

Does serum uric acid to high-density lipoprotein cholesterol ratio predict coronary slow flow?

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Abstract

Aim: Several studies have found a correlation between coronary slow flow (CSF) and low serum high-density lipoprotein cholesterol (HDL-C) levels or high serum uric acid levels. The present study aimed to evaluate whether serum uric acid to HDL-C ratio predicts CSF.

Material and Methods: The experimental (CSF) group included 91 patients (40 females, 51 males, mean age: 52±9) who had angiographically normal coronary arteries but had slow flow in one or more coronary arteries. The control group included 96 patients (57 females, 39 males, mean age: 50±9) with normal coronary anatomy and without slow flow. The uric acid to HDL-C ratio was calculated for the two groups and compared.

Results: The HDL-C levels of the CSF group (37±8 mg/dL) were significantly lower compared to the controls (49±10 mg/dL, p<0.001), whereas serum uric acid levels (5.33±0.97 mg/dL) and uric acid to HDL-C ratio (0.14±0.03) of the CSF group were significantly higher compared to the controls (4.37±0.88 mg/dL and 0.09±0.02, p<0.001 and p<0.01, respectively). The receiver operating curve (ROC) analysis revealed that a cut-off >4.64 mg/dL uric acid and >0.119 % uric acid to HDL-C ratio had a sensitivity of 81% and 85% and specificity of 76% and 80% for determination of CSF, respectively (AUC=0.850, 95% CI: 0.792 - 0.908 and AUC=0.890, 95% CI: 0.841 - 0.940, respectively). Spearman's correlation test has been performed and a significant positive correlation has been detected between the uric acid to HDL-C ratio and the mean thrombolysis in myocardial infarction (TIMI) frame count (r=0.62, p<0.001).

Conclusion: In this study, higher uric acid to HDL-C ratio values of the CSF group was found compared to the control group. Furthermore, uric acid to HDL-C ratio performed better than serum uric acid levels in predicting CSF.

Keywords: Atherosclerosis; coronary slow-flow; high-density lipoprotein cholesterol; uric acid; uric acid to high-density lipoprotein cholesterol ratio

INTRODUCTION

Coronary slow flow (CSF) is the state of slow passage of contrast material through the coronary arteries (CAs) during angiography when there is no obstruction and a delay in the opacification of epicardial CAs (1). Various studies have reported that the prevalence of CSF ranges from 1% to 7%. CSF is related to myocardial ischemia, and it may cause myocardial infarction, life-threatening arrhythmias, and sudden cardiac death. Similar to coronary artery disease (CAD), CSF also has a high risk of cardiovascular mortality (1,2). The mechanism of CSF has not been completely understood despite several studies. Various mechanisms have been proposed in pathogenesis, including diffuse atherosclerosis, microvascular dysfunction, inflammation, endothelial dysfunction, and increased platelet aggregation (3-5).

Inflammation takes a role in the formation and progression of atherosclerosis. Etiological studies of CSF have found a significant relationship between the flow rate calculated through the thrombolysis in myocardial infarction (TIMI) frame count and inflammatory markers (6,7). The increased serum uric acid (UA) level is an independent risk factor for atherosclerotic cardiovascular diseases (CVDs) (8). Furthermore, hyperuricemia has a close relationship with the inflammatory course. Xanthine oxidase, the enzyme that synthesizes UA in purine metabolism in the epithelial cells, can be activated by inflammatory cytokines, leading to hyperuricemia. An association has been found between hyperuricemia and increased interleukin-6 and C-reactive protein (CRP) levels in several inflammatory diseases (9,10).

Received: 26.06.2020 Accepted: 28.09.2020 Available online: 21.10.2020

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Some studies have found that patients with CSF had decreased plasma high-density lipoprotein cholesterol (HDL-C) levels and suggested that decreased HDL-C levels could be a predictor of CSF (11). Serum UA to HDL-C ratio (UHDL) was examined for the first time by Koçak et al. in cases with metabolic syndrome (MS) and type II diabetes mellitus (DM) (12). They found that high UHDL reflects poor glycemic control and that UHDL performs better than UA in predicting MS. The present study evaluates whether the UHDL predicts CSF.

