Coronary Artery Disease

Roles of Serum Total *P*-Cresylsulfate and Chronic Kidney Disease in Coronary Atherosclerotic Burden in Acute Coronary Syndrome Patients

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Objectives: Cardiovascular disease is prevalent among patients with chronic kidney disease (CKD). Additionally, patients with CKD have elevated levels of *p*-cresylsulfate (PCS), which have been linked to vascular impairment and hypercoagulability in the CKD population. The aim of this study was to evaluate the clinical significance of CKD in acute coronary syndrome (ACS) patients and to investigate whether a significant correlation exists between CKD, total PCS, and coronary atherosclerotic burden in ACS patients.

Methods: 221 consecutive ACS patients and 93 non-coronary artery disease controls were tested to establish total serum PCS concentration levels, which were measured using ultra performance liquid chromatography (UPLC). Thereafter, their associations with angiographic indices of the number of diseased vessels and modified Gensini score were estimated. CKD was defined as an estimated glomerular filtration rate (eGFR) of < 60 ml/min per 1.73 m^2.

Results: ACS patients had increased median total serum PCS levels related to patients with normal coronary arteries. When the patients were divided into 4 groups on the basis of their CKD status and total PCS level, patients with high total PCS (> 1.26 mg/L) levels and CKD had significantly increased numbers of diseased vessels and Gensini score. By multivariate analysis, high total serum total PCS level and CKD were independently associated with ACS. Furthermore, the odds ratio for stenotic vessel disease in the group with both CKD and high total PCS level was 4.100 relative to the group without CKD and a low total PCS level (p = 0.0003).

Conclusion: Our study suggests that total PCS is related to the extent of coronary atherosclerosis, and might play a role in the consequence of plaque vulnerability in ACS patients with low eGFR.

Key Words: Acute coronary syndrome • Chronic kidney disease • Coronary atherosclerotic burden • Total *p*-cresylsulfate

INTRODUCTION

High cardiovascular disease (CVD) prevalence and mortality in chronic kidney disease (CKD) patients have presented challenges to clinicians for years. Large-scale clinical evidence demonstrating the close correlation between CKD and cardiovascular events such as acute coronary syndrome (ACS) have been widely investigated.[1,2] Uremic retention solutes have been implicated in the pathogenesis of accelerated atherosclerosis. Although the link between CKD and uremic retention

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solutes has been reviewed,[3] uremic retention solutes are the main compounds that exhibit direct toxic effects resulting in coronary artery injury.[4,5]

P-cresol (4-methylphenol, 108.1 D) is a small molecule derived from the ingestion of the amino acids tyrosine and phenylalanine. In humans, total *p*-cresylsulfate (PCS) exists predominantly as the conjugated PCS and a rare, sometimes undetectable form of unconjugated *p*-cresol (free-form).[6,7] PCS is strongly bound to protein and is poorly cleared by conventional hemodialysis.[6] Its concentration in uremic plasma is approximately 10 times higher than that of normal control subjects.[8] PCS induces endothelial dysfunction by enhancing baseline leukocyte activity and increasing leukocyte transmigration into the endothelium, which may contribute to the promotion of vascular damage in CKD patients.[9,10]

The pathogenesis of ACS, characterized by thrombosis, underlies most acute complications of atherosclerosis, notably unstable angina and acute myocardial infarction. Most coronary thromboses result from a fracture in the protective fibrous cap of the plaque, which is closely associated with the active expression of proinflammatory factors and ACS-related events.[11,12] In view of the possible association of PCS with inflammation and pathogenesis of coronary lesion vulnerability, the aim of this study was to evaluate the clinical significance of CKD in ACS patients and to investigate whether a significant correlation existed between CKD, total serum PCS level, and coronary atherosclerotic burden in ACS patients.

