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Original Article

Serum uric acid and uric acid to HDL-cholesterol ratio in coronary artery fistulas

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Abstract

Aim: In this study, we aimed to evaluate retrospectively uric acid and uric acid / high-density lipoprotein (HDL) ratio in patients with coronary artery fistula who underwent coronary angiography in our cardiology clinic. Coronary artery fistulas (CAF) are seen most often congenitally but also may be acquired and often encounter an asymptomatic clinic. In chronic diseases, e.g., chronic kidney disease, metabolic syndrome, a decrease in HDL is observed, while high uric acid levels have been associated with adverse events.

Material and Methods: A total of 111 patients were included in the study, including 46 patients with coronary fistula and 65 controls with normal coronary arteries. Demographic data, laboratory parameters and structural features of the fistula were recorded. Transthoracic echocardiography was performed in all patients.

Results: Baseline characteristics were similar between the groups. Previous medications were similar between the two groups. Uric acid [5.9 (4.0-8.0) vs. 4.5 (3.5-8.3)) and uric acid / HDL ratio (14 (7-30) vs. 10 (5-32)] were found to be significantly higher in the fistula group (p <0.001). The creatinine, fasting glucose, cholesterol panel, and hemogram parameters were not significantly different between the groups. Right ventricular end-diastolic (RVED) diameter was significantly higher in CAF group (2.68±0.79, 2.50±0.35; p=0.03). The other echocardiographic measurements were not significantly different between the two groups.

Conclusion: The uric acid and uric acid / HDL ratio (UHR), which we can easily look at in peripheral blood, were found to be significantly elevated in fistula patients compared to the control group. The clinical significance of the result could be supported by large-scale studies in the future.

Keywords: Coronary fistula; uric acid; uric acid/HDL ratio

INTRODUCTION

Coronary artery fistulas (CAFs) are abnormal direct connections of coronary arteries to any cardiac cavity or major thoracic vessels (1). The frequency of CAF, which is seen equally in both sexes, is 0.002% in the general population (2, 3). Although fistulas are usually congenital; they may also be acquired secondary to biopsies after cardiac transplant or cardiac surgery (4, 5). About 80% of congenital fistulas are isolated whereas 20% may be associated with other congenital malformations including atrial or ventricular septal defects, Tetralogy of Fallot and patent ductus arteriosus (6). Most cases of CAFs are clinically asymptomatic and incidentally detected. However, they can be associated with dyspnea, angina, arrhythmia, congestive heart failure clinic (7). The most common (50-60%) origin of the fistula is the right coronary artery (RCA) and the most common drainage sites are the right heart chambers (80%) (8).

Uric acid is synthesized by xanthine oxidase during purine metabolism. It is known that hyperuricemia is closely associated with obesity, hypertension, elevated triglycerides (TG), and low high-density lipoprotein (HDL) cholesterol (9-11). Epidemiological studies have also shown that elevated uric acid is a risk factor for adverse cardiovascular events and a negative prognostic factor for mortality in patients with heart failure (12). Studies have shown a positive and significant relationship between uric acid and inflammation. It has been claimed that the effects of uric acid on mortality and poor prognosis are through its pro-inflammatory mechanism (13).

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Low HDL-cholesterol and high low-density lipoprotein (LDL) cholesterol and TG levels are known to be risk factors for diabetes mellitus (DM) type 2, metabolic syndrome and cardiovascular diseases. HDL levels have a negative correlation with oxidative stress and degree of inflammation in chronic diseases (14-16).

Uric acid to HDL-cholesterol ratio (UHR) has been studied in diabetic patients and was found to be a better metabolic control marker than uric acid (17). As far as we know, there is no previous study searching the relationship between uric acid, UHR and coronary artery fistulas.

For this reason, we aimed to investigate the relation of uric acid and UHR with CAF.

MATERIAL and METHODS

This is a single-center study performed in Bolu Abant Izzet Baysal University Medical Faculty Hospital. The local institutional board approved the study. A total of 111 patients; 46 patients with coronary fistula with no associated critical coronary artery stenosis and 65 controls with normal coronary arteries detected by coronary angiography, were analyzed retrospectively. Coronary angiography was performed in patients having typical angina complaints, ischemic changes in the electrocardiogram (ECG), ST-segment depression on the treadmill stress test or reversible perfusion defect in myocardial perfusion scintigraphy. Patients present with acute coronary syndromes were not included. CAF patients had normal coronary arteries or non-critical coronary artery stenosis except fistula. Demographic data and laboratory parameters of all participants were recorded. The fistula localization and drainage location and structural features of the fistula were recorded.

Exclusion criteria of our study were patients with history of acute coronary syndrome within 6 months, history of coronary artery stenting or by-pass operation, pregnancy, active cancer, drug use (thiazides, furosemide, etc.) which may affect uric acid levels, presence of systemic inflammatory disease, presence of known hemolytic status and presence of end-stage renal failure (eGFR <15 ml/min /1.73 m2). Hypertension (HT) was defined as blood pressure >140/90 mmHg or using antihypertensive drugs. The definition of diabetes mellitus (DM) was defined as getting anti-diabetic drug or fasting blood glucose level> 126 mg/dl.