MATERIAL and METHODS

Study Population

The patients were chosen from among 10,900 cases who underwent elective coronary angiography (CAG) because of typical angina or after having diagnosed with significant myocardial ischemia on noninvasive stress tests at Mehmet Akif Inan Research and Training Hospital between January 2014 and December 2017. The experimental (CSF) group included 91 consecutive patients (40 females, 51 males, mean age: 52±9) who had angiographically normal CAs but had slow flow in one or more CAs. The age- and gender-matched control group included 96 consecutive patients (57 females, 39 males, mean age: 50±9) who underwent CAG in the same period but had normal coronary anatomy (NCA) and without slow flow. Patients without obliterative or non-obliterative injuries in the main CA and the other three major CAs were regarded as having normal CAs.

Patients who had a history of CAD or exhibited the findings of CAD in CAG performed, those with CA ectasia, acute coronary syndrome, congestive heart disease (ejection fraction - EF <45%), severe valvular heart disease, hepatic or hemolytic disorders, chronic obstructive pulmonary disease, history of gout, renal failure (creatinine >1.5 mg/dL), anemia, chronic inflammatory conditions, or neoplastic diseases were excluded. Patients who received UA-lowering medications were also not included.

Detailed medical history of the study population was retrieved from the medical records and recorded on the forms prepared for the study. The results of all routinely performed laboratory tests before CAG were retrieved from the digital records of the hospital. A patient who had a systolic blood pressure (BP) of ≥140 mmHg or diastolic BP of ≥90 mmHg or both, or was using antihypertensive drugs was considered to have hypertension. Those who used anti-diabetic medications, or had fasting plasma glucose levels ≥126 mg/dL in at least two measurements or a glycated hemoglobin ratio (HbA1c) of ≥6.5% were considered to have DM. We calculated body mass index (BMI) for all patients by dividing weight (kg) by the square of the height (m²). A BMI of ≤25 kg/m² was regarded as normal weight, a BMI of 25-30 kg/m² as overweight, and a BMI of >30 kg/m² as obese. The study protocol was approved by the institutional review board and executed according to the principles of the Helsinki Declaration. (R.T. Harran University, Ethics Committee, number :76244175-050.04.04)

Angiographic Evaluation

All of the patients underwent CAG with a femoral approach performed by experienced cardiologists who preferred the standard Judkins method. The images were saved and stored in digital format for later analysis. Two experienced cardiologists who were blind to each other's findings were performed the visual evaluation. The images of CAs were taken at 30 frames per second (fps) at caudal and cranial angles in the right and left oblique planes. The coronary blood flow was calculated by using TIMI frame count (TFC) method, as previously described elsewhere (13). The first counting frame was recorded when the opaque material filled 70% of the diameter of the CA after injection. The image where the contrast agent filled the 1st branch of the posterior lateral branch of the right coronary artery (RCA), the distal bifurcation of the most distant and widest lateral branch of the circumflex artery (Cx), and the apical portion of the left anterior descending coronary artery (LAD) was considered as the last frame. TFC is divided by 1.7 to calculate the corrected TFC, since the other arteries are shorter than the LAD. While calculating the average TFC, corrected TFC for LAD and TFCs for Cx and RCA were summed and divided by 3. Based on the method mentioned above, the mean normal TFC was 20.4±3 squares for RCA, 22.2±4.1 squares for Cx, and 21.1±1.5 squares for LAD. A TFC value higher than the normal values by more than two standard deviations was regarded as CSF.

Blood Sampling and Laboratory Assays

Peripheral blood collection by antecubital venipuncture was performed following 12-hour overnight fasting. Serum glucose, lipid profile, and creatinine were determined using standard methods. Complete blood count was performed with samples collected into tubes containing dipotassium EDTA on XE-1200 (Sysmex, Kobe, Japan), an automated hematology analyzer. Serum UA levels were measured on a Roche / Hitachi automated analyzer using an enzymatic colorimetric test. The UHDL was calculated by dividing serum UA by HDL-C.

Statistical Analysis

Statistical Package for Social Sciences 18.0 for Windows (SPSS Inc, Chicago, Illinois, USA) was used for all data analysis. Quantitative variables were expressed as mean±standard deviation (SD) values, while qualitative variables as numbers and percentages, and. For quantitative variables, Student's t-test was performed to analyze the differences between the independent groups with normal distribution, Mann-Whitney U-test was used those without normal distribution. The chi-square test was performed to analyze qualitative variables. Spearman's correlation coefficient was performed to analyze the correlations between the CSF and other variables. Multiple logistic regression analysis was used to analyze the value of UHDL, uric acid, HDL and LDL as independent predictors of CSF.

