Original Article

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Association of serum uric acid level with coronary artery stenosis severity in Korean end-stage renal disease patients

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Background: Hyperuricemia is common in end-stage renal disease (ESRD) patients, and many previous studies have reported the associations between hyperuricemia and adverse cardiovascular outcomes, which are the major cause of death in such patients. We investigated the relationship between serum uric acid level and the severity of coronary stenosis in ESRD patients on maintenance hemodialysis (MHD).
Methods: Among 721 patients who started MHD treatment, 102 underwent coronary angiographic tests complaining of chest discomfort that was new at initiation of MHD. We collected data on uric acid level and coronary artery luminal diameter, defining luminal diameter narrowing of more than 50% in any major coronary artery as critical-stenosis.
Results: We detected critical coronary artery stenosis in 52 (57.8%) patients. The mean uric acid level was 6.6 ± 2.2 mg/dL, and that was significantly higher in the critical-stenosis group (4.9 ± 1.4 mg/dL vs. 7.8 ± 2.0 mg/dL, $P < 0.001$). The only independent predictor of critical-stenosis in multivariate analysis was serum uric acid level ($P < 0.001$).
Conclusion: High serum uric acid was associated with severe coronary artery stenosis in Korean ESRD patients. Hyperuricemia is a readily modifiable factor, and appropriately preventing it could provide significant benefits in ESRD patients.

Keywords: Cardiovascular diseases, Chronic kidney disease, Coronary stenosis, Renal dialysis, Uric acid

Introduction

It is well known that chronic kidney disease (CKD) and end-stage renal disease (ESRD) are independent risk factors for cardiovascular events [1], and cardiovascular disease (CVD) is an important predictor of mortality in ESRD patients, accounting for almost 50% of deaths in that population [2]. A high level of serum uric acid has been identified as a possible risk factor for the development of CVD [3]. Some previous studies suggested that hyperuricemia could influence the atherosclerotic process through endothelial dysfunction and inflammation [4,5]. Hyperuricemia might also be related to hypertension and metabolic syndrome [6–8]. In addition, several studies have suggested a strong association between serum uric acid level and CVD in the general population [9,10].

Because most uric acid is excreted through the kidneys, hyperuricemia occurs when renal function declines [11] and is thus common among patients with CKD [12]. A study on stage 3 to 4 CKD patients suggested that hyperuricemia was a risk factor for all-cause and CVD mortality

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[13], and other studies on hemodialysis patients reported a relationship between uric acid and all-cause mortality [14,15]. However, those studies showed only a correlation between uric acid level and CVD outcomes; they did not investigate the relationship between serum uric acid level and the angiographic severity of CVD in dialysis patients.

In this study, we assessed the relationship between serum uric acid level and the severity of coronary stenosis in ESRD patients on maintenance hemodialysis (MHD).

Methods

Patients

This was a retrospective case-control study of patients who received MHD. All patients had ESRD and were treated with MHD at the CHA Bundang Medical Center hemodialysis center between 2005 and 2015. We selected patients who started MHD treatment in our center and underwent coronary angiography to address chest discomfort that began after initiation of MHD.

The coronary angiography was recorded at 25 frames/second. The luminal diameter was measured at end-diastole via quantitative coronary angiography using the autonomic software program provided by the manufacturer (Philips Med, Best, The Netherlands). Luminal diameter narrowing of more than 50% in any major coronary artery was defined as critical stenosis. We excluded patients with cancer, coagulation disorders, or active infections at the time of coronary angiography, along with patients taking uric acid-lowering agents. In addition, patients with any previous history of CVD like angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, or congestive heart failure were excluded. All patients were undergoing chronic bicarbonate hemodialysis for a mean time of 4.0 hours, three times a week. The blood flow rate ranged between 250 and 300 mL/minute, and a dialysate flow rate of 500 mL/minute was routinely used. Kt/V was evaluated monthly as a marker of dialysis efficiency. This study was approved by the Institutional Review Board of CHA Bundang Medical Center, CHA University (No. 2017-03-021). Because the study involved the analysis of data already collected and anonymized, the ethics board waived the need for individual patient consent.

