi-square test was used to compare the differ-

Table 2. Multivariable predictors of CAD

Indicators	*β*	*S.E*	B	*Wald* x^2	*OR*	*OR 95% CI*	*P values*
Cys C	1.31	0.45	0.26	8.51	3.70	1.54-8.92	<0.01
CRP	1.18	0.39	0.29	8.98	3.26	1.51-7.08	<0.01
Gender: Male	0.79	0.30	0.21	6.73	2.21	1.21-4.01	0.01
Smoking	0.78	0.36	0.20	4.79	2.18	1.09-4.39	0.03
Intercept	-0.56	0.24		5.66			0.02

ences of the baseline characteristics of study population. T-test was used to compare the severity of CAD (including stenosis score and extent score) between calcified plaque and non-calcified plaque. One-way ANOVA was used to compare the differences of the severity of CAD between three tertiles of Cys C serum. Pearson correlation analysis was used to evaluate correlations between stenosis score, extent score, CRP and serum Cys C after adjusting the factors of age, gender and LDL. Finally, to evaluate whether Cys C was associated with CAD, the three case groups were used as the dependent variable (control group was recorded "0", case group was recorded "1"); to evaluate whether Cys C was associated with plaque morphology, the three case groups were used as the dependent variable (calcified plaque and no-plaque was recorded "0", non-calcified plaque was recorded "1"), all of above mentioned characteristics as independent variables. Then multivariate logistic regression analysis was used to assess the association of Cys C with CAD and plaque morphology.

Results

Patient characteristics

There was no significant differences in age (*P*=0.28) between the three case groups and control group (**Table 1**). The concentration of LDL, Cys C and CRP in the case groups were significantly higher than those in control group (*P*<0.05). In addition, the incidence of CAD in male was significantly higher than that of female (*P*<0.01).

Multiple logistic regression analysis of CAD

In the multiple regression equation, CAD as the dependent variable (control group as "0", the three case group as "1") and the influencing factors including age, genders, serum Cys C, CRP, *etc.* as the independent variables (sis=0.05, els=0.10). The elevated level of Cys C (*OR*=3.70, *P*<0.01), CRP (*OR*=3.26, *P*<0.01) were risk factors in the process of CAD (**Table 2**). In addition, male (*OR*=2.21, *P*<0.01) and smoking (*OR*=2.18, *P*<0.01) were another two risk factors of CAD.

Baseline characteristics of participants with different plaque phenotype

The **Table 3** showed that serum LDL, Cys C and CRP in the patients with non-calcified plaque were significantly higher than those in calcified plaques and no plaques (*P*<0.05), and the number of smokers and the number of drinkers in patients with non-calcified plaque were significantly higher than the patients with calcified plaque or without plaque (*P*<0.01). The **Figure 1A** and **1B** showed that the non-calcified plaque's has higher stenosis score and extent score compared with the patients with calcified plaque (*P*<0.01).

Multiple logistic regression analysis of noncalcified plaque

In the multiple regression equation, non-calcified plaque as the dependent variable (calcified plaque and no plaque as "0", non-calcified plaque as "1") and age, gender, serum Cys C, CRP, *etc.* as independent variables (sis=0.05, els=0.10). The **Table 4** showed that the elevated level of LDL (*OR*=11.32, *P*<0.01) and CRP (*OR*=3.22, *P*<0.01) were risk factors of non-calcified plaque and the elevated level of Cys C (*OR*=0.27, *P*<0.01) was an inhibitory factor in the process of non-calcified plaque.

Comparison of the severity of CAD at different levels of Cys C

The **Figure 1C** showed that the third tertile of serum Cys C had higher stenosis score than those in the first tertile and second tertile, but there was no significant differences of stenosis score in the first tertile and second tertile of serum Cys C (2.27±2.13 *vs.* 2.21±2.02 *vs.* 4.38±2.15, *F*=20.30, *P*<0.01); the **Figure 1D** showed that the third tertile of serum Cys C had higher extent score than those in the first tertile and second tertile, but there was no significant differences of extent score in the first tertile and second tertile of serum Cys C (45.38±42.54

Table 3. Baseline characteristics of participants with different plaque phenotype