METHODS

Study population

The present study enrolled 221 ACS patients from June 2006 to June 2009 at the Cardiovascular Clinic of E-Da Hospital. Among these patients, 201 underwent first-time angiography. In addition, we included 93 non-coronary artery disease (CAD) control individuals who presented with chest pain syndrome and had received coronary angiography examination documenting insignificant coronary stenosis. To reduce the interference between inflammatory markers and systemic inflammatory diseases, the present study did not include patients or control subjects with a history of malignancy, hemodialysis, viral hepatitis, infection, autoimmune disease, steroid use or any surgical procedure in the preceding 6 months. All study subjects were of Han Chinese origin, without any known ancestors of other ethnic origin, and living in the same region (Kaohsiung City) at the time of the study. Written informed consent was obtained from the patients before enrollment, and the study was designed and conducted in conformity with the guidelines approved by the Human Research Ethics Committee at our hospital.

Patients with acute ST-elevation myocardial infarction (STEMI) were diagnosed if they had typical rise and gradual fall (in troponin-I) or more rapid rise (2 times the upper limit of normal) and fall [creatine kinase-MB (CK-MB)] of myocardial necrosis biochemical markers, ischemic symptoms lasting ≥ 30 minutes, and ST-segment elevation ≥ 2.0 mm in ≥ 2 contiguous electrocardiographic leads.[13] The diagnosis of non-ST elevation myocardial infarction (NSTEMI) was made in patients who presented with retrosternal chest pain radiating to the neck, jaw, epigastrium, shoulder, and left arm with a sudden onset and duration of ≥ 30 minutes with varying degrees and symptoms; these patients had no ST-segment elevation on electrocardiogram, but had elevated levels of biochemical markers of myocardial necrosis-creatine phosphokinase, CK-MB, and troponin-I.[12] Patients were classified as having unstable angina pectoris (UAP) if they had new onset chest pain or if they had significant unexplained changes in the pattern of stable angina (such as increased frequency, increased intensity, increased duration, or decreased response to nitrates) in the previous 2 months.[14] Subjects with 1 or more lesions that significantly narrowed the lumen of the main coronary artery (≥ 75%) were considered to be angiographic CAD cases, whereas those without any narrowing (< 10%) were considered as controls.

Angiographic definitions

Angiograms and quantitative coronary angiographic (QCA) analysis were scored according to 2 scoring systems: (1) in each case, coronary angiography was performed in standard projections for different coronary arteries (Philips Integris Allura 9/9 bi-plane systems). QCA analysis was performed by an independent laboratory and was blinded to the PCS results. CAD with ≥ 75% stenosis in 3 main coronary arteries supplying the

myocardium was confirmed by coronary angiography and was classified as having single-, 2- or 3-vessel disease. If the diameter of stenosis of the left main coronary artery exceeded 50%, it was excluded due to an undefined number of diseased vessels; (2) In the modified Gensini scoring system, weights are assigned to each coronary segment depending on vessel size and importance, ranging from 0.5 to 5.0; segments serving larger regions of the myocardium are more heavily weighted. The narrowing of the coronary artery lumen is rated 2 for 0-25% stenosis, 4 for 26-50%, 8 for 51-75%, 16 for 76-90%, 32 for 91-99%, and 64 for 100%. The modified Gensini index is the sum of the total weights for each segment.[10]

Laboratory measurements

Peripheral blood samples were taken from an antecubital vein following hospital admission. Blood for total PCS measurement was drawn before intervention and was centrifuged and stored at -80 °C for analysis. Before coronary angiography, complete blood counts and serum biochemical data were measured by standard commercial methods on a parallel, multi-channel analyzer (Hitachi 7170A, Tokyo, Japan) as previously described.[15]