Clinical variables

Patient demographic and clinical data, including age, gender, etiology of ESRD (diabetes, hypertension, glomerulonephritis, polycystic kidney disease, or unknown), vascular access sites (arteriovenous fistula, arteriovenous graft, or permanent catheter), medications (antihypertensive drugs, antiplatelet agents, calcium-containing agents, vitamin D analogues, and uric acid-lowering agents), heparin dose, and comorbidities (ischemic heart disease, cerebrovascular disease, or peripheral vascular disease) were obtained by medical record review. We identified patients as having cerebrovascular disease if they had any medical history of stroke, transient ischemic attack, or intracranial hemorrhage. We also collected data from laboratory findings at the time of the coronary angiographic test; serum hemoglobin, white blood cell (WBC), platelet, serum calcium, blood urea nitrogen, creatinine, calcium, phosphate, intact parathyroid hormone, uric acid, total cholesterol, low-density lipid cholesterol, high-density lipid cholesterol, C-reactive protein, total protein, and albumin. We used blood flow rate data from the last three hemodialysis treatments before angiography.

Statistical analysis

Categorical variables are given as the number and percentage. Continuous variables are presented as the mean ± standard variation or median (interquartile range). We used the Student's *t*-test and Mann-Whitney *U* test to compare continuous variables and the χ^2 test or Fisher's exact test to compare categorical variables. We performed binary logistic regression analysis to investigate the effects of covariates on critical stenosis of coronary arteries. PASW Statistics ver. 17.0 (IBM Co., Armonk, NY, USA) was used for statistical analysis.

Results

Study population

Clinical and biochemical characteristics are shown in Table 1. Initially, 721 patients started MHD treatment at the hemodialysis center of CHA Bundang Medical Center between 2005 and 2015. Among them, 102 patients underwent coronary angiographic testing for chest discom-

Table 1. Baseline characteristics of the study population

Characteristic	Overall (n = 90)	Non-critical stenosis (n = 38)	Critical stenosis (n = 52)	*P* value
Male	49 (54.4)	19 (50.0)	30 (57.7)	0.469
Age (yr)	62.3 ± 10.8	60.0 ± 10.8	64.0 ± 10.6	0.099
Body mass index (kg/m^2)	22.6 ± 4.9	22.4 ± 5.0	22.7 ± 4.8	0.091
Blood pressure (mmHg)	92.9 ± 12.8	93.3 ± 13.7	92.7 ± 12.3	0.533
Hypertension	81 (90.0)	32 (84.2)	49 (94.2)	0.118
Diabetes	61 (67.8)	20 (52.6)	41 (78.8)	0.009
Cerebrovascular	6 (6.7)	2 (5.3)	4 (7.7)	0.648
Heparin, loading (IU/mL)	780.9 ± 563.8	828.9 ± 607.1	745.1 ± 532.6	0.491
Heparin, continuous (IU/mL)	243.2 ± 215.3	243.4 ± 213.4	243.1 ± 218.8	0.995
Blood flow rate (mL/min)	242.7 ± 35.8	240.0 ± 34.5	244.8 ± 36.9	0.532
MHD duration (mo)	11.5 (1.0–66.0)	22.5 (1.0–85.0)	6.5 (1.0–56.0)	0.083
Uric acid (mg/dL)	6.6 ± 2.2	4.9 ± 1.4	7.8 ± 2.0	< 0.001
Hemoglobin (g/dL)	10.2 ± 1.3	10.2 ± 1.4	10.2 ± 1.2	0.942
WBC (/μL)	8,309.2 ± 3,874.0	7,378.4 ± 2,723.5	9,016.7 ± 4,456.8	0.036
Platelet (× 10^3/μL)	195.4 ± 65.3	191.5 ± 60.5	198.7 ± 69.1	0.586
Protein (g/dL)	6.4 ± 0.9	6.6 ± 0.9	6.2 ± 0.8	0.037
Albumin (mg/dL)	3.6 ± 0.7	3.8 ± 0.5	3.5 ± 0.8	0.095
BUN (mg/dL)	44.0 ± 20.1	47.1 ± 22.4	41.9 ± 18.2	0.235
Creatinine (mg/dL)	6.3 ± 2.7	6.9 ± 2.3	5.9 ± 2.9	0.082
Calcium (mg/dL)	8.9 ± 1.1	9.2 ± 1.0	8.7 ± 1.0	0.015
Phosphate (mg/dL)	4.1 ± 1.5	4.4 ± 1.4	3.9 ± 1.6	0.155
iPTH (mg/dL)	57.1 (25.5–124.7)	73.7 (25.7–125.8)	56.6 (24.9–121.0)	0.914
T. cholesterol (μg/dL)	152.5 ± 47.5	147.8 ± 42.0	156.1 ± 51.5	0.421
HDL cholesterol (mg/dL)	36.5 ± 11.4	37.5 ± 12.1	35.8 ± 10.9	0.513
LDL cholesterol (mg/dL)	95.4 ± 93.3	85.6 ± 31.3	103.0 ± 121.3	0.391
CRP (mg/dL)	0.7 (0.2–3.0)	0.3 (0.1–2.4)	0.7 (0.2–3.6)	0.065
Glucose (mg/dL)	174.7 ± 98.8	141.4 ± 64.8	198.4 ± 111.9	0.003
HgbA1c (%)	8.1 ± 6.8	9.4 ± 10.8	7.3 ± 1.6	0.410
spKT/V	1.58 ± 0.254	1.69 ± 0.199	1.54 ± 0.271	0.398