Baseline Characteristics		No Plaque (n=57, %)	Calcified plaque (n=126, %)	Non-calcified plaque (n=60, %)	*P values*
Age (years)	40-	8 (14.04)	14 (11.11)	12 (20.00)	0.15
	50-	15 (26.32)	25 (19.84)	18 (30.00)	
	60-75	34 (59.65)	87 (69.05)	30 (50.00)	
Gender	Male	21 (36.84)	88 (69.84)	36 (60.00)	<0.01
	Female	36 (63.16)	38 (30.16)	24 (40.00)	
Hypertension	Absence	22 (38.60)	35 (27.78)	24 (40.00)	0.16
	Presence	35 (61.40)	91 (72.77)	36 (60.00)	
Diabetes	Absence	38 (66.67)	100 (79.37)	47 (78.33)	0.79
	Presence	19 (33.33)	26 (20.63)	13 (21.67)	
Smoking	Absence	43 (75.44)	74 (58.73)	30 (50.00)	0.02
	Presence	14 (24.56)	52 (41.27)	30 (50.00)	
Drinking	Absence	49 (85.96)	79 (62.70)	44 (73.33)	0.01
	Presence	8 (14.04)	47 (37.70)	16 (26.67)	
Physical exercise	Regularly	46 (80.70)	79 (62.70)	31 (51.67)	0.01
	Occasionally	11 (19.30)	47 (37.30)	29 (48.33)	
BMI (Kg/m^2)	1st tertile <25	35 (61.40)	83 (65.87)	40 (66.67)	0.92
	2nd tertile 25~	16 (28.07)	31 (24.60)	16 (26.67)	
	3rd tertile ≥ 28	6 (10.53)	12 (9.53)	4 (6.66)	
TC	≥ 5.69 (mmol/L)	3 (5.26)	8 (6.35)	6 (10.00)	0.56
	<5.69 (mmol/L)	54 (94.74)	118 (93.65)	54 (90.00)	
TG	≥ 5.69 (mmol/L)	7 (12.28)	13 (10.32)	11 (18.33)	0.31
	<5.69 (mmol/L)	50 (87.72)	113 (89.68)	49 (81.67)	
HDL	≥ 1.04 (mmol/L)	36 (63.16)	84 (66.67)	38 (63.33)	0.86
	<1.04 (mmol/L)	21 (36.84)	42 (33.33)	22 (36.67)	
LDL	≥ 3.62 (mmol/L)	1 (1.75)	4 (3.17)	16 (26.67)	<0.01
	<3.62 (mmol/L)	56 (98.25)	122 (96.83)	44 (73.33)	
Cys C (mg/L)	1st tertile <0.75	8 (14.04)	3 (2.38)	15 (25.00)	<0.01
	2nd tertile 0.75~	49 (85.96)	81 (64.29)	31 (51.67)	
	3rd tertile ≥ 1.15	0	42 (33.33)	14 (23.33)	
CRP (mg/L)	1st tertile <3	52 (91.23)	73 (57.94)	15 (25.00)	<0.01
	2nd tertile 3-	2 (3.51)	25 (19.84)	11 (18.33)	
	3rd tertile ≥ 5	3 (5.26)	28 (22.22)	34 (56.67)	
	Stenosis score	0	3.17±1.81	4.25±2.47	<0.01
	Extent score	0	62.38±35.43	81.78±45.07	<0.01

vs. 42.70±42.58 *vs.* 85.00±40.32, F=21.44, P<0.01).

Correlation between stenosis score, extent score, serum CRP with serum Cys C

After adjusting the factors of age, gender and serum LDL, the correlation coefficients of stenosis score, extent score, serum CRP with serum Cys C were 0.42 (P<0.01), 0.42 (P<0.01) and 0.29 (P<0.01), respectively. The specific results are shown in **Figure 1E-G**.

Discussion

It is well recognized that patients with impaired renal function are at significantly higher risk for cardiovascular disease, congestive heart failure, all-cause mortality and adverse long-term outcomes in contrast to patients without renal disease [15]. Cys C has been regarded as a novel sensitive marker for the assessment of renal function, it can identify renal dysfunction. The serum level of Cys C can be significantly increased with renal dysfunction. The purpose