Laboratory data

Peripheral venous blood samples were drawn from the patients who were admitted for angiography. Serum glucose, creatinine, total cholesterol, HDL-cholesterol, LDL-cholesterol, TG, and uric acid were measured using an automatic biochemical analyzer (Architect C8000, USA). Complete blood count was determined using simultaneous optical and impedance measurements (Cell Dyn 3700; Abbott Diagnostics, Lake Forest, Illinois, USA). UHR was calculated by dividing serum uric acid level by HDL.

Echocardiographic evaluation

In all echocardiographic procedures, the 4-Mhz transducer of Vivid S6 (GE Vingmed, N-3191 Horten-Norway) was used. The study was performed by continuous single-lead ECG recording and the mean of 3 consecutive cardiac cycles were taken. Criteria of the American Society of Echocardiography were followed in two-dimensional and pulsed doppler measurements (18). Echocardiography was performed by a single-blind cardiologist while patients were in left lateral position and left ventricular end-diastolic diameter (LVEDD, mm), left ventricular end-systolic diameter (LVESD, mm), interventricular septum thickness, left ventricular posterior wall thickness, left atrium diameter, left ventricular ejection fraction (LVEF%), right ventricular end-diastolic diameter (RVEDD, mm) measurements were taken from each participant. Simpson's rule was used in the prediction of LVEF (19).

Coronary angiography evaluation

All coronary angiographies were performed through the femoral or radial artery using the Seldinger technique. The coronary angiographic evaluation of patients was made by at least two cardiologists who were blinded to the study. Origin of the fistulas, discharge site of the fistulas and shape of the fistulas were evaluated.

Statistical analysis

Statistical analyses were carried out using SPSS 18.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA). Distribution of the variables in study groups were analyzed by the Kolmogorov-Smirnov test. Homogenously distributed variables were compared by the student t-test and expressed as mean ± standard deviation. Non-homogenously distribution was compared with the Mann Whitney U test and expressed as median (interquartile range).The Chi-square test was used for comparison of nonparametric variables between study groups.

Univariate analysis was used to reveal the association of variables with CAF. Thereafter, to determine the independent prognostic factors of CAF, multivariate logistic regression model with the forward stepwise method was used with variables which were found significant in univariate analysis. All results were considered statistically significant at the level of $p < 0.05$.

RESULTS

Baseline clinical characteristics and previous medications were similar between CAF and control groups (Table 1).

Uric acid (5.9 (4.0-8.0) vs. 4.5 (3.5-8.3)) and UHR (14 (7-30) vs.10 (5-32)) were significantly higher in the fistula group ($p<0.001$). The creatinine, fasting glucose, cholesterol levels, and hemogram parameters were not significantly different between the groups (Table 2).

The angiographic features of fistula patients are shown in Table 3. The most common fistula localization was observed in RCA (33%). The most common drainage location of the fistula was the right ventricle (35%). The most common shape of the fistula was multiple tortuous form (22%).

Table 1. General characteristics of the study groups

Baseline characteristics	Fistula (n=46)	Control (n=65)	P
Age (mean ±SD) (years)	58±12	56±8	0.20
Male/female	25/21	30/35	0.39
Hypertension (%)	8(17%)	15 (23%)	0.407
Smoking	24 (52%)	33 (51%)	0.170
Family history	8 (17%)	10 (15%)	0.216
Diabetes mellitus	10 (21%)	9 (14%)	0.333
Acetyl salicylate	14 (30%)	18 (28%)	0.132
Statin	12 (26%)	15 (23%)	0.212
B-blocker	14 (30%)	17 (26%)	0.172

Abbreviation: SD: Standard deviation

Table 2. Laboratory data of the study cohort

	Fistula group (n=46)	Control group (n=65)	P value
	Median (Min-Max.)		
Creatinine (mg/dl)	0.80 (0.54-1.73)	0.79(0.35-1.35)	0.60
Fasting plasma glucose (mg/dl)	127(79-367)	98(68-414)	0.83
HDL-cholesterol (mg/dl)	42(25-81)	44(25-104)	0.06
Triglyceride (mg/dl)	149 (51-553)	150(43-553)	0.54
Uric acid (mg/dl)	5,9 (4-8)	4.5(3.5-8.3)	**<0.001**
UHR	14(7-30)	10(5-32)	**<0.001**
Hemoglobin (gr/dl)	13.8±1.8	13.4±1.8	0.28
Platelet counts (k/mm^3)	271±82.72	253±78	0.77
Total cholesterol (mg/dl)	187 ±53	181±45	0.53
LDL-cholesterol (mg/dl)	114±50	106±34	0.36

Abbreviation: LDL=Low density lipoprotein cholesterol,
HDL= High density lipoprotein cholesterol,
UHR =Uric acid to HDL ratio

The echocardiographic measurements, except RVDD, were not significantly different between two groups, RVEDD was slightly higher in the CAF group (2.68±0.79 mm vs. 2.50±0.35 mm; p=0.03).

