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The relationship between uric acid to high-density lipoprotein cholesterol ratio and collateral index in patients with chronic total occlusion

Background	High serum uric acid (UA) levels and low high-density lipoprotein cholesterol (HDL–C) levels are accepted as risk factors for cardiovascular mortality. Hyperuricemia and low HDL–C levels were associated with an increased risk of cardiovascular mortality and the development of diabetes and hypertension. However, the association of UA with cardiovascular (CV) mortality,collateral index are undetermined in patients with chronic total occlusion (CTO).
Material and methods	124 patients who underwent coronary angiography with the diagnosis of stable or unstable angina pectoris and had chronic total occlusion were included in our study. Blood samples were collected from all patients before the angiography procedure. Coronary collateral circulation (CCC) was graded according to the Rentrop grading system of 0–3. Rentrop grades of 0 and 1 indicated low-grade CCC group, whereas grades 2 and 3 indicated high-grade CCC group. We divided our patients into two groups as low-grade CCC and high-grade CCC and examined these two groups in terms of uric acid/HDL ratios. Group 1: Rentrop classification grade 0–1 (mean age, 63,9±9,9), Group 2: Rentrop classification grade 2–3 (mean age, 62,1±9,4).
Results	The baseline characteristics were similar in both groups. Uric acid/High density lipoprotein-cholesterol ratios and uric acid levels were higher in group 1 with poor collateral circulation [group 1; 0,21 (0,07–0,39) vs. group 2; 0,16 (0,08–0,31), group 1; 8,2 (3,4–10,4) vs. group 2; 5,85 (3,5–7,7), p<0,001, p<0,001 respectively].
Conclusions	We found that high Uric acid/High-density lipoprotein-cholesterol ratios and high uric acid levels are associated with poor collateral circulation.

Keywords	Uric acid; CTO; high-density lipoprotein cholesterol
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Introduction

Chronic total occlusion (CTO) is defined as the complete obstruction of a coronary artery for more than three months. When a coronary artery is almost completely occluded, collateral vessels gradually open and begin to carry blood to the ischemic or infarcting myocardium. The coronary collateral circulation (CCC) may prevent the loss of ventricular function and the formation of a ventricular aneurysm by maintaining the blood flow in the ischemic area.

Although the mechanism of CCC formation is still unclear, vascular growth factors and blood cells, such as monocytes, neutrophils, lymphocytes, have an important role [1]. Serum uric acid (UA), which is the end product of purine metabolism, plays an important role in the development and progression of coronary artery disease (CAD) [2–5]. The metabolism of amino acids, acyl-carnitines, and purines significantly changes in patients with myocardial infarction compared to healthy individuals [6]. In a large cohort study with a 10-yr follow-up period, it was found that in CAD, UA and xanthosine were increased and hypoxanthine and inosine were decreased in the major adverse cardiac and cerebrovascular event (MACCE) group compared to the non-MACCE group, without adjusting for other clinical factors [7]. In many epidemiologic studies, hyperuricemia was associated with an increased risk of coronary heart disease, heart failure, and fatal arrhythmias. Elevated UA predicted the progression coronary artery calcification [8–11] and elevated UA was associated with greater lipid content of coronary plaque in patients with acute coronary syndrome [12]. In addition, there are many factors such as age, gender, nutrition, medical treatment, that can change UA metabolism. However, in some epidemiological studies, increased UA was not associated with CAD [5, 13].

In previous meta-analyses of prospective studies, no significant association between hyperuricemia and CAD incidence or mortality in men was found, but there was an increased risk of CAD-related mortality in women [14]. In a re-

cent cross-sectional study, only a correlation was observed between hyperuricemia and CAD in female patients over 80 yrs old, but this was not observed in male patients [15]. In the current study, we investigated the relationship between hyperuricemia, the UA/high density lipoprotein cholesterol (HDL–C) ratio, and the coronary collateral index.

Material and methods

Study population

Angiography was performed on 3000 patients in our clinic between June 2018 and December 2021. Chronic total occlusion (CTO) was observed in 140 patients. Among these patients, after exclusion criteria, 124 patients with stable or unstable angina pectoris with CTO were consecutively included in this study. Patients with severe renal insufficiency (creatinine >2mg/dl), active infection, or malignancy were excluded from the study. The basic clinical characteristics of the patients were obtained by examining the database of our hospital.