To determine serum total PCS levels, samples were deproteinized by adding 3 parts methanol to 1 part serum. The total PCS level was measured in serum ultrafiltrates obtained using an ultra performance liquid chromatography (UPLC) assay. Samples were detected at 280 nm on the photodiode array detector in this assay, which was performed at room temperature on a 2.1 × 100 mm ACQULITY UPLC® BEH phenyl column. The buffer flow was 0.4 mL/min using 10 mM $NH_4H_2PO_4$ (Ph = 4.0) (A) and 100% acetonitrile (B) with a gradient of 82.5%A/17.5%B to 55%A/45%B, over 9 min. Under these conditions, PCS was detected at 260 nm and appeared at 1.7 min. Standard curves were generated from the total PCS levels at 0.5, 1, 2.5, 5, and 10 mg/L; processed like-serum samples had average r2 values of 0.999 ± 0.001. Quantitative results were obtained and calculated as concentrations (mg/L). The method detection limit of this assay was 1 mg/L;[10] the detection limit of this assay was 0.50 mg/L and the intra-assay coefficient of variation of assay was 7.00% (n = 16) for total PCS.[10] The concentration of plasma C-reactive protein (CRP) was measured using a high-sensitivity method (IMMAGE, Beckman Coulter, Immunochemistry Systems, La Brea, CA, USA). The intra-assay variation coefficients of the assay were 4.2-8.7% for high-sensitivity CRP (hs-CRP). All samples were measured in duplicate in a single experiment.

The estimated glomerular filtration rates (eGFR; mL/min/1.73 m^2) of individual patients were calculated using the Modification of Diet in Renal Disease Study (MDRD) simplified equation.[16] CKD was defined as an eGFR < 60 ml/min per 1.73 m^2; stage 1 or 2 CKD (eGFR ≥ 60 ml/min per 1.73 m^2) was referred to as "no CKD" for purposes of this study.[17] High total PCS level was defined as a total PCS level above the median value of 1.26 mg/L.

Statistical analysis

Descriptive data were examined for all variables. For continuous variables, results were presented as the mean ± standard deviation (SD), median, as appropriate. Statistical differences in variables were compared using unpaired Student's *t*-tests and one-way analysis of variance (ANOVA) for normally distributed variables followed by Tukey's pair-wise comparison. Categorical variables were recorded as frequency counts, and intergroup comparisons were analyzed by the chi-square test. General linear modeling function analysis was used to control potential confounders other than fasting sugar [e.g., systolic blood pressure (SBP), diastolic blood pressure (DBP), and smoking status]. Using univariate and multivariate logistic regression, these variables were assessed for independent associations with the presence of ACS. Odds ratios for stenotic vessel disease were estimated, using the logistic regression model, by comparing the following 3 groups of patients to those with low total PCS levels and without CKD (low total PCS − CKD): patients with low total PCS level and CKD (low total PCS + CKD), patients with high total PCS level but no CKD (high total PCS − CKD), and patients with high total PCS level and CKD (high total PCS + CKD). To determine the difference of total PCS levels between ACS patients and non-CAD control subjects, power calculations were performed using Power Analysis and Sample Size (PASS) 2008 Software. Results were deemed statistically significant if $p < 0.05$. All of the statistical analyses were performed using SAS statistical soft-

ware, version 8.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

Of the 314 patients included in our study, 221 (70.4%) had CAD [78 with STEMI (mean age, 64 ± 14 years; 55 men), 110 with NSTEMI (mean age, 66 ± 14 years; 89 men), 33 with UAP (mean age, 64 ± 12 years; 23 men)] and 93 (29.6%) were non-CAD control subjects (mean age, 60 ± 10 years; 35 men), of which 167 (75.6 %) were males with a predominance of acute coronary syndrome (Table 1). Patients with ACS were of significantly higher age, and had elevated hypertension, diabetes mellitus, smoking rates, use of anti-hypertensive drugs, statins, and anti-diabetic drugs, waist circumference, waist-hip ratio, fasting sugar, HbA1C, uric acid, creatinine, hs-CRP, Gensini score, and total PCS levels. In addition, these patients had lower high-density lipo-

Table 1. Baseline clinical and biochemical characteristics of the study population