The sensitivity and specificity of UA and UHDL in predicting the presence of slow flow were determined with the receiver operating characteristic (ROC) curve analysis. Statistical significance level was set as P<0.05.

RESULTS

The main features and laboratory test results of the research groups were presented in the Tables 1 & 2. There were no statistically significant differences between the CSF group and the control group in terms of age, gender, history of DM, dyslipidemia, hypertension, family history of CVD, initial medications, smoking status, low-density lipoprotein cholesterol (LDL-C), triglyceride, and total cholesterol (Tables 1 & 2). The mean HDL-C of the CSF

group was significantly lower compared to the controls (37 ± 8 mg/dL vs. 49 ± 10 mg/dL, $p < 0.001$), whereas the mean serum UA level and UHDL in the CSF group were significantly higher than those in the controls (5.33 ± 0.97 mg/dL vs. 4.37 ± 0.88 mg/dL, $p < 0.001$ and $0.14 \pm 0.03\%$ vs. $0.09 \pm 0.02\%$, $p < 0.001$, respectively) (Table 2 and Figure 1). The average TFC and the TFCs measured in the LAD, RCA, and CX were statistically significantly higher in the CSF group than in the controls (Table 1).

Table 1. General characteristics of the work population

Baseline characteristics	control(n=96)	Slow flow(n=91)	P
Age (mean \pm SD) (years)	50 \pm 9	52 \pm 9	0.49
Male/female	39/57	51/40	0.09
BMI (kg/m ²)	27.4 \pm 4.1	25.7 \pm 3.7	0.217
Hypertension (%)	13 (14%)	13 (15%)	0.83
Smoking	38(40%)	42(46%)	0.19
Family history	9 (9%)	11 (11%)	0.23
Diabetes mellitus	15(16%)	16 (18%)	0.66
Acetyl salicylate	15 (16%)	18(20%)	0.09
Statin	6 (6%)	10 (11%)	0.07
ACE inhibitor	14(15%)	10 (11%)	0.46
B-blocker	10 (10%)	12 (13%)	0.11
TIMI frame count measurements			
cLAD-TFC	32(27-34)	43(24-58)	<0.001
CX-TFC	22(17-24)	28(17-45)	<0.001
RCA-TFC	20(15-23)	28(16-52)	<0.001
Mean TFC	24(20-27)	33(26-49)	<0.001

ACE: Angiotensin-Converting Enzyme, BMI: Body-Mass Index ,TFC: TIMI Frame Count, cLAD: Corrected Left Anterior Descending Artery, RCA: Right Coronary Artery ,CX: Circumflex ,SD: Standard deviation, data were compared with student t-test and Chi-square test

Table 2. Laboratory data of the study groups

	control(n=96)	Slow flow(n=91)	P
Creatinine(mg/dl)	0.80 \pm 0.12	0.81 \pm 0.15	0.44
Fasting plasma glucose (mg/dl)	118 \pm 51	120 \pm 56	0.39
LDL-cholesterol (mg/dl)	116 \pm 37	123 \pm 36	0.02
HDL-cholesterol (mg/dl)	49 \pm 10	38 \pm 7	<0.001
Triglyceride (mg/dl)	194 \pm 110	192 \pm 67	0.18
Total cholesterol (mg/dl)	192 \pm 46	205 \pm 43	0.06
Uric acide((mg/dl)	4.37 \pm 0.88	5.33 \pm 0.97	<0.001
UHDL (%)	0.09 \pm 0.02	0.14 \pm 0.03	<0.001
Hemoglobin (gr/dl)	13.7 \pm 1.7	13.4 \pm 1.8	0.16
Platelet counts (k/mm ³)	242 \pm 72	246 \pm 76	0.15
WBC (x10 ³ μ l)	8.1 \pm 2.2	8.20 \pm 2.3	0.88

WBC: White Blood Cell ,LDL=Low Density Lipoprotein Cholesterol, HDL= High Density Lipoprotein Cholesterol , UHDL=Uric Acid to HDL-Cholesterol Ratio