Fasting blood samples were obtained from all patients during their hospitalization. Whole blood counts were performed with an automated whole blood analyzer, and biochemical values were measured with an automatic device. Hypertension was defined as blood pressure above 140/90 mmHg or taking antihypertensive medication. Diabetes mellitus was defined as fasting plasma glucose level ≥7.0 mmol/l (126 mg/dl) or glycated hemoglobin A1c ≥6.5% or using antidiabetic drugs. Hyperlipidemia was defined as being on lipid-lowering therapy or having a total cholesterol level above 220 mg/dl.

The study was performed according to the Helsinki declaration, and it was approved by the ethics committee of Tekirdağ Namık Kemal University Hospital.

Coronary Angiography

After obtaining informed consent, coronary angiography was performed using a standard Judkins' technique through the right femoral artery with standard projections. Coronary angiograms were interpreted by two independent cardiologists who were blinded to the patients' data. The presence of 50% or more stenosis in at least a main coronary artery was considered significant. Less than 50% stenosis in coronary arteries was considered non-critical. The CCC was evaluated according to the Rentrop classification as follows: grade 0, no discernible collaterals; grade 1, filling of the side branch via collateral vessels without visualization of the epicardial segment;

Table 1. Baseline characteristics of the groups

Variable	Group 1, n=47	Group 2, n=77	Total, n=124	p
Age, yrs	63.9±9.9	62.1±9.4	62.8±9.6	0.30*
Male	39 (83%)	63 (81.8%)	102 (82.3%)	0.87†
Female	8 (17%)	14 (18.2%)	22 (17.7%)	0.87†
Height, m	1.67±0.69	1.66±0.80	1.66±0.073	0.80*
Hyperlipidemia	33 (70.2%)	60 (77.9%)	93 (75%)	0.3†
Hypertension	28 (59.6%)	46 (59.7%)	74 (59.7%)	0.98†
Weight, kg	78.67±12.8	79.18±12.3	78.75±12	0.61*
Smoker	26 (55.3%)	36 (46.8%)	62 (50%)	0.35†
Diabetes mellitus	23 (48.9%)	26 (33.8%)	49 (39.5%)	0.09†
Body mass index, kg/m^2	28.1±4.04	28.7±4.85	28.4±4.3	0.65*
Vessel with CTO				
LAD	24 (51.1%)	48 (62.3%)	72 (58.1%)	0.42†
Cx	20 (42.6%)	24 (31.2%)	44 (35.5%)	0.42†
Rca	3 (6.4%)	5 (6.5%)	8 (6.5%)	0.42†
Pharmacological Treatment				
Beta blocker, %	37 (78.7%)	51 (66.2%)	88 (71%)	0.13†
Ca – channel blocker	4 (8.5%)	5 (6.5%)	9 (7.3%)	0.67†
ACE-I	27 (57.4%)	41 (53.2%)	68 (54.8%)	0.64†
Diuretic	5 (10.6%)	13 (16.9%)	18 (14.5%)	0.33†
Acetyl salicylic acid	27 (57.4%)	43 (55.8%)	70 (56.5%)	0.86†
Oral antidiabetic	9 (19.1%)	10 (13%)	19 (15.3%)	0.35†
Statin	29 (61.7%)	51 (66.2%)	80 (64.5%)	0.60†
Number of vessels with coronary artery disease				
One vessel	5 (10.6%)	15 (19.5%)	20 (16.1%)	0.41†
Two vessel	41 (87.2%)	60 (77.9%)	101 (81.5%)	0.41†
Three vessel	1 (2.1%)	2 (2.4%)	3 (2.4%)	0.41†

Data are mean±SD or value (percentage). *Student's t-test. †Chi square test. ACE-I, Angiotensin-converting enzyme inhibitors; CTO, chronic total occlusion; LAD, left anterior descending coronary artery; Cx, left circumflex coronary artery; Rca, right coronary artery.

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Table 2. Laboratory parameters of the groups

Variable	Group 1, n=47	Group 2, n=77	Total, n=124	p
Glucose, mg/dl	115 (68-371)	103.5 (71-215)	121.46 (68-371)	0.07*
Hemoglobin, g/dl	13.9±1.27	13.8±1.44	13.5±1.45	0.88†
Creatinin, mg/dl	1 (0.75-1.3)	0.9 (0.6-1.7)	0.97 (0.3-2.4)	0.79*
Uric acid, mg/dl	8.2 (3.4-10.4)	5.85 (3.5-7.7)	6.48 (2.3-11)	<0.001*
Total cholesterol, mg/dl	187.76±40.2	196.63±46.4	190.71±48.9	0.42†
HDL-C, mg/dl	38 (21-87)	38 (20-46)	37 (18-87)	0.35*
LDL-C, mg/dl	118.55±36.8	128.47±39.6	123.77±35.9	0.13†
Triglycerides, mg/dl	158.42±86.5	157.58±67.8	151.9±80.1	0.64†
White blood cell count ×10³/μl	7.93±2.31	7.75±1.74	8.1±2.27	0.13†
Neutrophil count ×10³/μl	4.81±1.78	4.62±1.44	4.95±1.95	0.46†
Lymphocyte count (×10³/μl)	2.16±0.9	2.27±0.7	2.19±0.89	0.92†
Monocyte count ×10³/μl	0.57 (0.3-1.44)	0.59 (0.28-2)	0.64±0.29	0.97*
MVP, fl	8.45±1.14	8.25±1.24	8.23±1.12	0.10†
Platelet count ×10³/μl	282.6±89.90	281.4±64.07	276.15±72	0.77†
RDW, %	15.6±1.47	15±1.16	15.2±1.41	0.37†
UA/HDL-C	0.21 (0.07-0.39)	0.16 (0.08-0.31)	0.18±0.77	<0.001*