Parameter	Non-CAD controls	Acute coronary syndrome	p value
No	93	221	
Sex (male/female)	35/58	167/54	< 0.0001
Age (years)	60.9 ± 10.3	64.9 ± 13.5	0.010
Hypertension (%)	45 (48.4)	173 (78.3)	< 0.0001
Diabetes mellitus (%)	10 (10.8)	86 (38.9)	< 0.0001
Hyperlipidemia (%)	77 (82.8)	178 (80.5)	0.641
Current smoker (%)	19 (20.9)	124 (57.4)	< 0.0001
Anti-hypertensive drug (%)†	30 (32.3)	141 (63.8)	< 0.0001
Statins (%)‡	17 (18.3)	117 (52.9)	< 0.0001
Anti-diabetic drugs (%)§	7 (7.5)	50 (22.6)	0.002
Body mass index (kg/m^2)	24.6 ± 4.0	24.5 ± 4.2	0.752
Waist circumference (cm)	87.8 ± 11.5	90.8 ± 9.7	0.026
Waist-hip ratio	0.90 ± 0.08	0.94 ± 0.08	< 0.0001
Systolic BP (mmHg)	130 ± 21	129 ± 22	0.736
Diastolic BP (mmHg)	76 ± 12	75 ± 14	0.522
Fasting glucose (mg/dL)	103.5 ± 40.0	159.7 ± 84.5	< 0.0001
HbA1C (%)	6.3 ± 1.1	7.0 ± 2.0	0.037
Total-cholesterol (mg/dL)	190.7 ± 51.3	182.4 ± 60.4	0.251
Triglyceride (mg/dL)*	127.8 ± 182.9 (87.0)	144.7 ± 103.8 (109.5)	0.306
HDL-cholesterol (mg/dL)	47.2 ± 13.4	38.5 ± 10.1	< 0.0001
LDL-cholesterol (mg/dL)	113.1 ± 41.3	111.1 ± 36.7	0.669
Uric acid (mg/dL)	5.8 ± 1.4	6.8 ± 2.2	0.001
Creatinine (mg/dL)*	1.03 ± 0.48 (0.9)	1.70 ± 1.30 (1.3)	< 0.0001
Hemoglobin (g/dL)	13.2 ± 1.6	13.3 ± 2.4	0.719
Albumin (g/dL)	4.1 ± 0.3	3.8 ± 0.4	< 0.0001
hs-CRP (mg/L)*	0.6 ± 1.0 (0.2)	2.6 ± 4.4 (0.7)	0.004
eGFR (mL/min/1.73 m^2)	74.4 ± 20.9	53.5 ± 21.7	< 0.0001
Gensini score	2.6 ± 8.7	70.5 ± 70.1	< 0.0001
Total *p*-cresylsulphate (mg/L)*	2.2 ± 2.2 (1.0)	4.5 ± 6.6 (1.6)	0.001

Data are shown as means ± standard deviation, number (percentage), and sometimes (median) for variables with a non-normal distribution. * The difference was tested using log-transformed data. Data are compared between ACS patients and non-CAD controls. BP, blood pressure; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

† Anti-hypertensive drugs: mainly angiotensin-converting enzyme inhibitors (captopril, enalapril, or lisinopril), with the addition of calcium antagonists or angiotensin II receptor antagonists (losartan) in some patients. ‡ Statins: mainly atorvastatin and rosuvastatin.

§ Anti-diabetic drugs: mainly metformin, sulphonylureas, α-glucosidase inhibitors, thiazolidinediones, and insulin.

protein (HDL)-cholesterol, albumin, and eGFR levels relative to non-CAD controls (all comparisons, $p < 0.05$, power = 1.00000).