Data are presented as number (%), mean ± standard deviation, median (interquartile range).

BUN, blood urea nitrogen; CRP, c-reactive protein; HDL cholesterol, high density lipid cholesterol; HgbA1c, hemoglobin A1c; iPTH, intact parathyroid hormone; LDL cholesterol, low density lipid cholesterol; T. cholesterol, total cholesterol; MHD, maintenance hemodialysis; WBC, white blood cell.

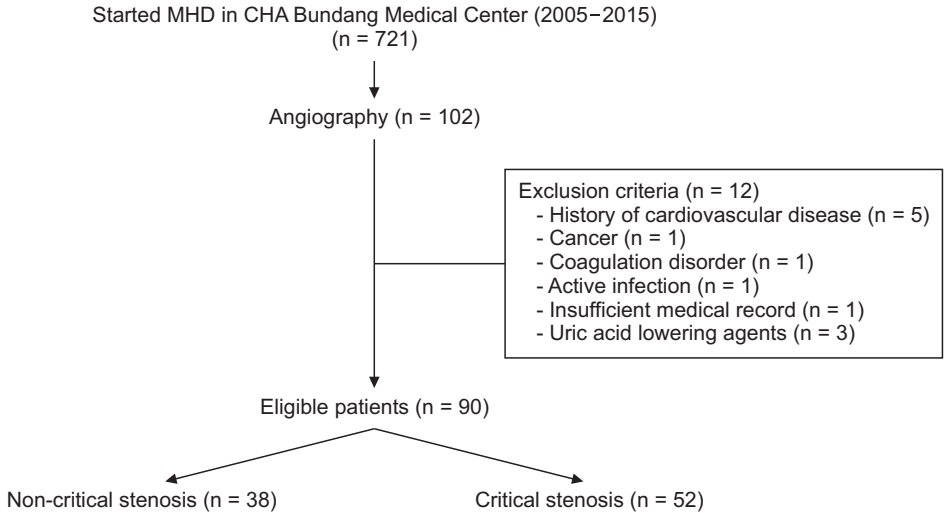

Figure 1. Flow chart illustrating study population enrollment. A total of 721 patients started maintenance hemodialysis (MHD) treatment at the CHA Bundang Medical Center hemodialysis center between 2005 and 2015. Ninety-seven patients underwent coronary angiographic testing for chest discomfort that began after initiation of MHD. After applying exclusion criteria, 90 patients were eligible.

fort that began after initiation of MHD. We excluded 12 patients with a past history of CVD, cancer, coagulation disorder, active infection, insufficient medical records, or a medical history of uric acid-lowering agents (Fig. 1).