Multivariate logistic analysis forward stepwise model including UHR, uric acid, HDL, LDL, and TG revealed that uric acid (95% CI for OR:1.909(1.332-2.736), p<0.001) and UHR (95% CI for OR:1.302(1.023-2.123), p=0.024) were significant predictors of CAF.

Table 3. Angiographic findings of the fistula group

Variables	Number (%)
Origin of fistulae	
RCA	15(33%)
CX	14(30%)
LAD	12(26%)
LMCA	5(11%)
Discharge site of fistulae	
Right ventricle	16(%35)
Pulmonary artery	13(%28)
Left ventricle	11(%24)
Right atrium	6(%13)
Shape of fistulae	
Multiple tortuous	22(%48)
Single tortuous	19(%41)
Straight	5(%11)

Abbreviation: SD: Standard deviation

DISCUSSION

In our study, we found that uric acid level and UHR were higher in patients with coronary fistula than in the control group. In addition, when we compared the transthoracic echocardiography findings of the two groups, we found that end-diastolic measurements of the right ventricle were significantly higher in fistula patients.

Coronary fistulas are most frequently detected incidentally during coronary angiography. However, when they are symptomatic, they may be present with dyspnea, fatigue, arrhythmia, congestive heart failure. Especially in large coronary fistulas, continuous flow leads to conditions such as angina and ischemia due to coronary stealing phenomenon even if there is no coronary artery disease (8).

The size of the fistula and the pressure difference, between the source of the fistula and the place where it drains, are decisive in the direction and amount of drainage (8). In approximately 90% of cases of coronary fistula, the direction of the shunt is from left to right (8). Similar to our study, the most common drainage site in the literature is the right ventricle (8). In animal models, Fiorilo's et al (26) have shown that continuous blood flow and volume load towards low-pressure right heart cavities may trigger oxidative stress and inflammation cascade in the chronic period. Therefore, our finding of higher uric acid level and UHR in the coronary fistula group may be potentially related to inflammation associated with fistula.

Coronary angiography is the gold standard method for the diagnosis of CAF. Other diagnostic tests were used physical examination, ECG, chest X-ray, transthoracic and transesophageal echocardiography, treadmill test, computed tomography, magnetic resonance imaging, intravascular ultrasound; but blood parameters were not mentioned in the literature (8). Echocardiography can be used to diagnose dilatation in various cardiac spaces depending on the location of the shunt (20). In our study, we found that RVEDD was significantly higher in fistula patients.

HDL and uric acid are easily measurable parameters in peripheral blood. Uric acid is a useful molecule for our body with its antioxidant and pro-inflammatory properties at normal levels. It increases the secretion of growth factors and cytokines in in-vitro studies (21). These positive effects are replaced by negative effects in the elevation of uric acid. Some studies suggest that elevated uric acid levels lead to deterioration of endothelial function, leading to the progression of atherosclerosis or hypertensive organ damage (13). Again; high uric acid levels were found to be independent risk factors for cardiovascular disease, and a predictor of mortality and negative prognostic factor for survival in patients with heart failure (12, 22). When studies are evaluated, it can be concluded that uric acid is not a catabolic marker alone and may also be associated with the common pathway associated with systemic inflammation resulting in HT, vascular diseases and renal insufficiency (23). Coronary fistulas are also thought to be associated with a low but continuous inflammatory burden (24).

In our study, HDL cholesterol levels were found to be low, although not statistically significant, in fistula patients. HDL cholesterol has antioxidant and anti-inflammatory mechanisms and mitigates endothelial dysfunction (25). Low HDL cholesterol levels may be one of the mechanisms leading to endothelial dysfunction in coronary artery fistula patients. We have found higher uric acid levels in fistula patients. Therefore, another mechanism that may be associated with endothelial dysfunction may be the deteriorative effects of high uric acid on the endothelium. Long-term volume loading into the low-pressure right heart cavities is another mechanism that may result in endothelial dysfunction.

In a recent study, UHR was found to be a predictor of metabolic syndrome in type 2 DM patients and was a better marker than uric acid alone. In the same study, UHR has been shown to be a marker for diabetes control with high sensitivity and specificity (17).

In the present study, uric acid and HDL cholesterol, which have been shown to be associated with a wide range of chronic diseases such as DM, chronic renal failure, congestive heart failure, and atherosclerosis, are the first to be studied in patients with coronary fistula.

Limitations of our study include being single-center and a retrospective cross-sectional design with a relatively small patient population. Another limitation of the study is the lack of mechanisms to fully explain the elevation of inflammatory markers such as uric acid and UHR in fistula patients. The lack of blood parameters used in the diagnosis and prognosis of coronary fistula patients in the literature makes it difficult to interpret the results of our study. However, our study is the first to show a high uric acid and UHR relationship with coronary fistulas.

CONCLUSION

The association of high uric acid and UHR levels with adverse events is known. In the future, large-scale and multi-centered studies may assess the role of uric acid and UHR levels in the diagnosis and prognosis of coronary fistula patients. In this way, these two parameters, which have the advantages of being cheap, simple and widely used, can be integrated into our daily practice in understanding the diagnosis and importance of fistulas.

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