Patient clinical and biochemical characteristics according to CKD and serum total PCS classification status

The study population was further divided into 4 groups based on their CKD status and total PCS level. High total PCS + CKD patients were significantly older and had a higher prevalence of hypertension, diabetes mellitus, ACS, and number of diseased vessels than low total PCS – CKD patients ($p < 0.05$ for all factors). There were significantly more smokers (n = 31; 58.5%) in the high total PCS – CKD group than in the low total PCS – CKD group ($p < 0.05$). There were no statistically significant differences with regard to sex or hyperlipidemia among the 4 groups. Waist-hip ratio as well as fasting glucose, HbA1C, uric acid, creatinine, eGFR, hemoglobin, albumin, hs-CRP, and total PCS levels differed between the 4 groups. Again, significant differences of fasting glucose, uric acid, creatinine, hs-CRP, total PCS, eGFR, hemoglobin, and albumin levels between the 4 groups were observed when adjusting for

Table 2. Clinical characteristics according to chronic kidney disease and serum total *p*-cresylsulphate classification status

Parameter	Low total PCS level without CKD	Low total PCS level with CKD	High total PCS level without CKD	High total PCS level with CKD	p value
No	91	66	53	104	
Sex (male/female)	55/36	38/28	37/16	72/32	0.296
Age (years)	57.3 ± 11.0	68.0 ± 11.6	58.5 ± 12.3	69.2 ± 11.6	< 0.0001
Hypertension	52 (57.1)	51 (77.3)	30 (56.6)	85 (81.7)	0.0002
Diabetes mellitus	16 (17.6)	19 (28.8)	13 (24.5)	48 (46.2)	0.0002
Hyperlipidemia	62 (68.1)	40 (60.6)	34 (64.2)	69 (66.4)	0.790
Current smoker	34 (37.4)	25 (37.9)	31 (58.5)	53 (51.0)	0.029
Acute coronary syndrome	50 (55.0)	54 (81.8)	30 (56.6)	87 (83.7)	< 0.0001
Number of diseased vessels					
Non-vessel disease	41 (45.1)	11 (16.7)	23 (43.4)	18 (17.3)	< 0.0001
Single-vessel disease	26 (28.6)	20 (30.3)	7 (13.2)	21 (20.2)	
Two-vessel disease	8 (8.8)	17 (25.8)	10 (18.9)	27 (26.0)	
Three-vessel disease	16 (17.6)	18 (27.3)	13 (24.5)	38 (36.5)	
Body mass index (kg/m^2)	25.2 ± 3.8	24.6 ± 4.2	24.2 ± 3.7	24.1 ± 4.5	0.312
Waist-hip ratio	0.91 ± 0.07	0.92 ± 0.06	0.91 ± 0.07	0.96 ± 0.10	0.002
Systolic blood pressure (mmHg)	128 ± 22	129 ± 19	125 ± 17	134 ± 25	0.082
Diastolic blood pressure (mmHg)	76 ± 13	75 ± 14	75 ± 13	76 ± 15	0.933
Fasting glucose (mg/dL)	119.1 ± 44.6	146.5 ± 69.3	139.3 ± 83.3	161.8 ± 98.2	0.006*
HbA1C (%)	6.6 ± 1.6	6.2 ± 0.7	7.2 ± 2.2	7.2 ± 2.2	0.006
Total-cholesterol (mg/dL)	192.4 ± 47.7	172.3 ± 47.0	187.8 ± 44.3	184.7 ± 75.5	0.199
Triglyceride (mg/dL)†	165.1 ± 190.0 (110.0)	122.6 ± 106.7 (92.0)	125.1 ± 74.1 (104.0)	135.6 ± 103.5 (105.0)	0.161
HDL-cholesterol (mg/dL)	43.4 ± 11.3	39.1 ± 11.1	40.9 ± 13.3	40.0 ± 11.6	0.120
LDL-cholesterol (mg/dL)	115.4 ± 42.0	105.5 ± 32.6	117.1 ± 33.6	109.5 ± 39.4	0.272
Uric acid (mg/dL)	5.9 ± 1.5	6.6 ± 2.0	5.8 ± 1.5	7.3 ± 2.5	< 0.0001*
Creatinine (mg/dL)	1.0 ± 0.2	1.5 ± 0.8	1.0 ± 0.2	2.2 ± 1.7	< 0.0001*
eGFR (mL/min/1.73 m^2)	80.7 ± 14.2	48.3 ± 13.8	78.0 ± 9.4	40.8 ± 18.4	< 0.0001*
Hemoglobin (g/dL)	13.9 ± 1.8	12.8 ± 2.3	13.9 ± 1.6	12.7 ± 2.4	< 0.0001*
Albumin (g/dL)	4.0 ± 0.3	3.7 ± 0.3	4.0 ± 0.4	3.8 ± 0.4	< 0.0001*
hs-CRP (mg/L)†	11.8 ± 24.2 (3.7)	28.3 ± 44.5 (5.9)	11.3 ± 16.9 (3.7)	29.2 ± 52.1 (8.7)	0.032*
Total *p*-cresylsulphate (mg/L)†	1.0 ± 0.1 (1.0)	1.0 ± 0.2 (1.0)	3.9 ± 4.3 (2.7)	8.1 ± 7.8 (5.0)	< 0.0001*