Data are mean±SD or median (minimum-maximum). Group 1: Rentrop classification grade 0-1. Group 2: Rentrop classification grade 2-3.
* Mann–Whitney U test, †Student's t-test BUN, blood urea nitrogen; GFR, glomerular filtration rate; HDL, high density lipoprotein-cholesterol; MPV, mean platelet volume; LDL, low density lipoprotein-cholesterol, RDW, red cell distribution width; UA, uric acid; UA/HDL-C, uric acid/high density lipoprotein cholesterol ratio.

Table 3. Multivariate logiſtic regreſſion analyſiſ of variableſ related to CCC

Variable	Odds ratio	95% Confidence interval	P
UA/HDL–C	0.8	0.787–0.906	<0.001
Gender	1.1	0.382–3.669	0.77
Age	0.9	0.919–1.010	0.12

UA/HDL–C, uric acid/high-density lipoprotein-cholesterol ratio

grade 2, partial filling of the epicardial coronary artery; grade 3, complete filling of the epicardial coronary artery [10]. The patients were divided into two groups according to the Rentrop classification: Group 1 (grades 0 and 1) and Group 2 (grades 2 and 3).

Statistical analysis

Statistical analyses were performed with SPSS 22.0 statistical software (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean±standard deviation (SD) or median (minimum-maximum). Categorical variables were expressed as a percentage and compared with chi-square or Fischer's exact tests. The normality of data distributions was evaluated with the Kolmogorov-Smirnov test. Independent samples t-tests were used for normally distributed, continuous data. Non-normally distributed were evaluated with the Mann–Whitney U test. Receiver-operating characteristic analyses (ROC) were used to detect the cutoff values of the UA/HDL–C ratio in the prediction of CCC. Multivariate logistic regression analysis was used to identify independent predictors of the degree of the CCC. Correlation analysis between the UA/HDL–C ratio and the coronary collateral index was performed with the Spearman correlation test. P-values≤0.05 were considered statistically significant.

Results

Tables 1 and 2 summarize the baseline characteristics and laboratory values of the patients. The mean age of the 124 patients was 62.8±9.6 yrs; 82.3% were male. The height, body mass index, and weight of the patients in both groups were similar. The frequencies of hyperlipidemia, hypertension, diabetes mellitus, and smoking were also similar. Likewise, the vessel with CTO, the number of vessels with CAD, and medical treatments were similar.

Patients in group 1 had a lower ejection fraction than those in group 2 (44.4±11.2 vs. 52.3±11.5 p=0.04). The laboratory variables of the two groups were similar except for UA and the UA/HDL–C ratio, which were higher in group 1 [UA 8.2 (3.4–10.4) vs. 5.85 (3.5–7.7), p<0.001; UA/HDL–C 0.21 (0.07–0.39) vs. 0.16 (0.08–0.31), p<0.001]. The result of the ROC analysis for the UA/HDL–C ratio to predict a low degree of CCC was as follows: AUC 0.769; 95% confidence interval (CI) (0.682–0.856) with 70.2% sensitivity and 70.1% specificity (Figure 1). In the correlation analysis, a moderate negative correlation was found between the UA/HDL–C ratio and the coronary collateral index (r=–0.452, p<0.001). Multivarite logistic regression results were shown in Table 3. Age, gender and UA/HDL–C ratio were included to the analysis. As a result of multivariate logistic regression analysis, a high UA/HDL–C ratio was determined as an

independent predictor of poor CCC (odds ratio: 0.8; 95% CI (0.787–0.906), p<0.001)