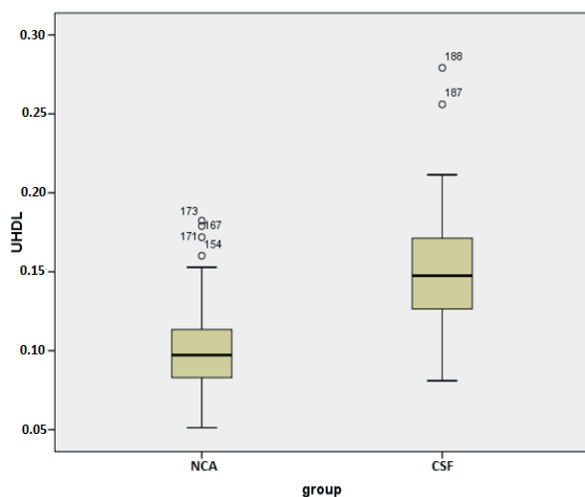


Figure 1. Comparison of uric acid to HDL-cholesterol ratio (UHDL) between the coronary slow flow and the normal coronary anatomys groups

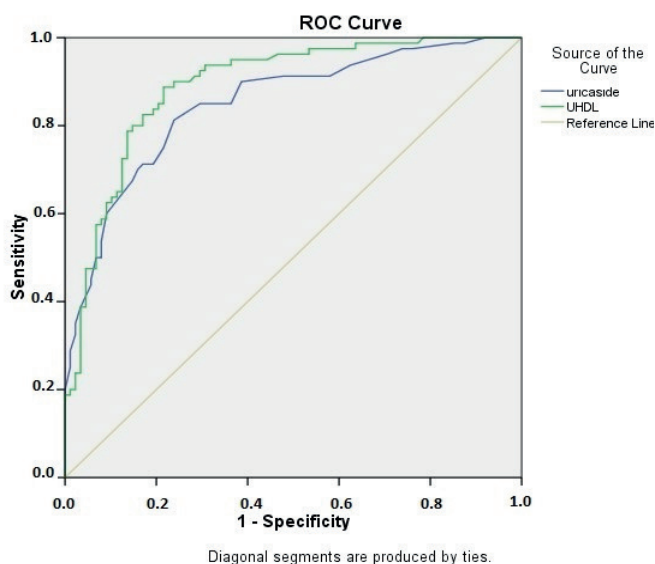


Figure 2. The receiver operating curve (ROC) analysis revealed that a cut-off >4.65 mg/dL UA and >0.119 % UHDL had a sensitivity of 81% and 85% and specificity of 76% and 80% for determination of CSF, respectively (AUC=0.850, 95% CI: 0.792 - 0.908 and AUC=0.890, 95% CI: 0.841 - 0.940, respectively)

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In multivariate analysis forward stepwise model, uric acid ($p=0.001$, 95% CI for OR:1.6 (0.56-41.8) and UHDL ($p<0.001$, 95% CI for OR:4.2 (1.1-47.2) a were found to be statistically significantly different in adequate contol group compared to CSF group.

The Spearman's correlation test indicated a significant positive correlation between the average TFC and the UHDL ($r=0.62$, $p<0.001$) or UA levels ($r=0.53$, $p<0.001$)

but a negative correlation between the average TFC and plasma HDL-C level ($r= -0.330$, $p<0.001$) (Table 3).

Table 3. Pearson correlation analysis between mean TFC and uric acid, HDL , UHDL measurements

	Pack.year	
	r	P
Uric acide , (mg/dL)	0.538	<0.0001
HDL-C, (mg/dL)	-0.330	<0.0001
UHDL(%)	0.620	<0.0001

HDL-C: High-Density Lipoprotein Cholesterol, UHDL=Uric Acid to HDL-Cholesterol Ratio

DISCUSSION

This study indicates that the UHDL performs better than UA and HDL-C in predicting the CSF. Another crucial finding of our study is that the UHDL shows a significant correlation with the average TFC. The positive correlation between serum UA and CVDs has been known for years (14,15). Several epidemiological studies have found significant relationships between serum UA levels and various cardiovascular conditions such as hypertension, MS, CAD, cerebrovascular disease, vascular dementia, (16-19).