Data are means ± standard deviation, number (percentage), and sometimes (median) for variables with a non-normal distribution. * $p < 0.05$ after adjusted by fasting glucose, systolic blood pressure, diastolic blood pressure, and smoking status. † The difference was tested using log-transformed data. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

fasting glucose, systolic blood pressure, diastolic blood pressure, and smoking status. However, there were no statistically significant differences in the body mass index, systolic or diastolic blood pressure, or total cholesterol, triglyceride, HDL-cholesterol, and low density lipoprotein (LDL) cholesterol levels between the 4 groups.

Association between CKD, high total serum PCS level, and ACS

We built a multivariate model adjusted for age, gender, hypertension, diabetes, total cholesterol, triglyceride, LDL- and HDL-cholesterol levels, and smoking status. From the 11 significant variables noted on univariate analysis, 7 (age, diabetes mellitus, smoking, HDL-cholesterol, CKD, albumin, and high total PCS level) had an independent significant impact on the development of ACS by multivariate analysis (Table 3). These findings clarified that CKD and high total PCS level were independently associated with the development of ACS despite adjustment for other traditional risk factors (odds ratio, 3.589; 95% confidence interval (CI), 1.605-8.420, p = 0.002 for CKD; odds ratio, 1.832; 95% CI, 1.095-4.145, p = 0.035 for high total PCS level, respectively).

Association between CKD and high total PCS levels in patients with coronary atherosclerotic burden

We divided the patients with or without CKD and high or low total PCS levels into 4 groups according to their eGFR and total PCS levels, respectively. The number of diseased vessels and Gensini score were the greatest in the high total PCS + CKD group ($p < 0.0001$, Figure 1A and $p = 0.045$, Figure 1B). Compared with the low PCS − CKD group, the high total PCS + CKD group had an odds ratio of 4.100 for the occurrence of stenotic vessel disease ($p = 0.0003$) and that of the low total PCS + CKD group was 3.918 ($p < 0.0001$, Table 4).

DISCUSSION

In the present study, we demonstrated that increased CKD and high total serum PCS concentrations were associated with ACS. Furthermore, we observed significant associations between CKD and high total serum PCS concentrations and the number of coronary arteries with significant luminal stenosis and plaque burden by modified Gensini score in ACS patients. Our previous

Table 3. Univariate and multivariate logistic regression analysis with presence of acute coronary syndrome as the dependent variable