The mean age of the study population was 62.3 ± 10.8 years, and 54.4% of the population was male. The etiologies of ESRD were diabetic nephropathy (70.0%), hypertension (17.7%), glomerulonephritis (1.1%), autosomal dominant polycystic kidney disease (1.1%), and unknown (7.8%). Most patients had arteriovenous fistulas or arteriovenous grafts (53.3% and 32.2%, respectively). The mean initial dose of heparin was 780.9 ± 563.8 IU/mL, and the maintenance dose was 243.2 ± 215.3 IU/mL/hour.

Hyperuricemia (serum uric acid level > 6.0 mg/dL in females and > 7.0 mg/dL in males) affected 47.7% of the total study population, and it was more prevalent in the critical stenosis group (73.0% vs. 13.1%, $P < 0.001$).

An analysis using Pearson's correlation coefficient revealed an inverse correlation between serum uric acid level and protein (r = −0.261, $P = 0.015$), albumin (r = −0.213, $P = 0.043$), serum potassium (r = −0.318, $P = 0.002$), creatinine (r = −0.219, $P = 0.038$), and calcium (r = −0.303, $P = 0.004$). Patient age (r= 0.156, $P = 0.143$), body mass index (r = 0.117, $P = 0.273$), and serum glucose (r = 0.198, $P = 0.063$) levels were positively correlated with serum uric acid level, but those associations were not statistically significant (Table 2).

Clinical characteristics of patients with critical coronary artery stenosis

The mean time from first hemodialysis treatment to angiography for chest pain was 46.8 ± 81.6 months. The coronary angiographic test diagnosed 52 patients (57.8%) with critical coronary artery stenosis; the remaining 38 (42.2%) composed the non-critical stenosis group. We compare the baseline demographics and comorbidities of the critical stenosis and non-critical stenosis groups in Table 1.

We observed no difference in gender between those with or without critical stenosis. Patients with critical-stenosis were older, but not significantly (60.0 ± 10.8 vs. 64.0 ± 10.6, $P = 0.099$). Diabetes was the only significant comorbid condition for critical stenosis (52.6% vs. 78.8%. $P = 0.009$). Hypertension and cerebrovascular disease were more prevalent in the critical stenosis group, but without a statistically significant difference (84.2% vs. 94.2%, $P = 0.118$ and 5.2% vs. 7.6%, $P = 0.648$, respectively). Patients with critical stenosis had generally received hemodialysis for longer than patients without critical stenosis at the time of coronary angiography (median 22.5 months vs. 6.5 months, $P = 0.083$).

Compared with the non-critical stenosis group, patients with critical stenosis had significantly higher WBC (7,378.4 ± 2,723.5 vs. 9,016.7 ± 4,456.8, $P = 0.036$) and glucose levels (141.4 ± 64.8 vs. 198.4 ± 111.9, $P = 0.003$). Serum protein (6.6 ± 0.9 vs. 6.2 ± 0.8, $P = 0.037$) and calcium levels (9.2 ± 1.0 vs. 8.7 ± 1.0, $P = 0.015$) were significantly lower in the critical stenosis group. Most important, the uric acid level was significantly higher in the critical stenosis group (4.9 ± 1.4 vs. 7.8 ± 2.0, $P < 0.001$, Fig. 2). No differences in other medications were observed between the two groups except for insulin use (13.1% vs. 34.6%, $P = 0.018$) (Table 3).

Table 2. Pearson correlation results between uric acid and variables

Variable	r	*P* value
Age	0.156	0.143
Body mass index	0.117	0.273
Protein	−0.261	0.015
Albumin	0.213	0.043
Potassium	−0.318	0.002
Creatinine	−0.219	0.038
Calcium	−0.303	0.004
Glucose	0.198	0.063

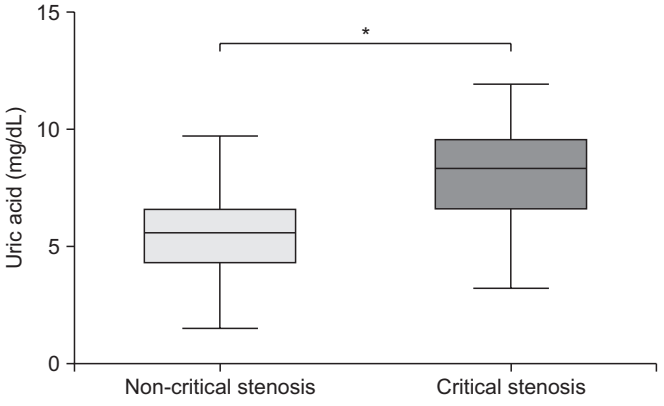

Figure 2. Comparison of serum uric acid level according to severity of coronary artery narrowing. *$P < 0.001$.