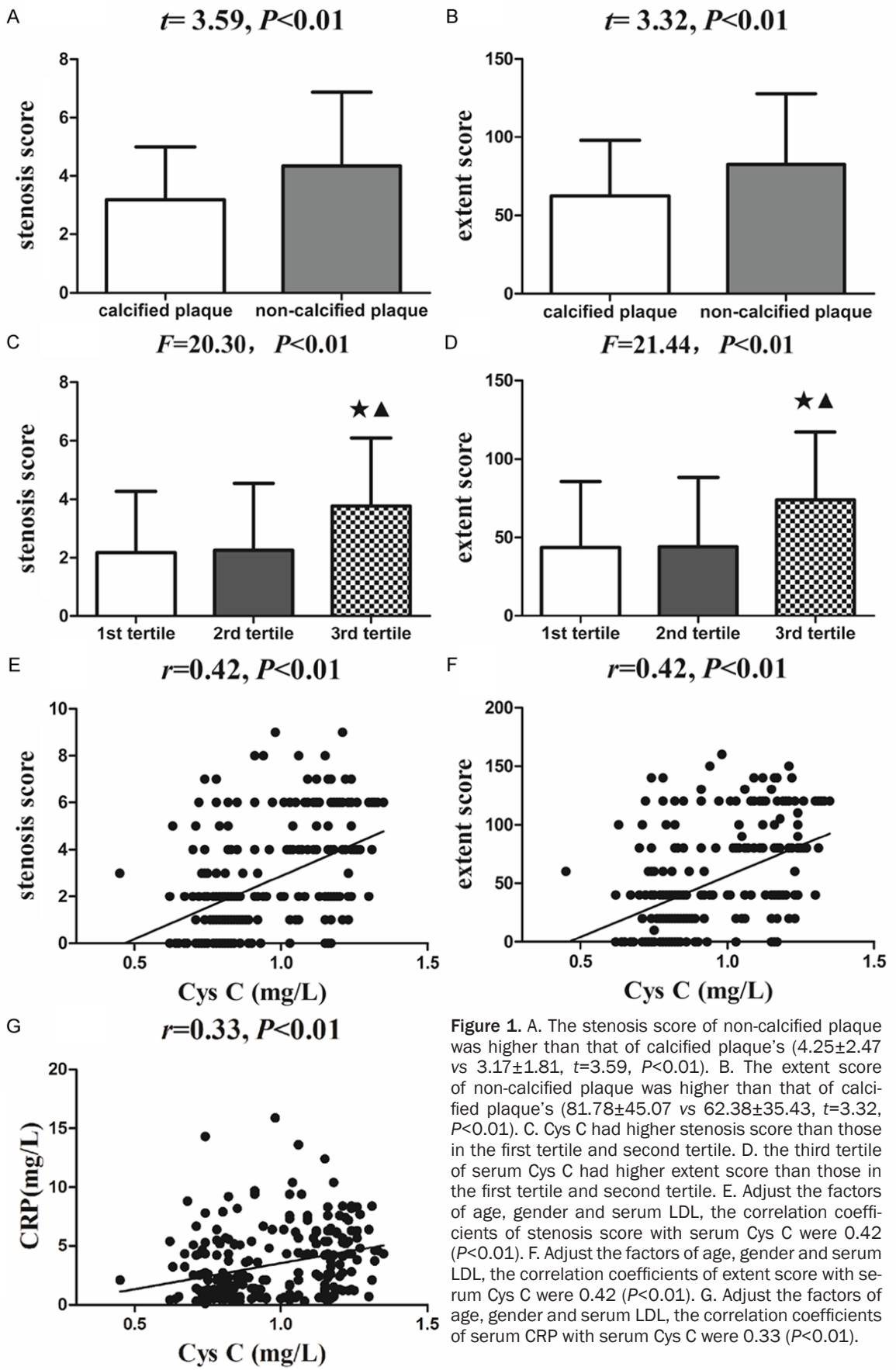

Figure 1. A. The stenosis score of non-calcified plaque was higher than that of calcified plaque's (4.25±2.47 *vs* 3.17±1.81, *t*=3.59, *P*<0.01). B. The extent score of non-calcified plaque was higher than that of calcified plaque's (81.78±45.07 *vs* 62.38±35.43, *t*=3.32, *P*<0.01). C. Cys C had higher stenosis score than those in the first tertile and second tertile. D. the third tertile of serum Cys C had higher extent score than those in the first tertile and second tertile. E. Adjust the factors of age, gender and serum LDL, the correlation coefficients of stenosis score with serum Cys C were 0.42 (*P*<0.01). F. Adjust the factors of age, gender and serum LDL, the correlation coefficients of extent score with serum Cys C were 0.42 (*P*<0.01). G. Adjust the factors of age, gender and serum LDL, the correlation coefficients of serum CRP with serum Cys C were 0.33 (*P*<0.01).

Table 4. Multivariable predictors of non-calcified plaque

Indicators	*β*	*S.E*	B	*Wald* x^2	*OR*	*OR 95% CI*	*P values*
CRP	1.17	0.21	0.56	30.34	3.22	2.12-4.87	<0.01
LDL	2.43	0.64	0.38	14.39	11.32	3.23-39.66	<0.01
Cys C	-1.30	0.33	-0.41	15.53	0.27	0.14-0.52	<0.01
Intercept	-0.97	0.38		6.65			0.01

of the study was to explore whether cystatin C was associated with CAD and coronary atherosclerotic plaque morphology in patients with normal kidney function in order to avoid the well-known effect of overt renal insufficiency on coronary atherosclerosis.