	Univariate		Multivariate*	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.026 (1.006-1.046)	0.011	1.033 (1.002-1.065)	0.039
Male	5.125 (3.048-8.618)	< 0.0001	1.411 (0.566-3.517)	0.460
Hypertension	1.118 (0.682-1.833)	0.657	1.825 (0.789-1.736)	0.608
Diabetes mellitus	11.167 (5.816-21.439)	< 0.0001	9.911 (4.536-21.654)	< 0.0001
Smoking	5.108 (2.880-9.058)	< 0.0001	4.945 (1.836-13.322)	0.002
Waist	1.034 (0.996-1.072)	0.079	0.999 (0.962-1.038)	0.969
Total cholesterol	0.997 (0.993-1.001)	0.136	1.007 (0.988-1.025)	0.489
HDL-cholesterol	0.940 (0.917-0.962)	< 0.0001	0.954 (0.918-0.991)	0.016
LDL-cholesterol	0.998 (0.991-1.005)	0.535	0.991 (0.970-1.013)	0.427
Triglyceride	1.001 (0.999-1.004)	0.312	0.999 (0.996-1.002)	0.401
CAD family history	2.046 (1.006-4.161)	0.048	2.809 (0.980-8.052)	0.055
hs-CRP	1.058 (1.014-1.104)	0.010	1.031 (0.979-1.084)	0.246
Uric acid	1.314 (1.122-1.539)	0.001	1.154 (0.917-1.454)	0.223
Chronic kidney disease	4.763 (2.700-8.809)	< 0.0001	3.589 (1.605-8.420)	0.002
Hemoglobin	1.021 (0.913-1.142)	0.718	0.884 (0.698-1.119)	0.305
Albumin	0.068 (0.027-0.170)	< 0.0001	0.109 (0.029-0.410)	0.001
High total *p*-cresylsulphate	2.654 (1.511-4.860)	0.001	1.832 (1.095-4.145)	0.035

* Adjusted for age, gender, hypertension, diabetes, total cholesterol, triglyceride, LDL- and HDL-cholesterol, and smoking status.
CAD, coronary artery disease; CI, confidence interval; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; OR, odds ratio.

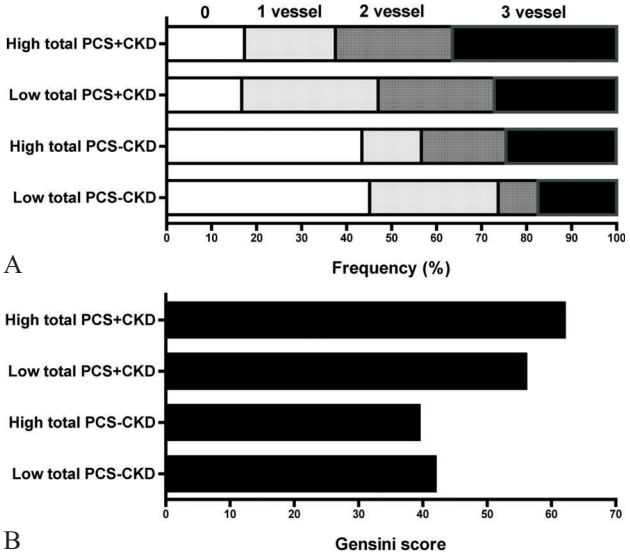

Figure 1. *The number of diseased vessels (A) and Gensini score (B) according to the combination of chronic kidney disease (CKD) and total p-cresylsulfate (PCS) levels. CKD was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. High total PCS level was defined as > 1.26 mg/L. The high total PCS + CKD group was associated with an increased number of diseased vessels (p < 0.0001, A) and Gensini score (p = 0.045, B).*

studies showed that total serum PCS levels were significantly elevated in the presence of CAD and were correlated with disease severity.[10] The present study further implicates high total PCS levels not only associated with coronary atherosclerosis in stable angina patients but also in ACS patients with CKD. This finding is quite interesting, and may provide useful information regarding the uremic toxins related to ACS beyond the present traditional CAD risk factors.