Discussion

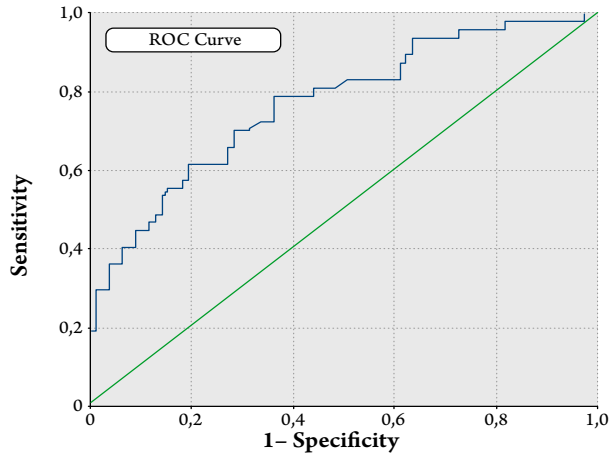
In this study, we examined the relationship between the coronary collateral index and UA and the UA/HDL–C ratio. In many previous studies, it has been observed that having UA above 7 mg/dl increases cardiovascular mortality in people aged 70 yrs and over. In previous studies, UA levels were elevated in patients with systemic hypertension and diabetes mellitus and with acute myocardial infarction [16]. High UA levels have been associated with a reduction of nitric oxide (NO), endothelial dysfunction, arterial stiffness, hypertension, insulin resistance, metabolic syndrome, and inflammation [17]. Furthermore, in previous studies, UA was associated with increased platelet adhesiveness, smooth muscle cell proliferation, and elevated coronary artery calcium [18]. However, the underlying mechanism has not been fully elucidated.

UA penetrates the cell membrane and damages the cell by effects such as oxidation and inflammation [19, 20]. Various studies have shown that hyperuricemia reduces the amount of NO released from the vascular endothelium [21, 22]. On the other hand, UA reduces NO bioavailability and inhibits cell migration and proliferation [20, 23]. High UA levels increase the production of reactive oxygen species, facilitate the activation of the renin-angiotensin system, and cause endothelial dysfunction [24]. UA increases the expression of pro-inflammatory cytokines such as C-reactive protein [25, 26], and thus it contributes to atherosclerosis. UA causes microvascular damage by acting directly on vascular smooth muscle and endothelium [27].

In another study, elevated UA levels were observed in patients with coronary artery ectasia [28]. Unlike other studies, we examined the relationship between UA levels and CCC in patients with CTO.

When the stenosis in the epicardial coronary arteries exceeds 80%, the pressure in the CCC increases, and these vessels are visible on the coronary angiogram [29, 30]. Many factors affect the formation of coronary collateral vessels. In addition to for the classic cardiovascular risk factors, such as diabetes mellitus, hypertension, and dyslipidemia, endogenous mediators, including TGF-α or -β, NO, vascular endothelial growth factor, also play a role in the formation of the CCC. In addition, inflammatory cells such as monocytes, neutrophils, lymphocytes, and eosinophils, also play a role in the formation of the CCC [1]. According to Jiang et al. [31], a decrease in the percentage of eosinophils indicates severe myocardial damage. Eosinophils play a significant role in thrombosis in patients with acute coronary syndrome [31], and eosinophils play an important role in the initiation, generation, and maintenance of the CCC. This may explain why the number of eosinophils was higher in the high-grade CCC group compared to the low-grade CCC group. In previous studies, high UA was found to be associated with CAD only in females aged ≥80 yrs. However, we did not observe any difference in terms of age and gender in the current study. This might be due to the small number of patients in our study. Various studies have shown the relationship between elevated low-density lipoprotein cholesterol (LDL–C) and decreased HDL–C levels with cardiovascular diseases [32, 33]. The Atherogenic Index of Plasma (AIP) [log (Triglyceride/HDL–C)] is a strong marker for predicting the risk of atherosclerosis and coronary heart disease [34]. Similar to these studies, we found a relationship with high UA/HDL–C ratioand a low collateral index in this study.

Figure 1. ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for UA/HDL-C ratio for predicting low coronary collateral circulation grade



Cut off: 0.18, AUC: 0.769, 95% CI:0.682- 0.856, p<0.001, 70.2% sensitivity and 70.1% specificity.

Limitations

The most important limitation of our study is that it was conducted with a small group of patients at a single center. The findings may not be applicable to other demographic groups. Another issue is that some patients were taking antihypertensive therapy containing diuretics, which may affect their UA levels. Further large-scale and multi-center prospective studies are required to validate the findings of this study.

Conclusion

High UA and UA/HDL–C levels are associated with poor collateral circulation in patients with CTO. A high UA/HDL–C ratio is an important predictor of a poor CCC grade.

No conflict of interest is reported.

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