Table 3. Medications taken by the study population

Medication	Overall (n = 90)	Non-critical stenosis (n = 38)	Critical stenosis (n = 52)	*P* value
ACEi	48 (53.3)	21 (55.3)	27 (51.9)	0.754
ARB	9 (10.0)	3 (7.9)	6 (11.5)	0.569
Beta blocker	35 (38.9)	12 (31.6)	23 (44.2)	0.224
Calcium channel blocker	34 (37.8)	14 (36.8)	20 (38.5)	0.876
Aspirin	48 (53.3)	16 (42.1)	32 (61.5)	0.053
Clopidogrel	26 (28.9)	9 (23.7)	17 (32.7)	0.352
Cilostazol	3 (3.3)	1 (2.6)	2 (3.8)	0.421
Insulin	23 (25.6)	5 (13.2)	18 (34.6)	0.018
Oral antidiabetes drug	26 (28.9)	8 (21.1)	18 (34.6)	0.144
Calcium	29 (32.2)	12 (31.6)	17 (32.7)	0.911
Vitamin D	10 (11.1)	6 (15.7)	4 (7.7)	0.227

Data are presented as number (%).

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 4. Binary logistic regression analysis for critical stenosis

Variable	Univariate model		Multivariate model	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Uric acid (mg/dL)	2.360 (1.664–3.348)	< 0.001	3.740 (1.839–7.607)	< 0.001
Age (yr)	1.035 (0.995–1.078)	0.090	1.004 (0.941–1.070)	0.911
Protein (g/dL)	0.597 (0.363–0.981)	0.042	1.725 (0.749–3.975)	0.200
Glucose (mg/dL)	1.007 (1.002–1.013)	0.011	1.009 (0.999–1.019)	0.081
WBC (/μL)	1.000 (1.000–1.000)	0.056	1.000 (1.000–1.000)	0.201
Calcium (mg/dL)	0.588 (0.376–0.919)	0.020	0.735 (0.379–1.425)	0.362
Diabetes	0.298 (0.119–0.749)	0.010	1.100 (0.215–5.635)	0.909
Insulin use	0.278 (0.092–0.836)	0.023	0.131 (0.015–1.155)	0.067

CI, confidence interval; WBC, white blood cell.

Multivariate analysis

We performed a binary logistic regression analysis to assess the effects of covariates on critical coronary artery stenosis (Table 4), using variables found to be significantly correlated with critical stenosis in the univariate analysis. Variables that met this criterion were uric acid level, protein, glucose, calcium, diabetes, and insulin use. Interestingly, serum uric acid level remained significant after adjustment for other variables ($P < 0.001$, Table 3).

Discussion

In this study, we retrospectively selected patients who experienced new chest discomfort and underwent coronary angiographic testing after initiation of hemodialysis. The results indicate that high serum uric acid level is associated with critical coronary artery stenosis. Thus, high uric acid could be associated with severity of coronary artery disease in ESRD patients. Notably, we found a significant relationship between uric acid level and coronary artery stenosis according to a multivariate analysis. To our knowledge, no investigation has previously explained the influence of uric acid on CVD using coronary angiographic views from CKD patients.

Several epidemiologic studies have reported a relationship between uric acid and cardiovascular conditions, including hypertension, metabolic syndrome, cerebrovascular disease, coronary artery disease, and kidney disease [7,16–20]. A previous meta-analysis of 16 observational studies examined the association between hyperuricemia and coronary heart disease (CHD) in the general population and found an odds ratio of 1.13 (95% confidence interval, 0.97–1.30) [21]. Another meta-analysis included only prospective cohort studies and found that hyperuricemia could increase the risk of CHD events

in the general population, independent of traditionally known CHD risk factors [9].