The biological mechanisms involving total serum PCS level in the pathogenesis of coronary atherosclerosis and ACS are not well understood. The endothelium is a key player in the initiation and development of CAD.[18] Endothelial dysfunction, frequently defined as an imbalance between vasodilating and vasoconstricting substances,[18] is abundant in patients with renal failure.[19] In patients with CKD, the serum levels of total PCS are markedly increased.[20] A previous study demonstrated that PCS has a pro-inflammatory effect on unstimulated leukocytes in keeping with the activity of leukocyte functions. This effect could contribute to the susceptibility to vascular disease observed in the uremic population.[9] PCS was also found to induce shedding of endothelial microparticles in the absence of overt endothelial

Table 4. Association between chronic kidney disease and high total *p*-cresylsulfate levels in stenotic vessel disease

Group	OR	95% CI	p value
Low total PCS − CKD (n = 91)	1.00	-	-
Low total PCS + CKD (n = 66)	3.918	2.063-7.681	< 0.0001
High total PCS − CKD (n = 53)	1.070	0.541-2.127	0.847
High total PCS + CKD (n = 104)	4.100	1.955-9.180	0.0003

CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio; PCS, *p*-cresylsulfate.

damage *in vitro*, and is independently associated with the number of endothelial microparticles in hemodialysis patients. This evidence suggests that PCS alters endothelial function and directly contributes to endothelial dysfunction and coronary atherosclerosis in CKD patients.[21] Our recent studies[10,22] have also shown that total PCS levels are associated with the severity of coronary atherosclerosis of patients in the early stages of renal failure and of those with diabetic nephropathy. These findings are consistent with those of previous reports regarding the associations between free PCS, endothelial damage, and CVD.[23,24] CKD causes an elevation in total serum PCS levels, and these observations imply that total serum PCS level is a potential risk factor of atherosclerosis and CAD development. In the current study, coronary stenotic vessel disease occurred significantly more often among high total PCS + CKD patients than in low total PCS − CKD patients. Eighty-five patients had only 3 vessel disease. Of these patients, 38 (36.5%) had high total PCS + CKD, 13 (24.5%) had high total PCS − CKD, 18 (27.3%) had low total PCS + CKD and 16 (17.6%) had low total PCS − CKD. Therefore, high total PCS levels may be associated with coronary atherosclerosis burden and plaque vulnerability in ACS patients with CKD. To our knowledge, this is the first report of such a finding, which may provide new information regarding the acute coronary events in these patients.

It is unclear as to how concomitant high total PCS levels and CKD mediate increased risk of coronary atherosclerosis development, although several possibilities exist. First, high total PCS level and CKD often coexist with other CV risk factors.[25,26] Second, rather than being causally linked to CVD, high total PCS level and CKD may be markers of endothelial dysfunction, inflammation, severity of vascular disease and atherosclero-

sis.[9,10,21,22,27] Finally, the CV outcomes may be worse for CKD patients with high total PCS levels than for those with either parameter alone.[28] In addition, several potentially important risk factors were identified by univariate analysis (such as age, smoking, diabetes, HDL-cholesterol, albumin, and CKD) and were also significantly associated with ACS by multivariate analysis. It is well known that patients with certain risk factors, including increased age, smoking, low HDL-cholesterol levels, and diabetes have an elevated risk of ACS.[29-32] Furthermore, albumin has numerous physiological functions related to atherothrombogenesis, the key pathogenesis of ACS.[33] Additionally, CKD was associated with ACS. It had been demonstrated that decreased renal function was associated with an increased frequency of CVD and the number of stenotic coronary arteries was significantly associated with percent eGFR deterioration.[34]

LIMITATIONS OF STUDY

The limitation of our study is that the cross-sectional design restricted our ability to infer a causal relationship between total serum PCS level and CAD. Our analyses were based on single measurements of blood total PCS level, which may not reflect the relationship between total serum PCS level and CAD over time. Moreover, further experiments designed to investigate the role of total PCS level in association with the markers of endothelial dysfunction will clarify the role of total PCS in CAD.

CONCLUSION

The coexistence of CKD and high total serum PCS levels is significantly associated with the extent of coronary atherosclerosis in patients with ACS. This indicates that total serum PCS level may play a role in plaque vulnerability for ACS patients with low eGFR.

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