In the present study, we demonstrated that higher serum Cys C concentrations were associated with the severity of CAD and a stable phenotype of coronary atherosclerotic plaque in patients with normal glomerular filtration rate. Several studies demonstrated the association between increased serum cystatin C with CAD risk in individuals without chronic kidney disease [16, 17]. Although the mechanism of this association is unclear, this may be related to its physiological function and steady state environmental change.

Cys C, on the one hand, is a sensitive endogenous marker of renal function, which is freely filtered by the glomerulus and not secreted nor reabsorbed by tubular epithelial cells of kidneys. It will be sensitive to increase as the glomerular filtration rate decreased and blood flow reduction. CAD is an ischemic cardiovascular disease, and the ischemic symptoms will be more severe as the severity of CAD increasing. While in the circumstance of ischemia, there is increased activation of the renin-angiotensin-aldosterone system with potentially deleterious effects [18, 19]. Renin-angiotensin-aldosterone system can secrete a strong vasoconstrictor-angiotensin. In order to ensure the blood supply to the heart, angiotensin can promote systemic vasoconstriction and makes the systemic blood flow decreased. Then Cys C concentration was elevated because of the reduction of renal blood flow. Although the detailed mechanism of the connection between cystatin C and CAD has not been fully elucidated, the mechanism of blood flow decreased seems to be reasonable to increase contact cystatin C and between CAD. Some studies also demonstrated the association between increased serum cystatin C with CAD risk in individuals with normal kidney function and they also assumed to the mechanism of blood flow decreased seems to be reasonable to increase contact cystatin C [17, 20].

Cys C, on the other hand, is an endogenous inhibitor of matrix-degrading cathepsin cysteine proteases and is important in regulating tissue homeostasis, it is constitutively secreted a short time after its synthesis by virtually all nucleated cells (including a large number of smooth muscle cells and a small amount of macrophages). Although the other the physiological function on Cys C is not comprehensive enough, the growing evidences show that Cys C inhibits the activity of cysteine protease [21]. Even some studies regarded it as the most important extracellular inhibitor of cathepsin. While the steady state unbalanced of cathepsin and its inhibitors-Cys C was the main reason lead to vascular remodeling. Previous study have found that vascular remodeling is one of the main pathogenesis of atherosclerosis (AS) [22, 23], and increased cathepsin expression and greatly decreased Cys C expression which is the important processor to promote the degradation of ECM during vascular remodeling.

Normal physiological remodeling allows the adult blood vessel to adapt and repair, whereas perturbations of vascular remodeling are an important component of the pathogenesis of atherosclerosis, plaque rupture, restenosis, and aneurysm formation. Overexpression of matrix metalloproteinase and cysteine protease, known as cathepsins, also has been implicated in atherogenesis, and the potential significance of imbalance between cysteine proteases and their most abundant inhibitor-Cys C has been highlighted by the demonstration of Cys C deficiency in human atherosclerosis and aortic aneurysms. In earlier years ago, Eriksson [24] and Noto [25] have found that Cys C was decreased in acute myocardial infarction (AMI) and the Cys C gene polymorphism functionally affected Cys C plasma levels. Shi et al. [26] have revealed that the levels of serum cystatin C in tissues of atherosclerotic plaque and abdominal aortic aneurysm (AAA) were decreased and the cathepsin was overexpressed. Deo R et al. [27] have also revealed that elevated levels of Cys C was associated with inducible ischemia among outpatients with stable coronary

disease. In this study, we found that the elevated level of Cys C was an inhibitory factor of coronary atherosclerotic noncalcified plaque. In other words, the elevated level of Cys C could help preventing plaque destabilization, which was accorded with the previous findings.

Additionally, we found a positive relationship between the severity of CAD and serum Cys C. Similar results were also reported by some previous studies [20, 28], which demonstrated that serum cystatin C levels are associated with coronary artery disease and its severity. We also found a positive relationship between the serum CRP and serum Cys C. Some studies have also suggested that cystatin C might interact with the inflammatory response, leading to activation of cathepsins and resulting in the degradation of collagen in the atheroma plaque, with an increased risk of rupture [29-31].

In summary, Cystatin C is associated with coronary artery disease and coronary atherosclerotic plaque morphology. However, the exact mechanisms remain to be further elucidated.

Disclosure of conflict of interest

None.

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