The exact relationship between uric acid and CVD in the CKD population remains controversial. In the randomized, controlled Modification of Diet in Renal Disease Study of 840 CKD patients in stage 3 to 4, high uric acid level was independently associated with a high risk for all-cause and CVD mortality [13], and that association did not change with adjustment for traditional CVD risk factors. Previous studies that examined the relationship between uric acid and CVD mortality in patients with kidney failure treated by dialysis suggested a 'J-shaped' association between uric acid and all-cause mortality [1,14,15,19]. However, Latif et al [1] analyzed data from the Dialysis Outcome and Practice Patterns Study of 5,827 hemodialysis patients and found the contrasting result that a higher uric acid level was associated with a lower risk of all-cause and cardiovascular mortality in hemodialysis patients. In our study, serum uric acid level was higher in the group with critical coronary artery stenosis findings on coronary angiography, which suggests that higher uric acid level could be associated with coronary artery disease in ESRD patients.

The duration of dialysis is a well-known risk factor of coronary stenosis [22]; however, in the present study, the group with non-critical stenosis had a longer duration of dialysis. This result corresponds with a recent study that demonstrated that hemodialysis patients with CVD had shorter dialysis duration than patients without CVD [23], and Eckardt et al [24] also suggested that the immediate period following dialysis initiation is a very high cardiovascular risk period. Age and diabetes are also known risk factors for CVD in hemodialysis patients [25], although no such associations were noted in our results. In this study, the prevalence of diabetes was more than 50% in the overall study group and in the non-critical stenosis group. When we included age as an independent variable in the regression model, the result was not different. This could be the result of our small study population, and further study with a larger patient group is necessary.

Several mechanisms link uric acid with cardiovascular risk. First, uric acid might affect cardiovascular and renal function and structure by endothelial dysfunction [6]. *In-vitro* and *in-vivo* studies have suggested that uric acid might contribute to endothelial dysfunction by inducing antiproliferative effects in the endothelium and impairing nitric oxide production [26,27]. High serum uric acid level reflects the degree of xanthine oxidase (XO) activation, and circulating XO contributed to vascular dysfunction in animal models [28]. In a randomized, placebo-controlled, double blind study, Farquharson et al [29] reported that XO inhibition with allopurinol improved endothelial dysfunction in chronic heart failure.

Uric acid could affect vascular smooth muscle cell (VSMC) proliferation. Rao et al [30] reported that uric acid stimulates VSMC growth via an autocrine mechanism and suggested that uric acid generation during ischemia/reperfusion contributes to atherogenesis and intimal proliferation. In addition, Corry et al [31] showed that uric acid stimulates proliferation and oxidative stress in VSMCs through the tissue renin-angiotensin system (RAS), and they concluded that uric acid might cause CVD by stimulating the vascular RAS.

As CKD prevalence has increased, the costs of caring for that population have also increased [32]. In the United States, patients with CKD aged 65 years or older accounted for 20% of all Medicare spending in that age group, exceeding 50 billion US dollars in 2013 [33]. Therefore, proper management of CVD and investigation and proper prevention of risk factors for CVD in CKD patients are critical to improving clinical outcomes and reducing medical costs. Our study revealed that the severity of coronary artery stenosis in ESRD patients was positively associated with a high serum uric acid level. Thus, serum uric acid could be a risk factor for CVD progression in the CKD population. Serum uric acid is an inexpensive and simple laboratory marker. Furthermore, previous studies have found that the hyperuricemia prevalence in CKD is readily modifiable [34]. Thus, our report could provide a basis and goal for hyperuricemia treatment in CKD patients.

This study has several limitations. It was a small, single center study. We only included laboratory data collected at the time of angiographic study. Because we used data from medical records, we could not include other possible factors, such as smoking history. Furthermore, we could not explore pathophysiological mechanisms or include a patient group with normal angiographic findings.

High serum uric acid level was associated with critical coronary artery stenosis in Korean ESRD patients. This association remained significant despite adjustment for other possible risk factors. Further research is needed to

investigate the biological role of uric acid and to determine whether decreasing serum uric acid level reduces the risk of severe coronary artery disease in ESRD patients.

Conflicts of interests

All authors have no conflicts of interest to declare.

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