Although several studies have addressed the CSF phenomenon, the pathophysiological mechanism of CSF has not been elucidated. Several mechanisms, including inflammation, diffuse atherosclerosis, increased platelet aggregation, small vessel dysfunction, and endothelial dysfunction, have been proposed in the CSF pathogenesis (4,20).

Some studies implicated decreased nitric oxide (NO) levels and increased endothelin-1 (ET-1) levels in the CSF pathogenesis (21,22). A relationship has been observed between serum UA levels and endothelial dysfunction. It is known that hyperuricemia induces endothelial dysfunction by decreasing NO production and resulting in mitochondrial calcium overload through the sodium-calcium ($\text{Na}^+/\text{Ca}^{2+}$) exchanger (23).

There are findings suggesting that inflammation takes a vital role in the pathogenesis of CSF, as in other CVDs (24). Turhan et al. (25) found higher levels of E-selectin, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), which are potential markers of inflammation or endothelial activation, in cases with CSF. UA can trigger the increase of vascular smooth muscle cells and pro-inflammation (21). By inducing CRP expression in the endothelial cells, UA exerts both proinflammatory and proatherogenic effects (26).

There is strong evidence to suggest that CSF develops due to the coronary microvascular dysfunction (27). Patients with CSF were reported to have impaired coronary flow reserve (CFR), which indicates impaired coronary microvascular function. Decreased CFR was considered as an early sign of coronary atherosclerosis (20).

Kanbay et al. (28) reported that UA plays a vital role in coronary microvascular disease.

Another mechanism involved in the CSF pathogenesis is diffuse atherosclerosis. Using intravascular ultrasound (IVUS) and CFR measurement, some studies have demonstrated widespread calcification along the walls of the coronary vessels, diffuse intimal thickening, and non-obliterative atheromatous coronary alterations in cases with CSF (22,29).

The oxidants produced by xanthine oxidase during the production of UA may impair the synthesis and availability of NO (30). UA can trigger vascular smooth muscle proliferation and proinflammatory state (10). UA can also stimulate CRP expression in endothelial cells and exert proinflammatory and pro-atherogenic effects (31). Also, hyperuricemia is a sign of insulin resistance and results in intracellular glucose uptake (32). All of these detrimental effects of UA result in endothelial dysfunction and atherosclerosis. Some studies have shown that UA may slow the coronary blood flow by increasing calcification in the CAs (33,34). It was also reported that increased serum UA levels could cause CSF by inducing oxidative stress through oxidation of low-density lipoproteins (33).

Several studies revealed an association between UA levels and the factors that were proposed in the CSF pathogenesis, such as inflammation, atherosclerosis, microvascular dysfunction, and endothelial dysfunction. Sanati et al. (11) did not find a significant difference between the serum UA levels of cases with CSF and NCA, although they found HDL-C levels lower in the CSF group. In their study, UA levels did not predict CSF, while serum HDL-C level was found to be a determinant of CSF development. Hawkins et al. (35) also suggested that a low serum HDL-C level could independently predict the CSF development. Naing et al. (36) showed that there was a significant relationship between serum UA levels and CSF, and serum UA was the one of independent determinants of CSF.

The present study found higher UA and lower HDL-C levels in the CSF group than those in the controls. Serum UA and HDL-C levels were found to predict CSF.

Koçak et al. (12) found that UHDL indicated poor glycemic control in patients with MS and type-II DM who had high risk of developing CVDs. Also, UHDL was found to be superior to serum UA levels in predicting MS.

Several studies found an association between UA levels and the CSF. However, to our knowledge, there has been no study investigating the association between UHDL and CSF so far. This study has found higher UHDL in cases with CSF compared to that in cases with NCA. Furthermore, UHDL performed better than UA and HDL-C levels in predicting the CSF.

The retrospective study design is among the limitations of this study, and the study design may have caused selection bias. The other limitation is the small size of the study sample.

CONCLUSION

The current study suggests that the UA levels and UHDL may be associated with the severity of CSF. Simple biochemical parameters such as UA and UHDL may serve as a predictor of CSF. More comprehensive prospective cohort studies are required to support current findings.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The retrospective study protocol was approved by the institutional review board and executed according to the principles in the Declaration of Harran University ethics committee number :76244175-050.04.04.

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