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Original Article

A promising marker in patients with coronary artery ectasia: Uric acid / HDL ratio

Asli Kurtar Mansiroglu, Mehmet Cosgun, Isa Sincer, Yilmaz Gunes

Department of Cardiology, Faculty of Medicine, Abant Izzet Baysal University Hospital, Bolu, Turkey

Abstract

Aim: Elevated levels of uric acid and low levels of high-density lipoprotein (HDL) cholesterol are associated with cardiovascular events and mortality. We investigated a novel marker, uric acid/HDLratio (UHR), in coronary artery ectasia patients (CAE).

Materials and Methods: The present study included 104 patients (58 male, 46 female; mean age, 61±12 years) diagnosed as having isolated CAE and 110 controls (44 male, 66 female; mean age, 60±12 years) whose coronary artery findings were normal as revealed by coronary angiography. Medical records of all the patients were reviewed and the data were collected retrospectively. Baseline characteristics, hematologic and biochemistry parameters were recorded, and we calculated the value of UHR

Results: The CAE group had significantly higher values of uric acid (6.48±1.62 vs. 5.37±1.12; p<0.001) and UHR (0.15±0.05 vs. 0.11±0.05; p<0.001). Spearman's correlation test showed a significant association of uric acid and UHR with CAE (r=0.40, p<0.001 and r=0.51, p<0.001, respectively). On the other hand, HDL had a negative correlation with the presence of CAE (r=0.44, p<0.001). A receiver operating curve (ROC) analysis revealed that a cut-off>0.120 UHR (%) values had a sensitivity of 72% and specificity of 68% for the determination of CEA.

Conclusion: We observed in our study the finding in which the uric acid and UHR values were higher in individuals with CAE compared to non-CAE subjects. There was an association between UHR and CAE.

Keywords: Coronary artery ectasia; uric acid; uric acid/ HDL ratio

INTRODUCTION

Coronary artery ectasia (CAE) refers to the dilatation of a coronary artery to1.5 folds or more than its normal diameter (1). It can be either congenital or acquired (2). Inflammation, neuro-humoral process, and cardiovascular risk factors have been associated with CEA, yet the underlying mechanism of ectasia is not fully understood (3). Etiological factors include a history of connective tissue diseases, inflammatory diseases, and coronary interventions, with atherosclerosis manifesting as the most common etiology (2). Coronary angiography is the gold standard for both diagnosing and providing information on location, size, and number of CAE (1).

The incidence of CAE in patients receiving coronary angiography was 0.3- 5.3% (4). CAE is mostly localized in the right coronary artery, while the left main coronary artery is the least affected (1). While it may be clinically asymptomatic, the most common presentation in CAE patients is stable angina (5). CAE is associated with thrombosis, distal embolization, vasospasm, slow flow, dissection, shunt formation, rupture, and development of myocardial infarction, which may lead to increased coronary mortality and morbidity (6).

Uric acid to HDL-cholesterol ratio is a new parameter investigated in patients with type 2 diabetes mellitus and coronary artery fistula (7). HDL levels have a negative correlation with oxidative stress and the degree of inflammation in chronic diseases (8). Additionally, studies have shown that elevated uric acid is a risk factor for adverse cardiovascular events (9). It is known that a positive and significant relationship exists between uric acid and inflammation. The effects of uric acid on mortality and poor prognosis may result from its pro-inflammatory mechanism. An increase in UHR may be due to increased uric acid or decreased HDL.

To the best of our knowledge, little is known about the relationship between CAE and UHR in the literature. Therefore, we have investigated the correlation between the presence of CAE and UHR.

MATERIALS and METHODS

This single-center study was conducted on a total of 104 patients (58 male, 46 female; mean age of 61±12 years)

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Corresponding Author: Asli Kurtar Mansiroglu, Department of Cardiolog, Abant Izzet Baysal University Hospital, Bolu, Turkey
E-mail: dr.asli.kurtar@gmail.com

with coronary ectasia with no associated coronary artery stenosis and 110 controls (44 male, 66 female; mean age of 60±12 years) whose coronary artery findings were normal as revealed by coronary angiography. Retrospective analyses were performed in the patients who had undergone coronary angiography in Bolu Abant Izzet Baysal University Hospital between January 2017 and July 2019. Patients' demographic data such as age, gender, height, weight, blood pressure, heart rate, medication, comorbidity, and smoking were obtained from database records and patient files. The study was approved by the institutional review board of the Bolu Abant Izzet Baysal University (33443051-929).

Falsetti and Carroll defined CAE as the dilation of a coronary artery to at least 1.5 to 2-fold than the diameter of the adjacent normal coronary vessels (10). A normal segment referred to a coronary artery segment without ectasia and stenosis on coronary angiography.

Patients who had blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs were considered as having hypertension (HT). Diabetes mellitus (DM) was determined by the current use of antidiabetic drugs, fasting blood glucose level> 126 mg/dl, or HbA1c ≥7.An individual who was active smoker or had a smoking history of > 10 packs per year was considered as a smoker.

Coronary angiography was used for all patients presenting with typical angina symptoms, suspected or positive results for ischemia in the treadmill stress test or myocardial perfusion scintigraphy.

Patients were excluded from the study for the following reasons: pregnancy, systemic inflammatory or infectious disease, any known hematological disease, neoplasm, surgery or trauma within 2 weeks, end-stage renal failure (eGFR< 15 ml/min/1.73 m²), liver failure, and use of thiazides, furosemide, and lipid-lowering drugs. Exclusion criteria also included a history of acute coronary syndromes, previous myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting, heart failure, and severe valvular disease.

Laboratory data

Peripheral venous blood samples were gathered from the patients who were admitted for coronary angiography. Levels of serum glucose, creatinine, uric acid, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol 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 uric acid level by HDL cholesterol.

Statistical analysis

The data were analyzed using statistical software called SPSS 18.0 Statistical Package Program for Windows (SPSS Inc., Chicago, Illinois, USA). Quantitative and qualitative variables are expressed as mean±standard deviation (SD) and numbers and percentages. Student t-test and Mann-Whitney U-test were used for categorical variables with normal and non-normal distributions, respectively. Chi-square test was employed for qualitative variables. Spearman's correlation analyses were used to evaluate the correlations between CAE and UHR. Multiple logistic regression analysis was used to analyze independent predictors of CAE. A receiver operating curve (ROC) analysis was used to find the sensitivity and specificity of UHR to predict the presence of CAE. P<0.05 was taken into account as a statistically significant value for all analyses.

RESULTS

Demographic and clinical data of patients are summarized in Table 1. No significant difference was found between demographic data of groups. Laboratory data of the study groups are summarized in Table 2. The values of uric acid (6.48±1.62 vs. 5.37±1.12, p<0.001) and UHR were significantly higher (0.15±0.05 vs. 0.11±0.05, p<0.001) whereas HDL value was significantly lower (47±12 vs. 51±15, p <0.001) in the CAE group. The creatinine, fasting glucose, cholesterol levels except for HDL, and hemogram parameters did not differ significantly between the groups (Table 2).

Table 1. General characteristics of the study group

Baseline characteristics	Control group (N=110)	CAE group (N=104)	p value
Age, years (mean ± SD)	60 ± 12	61 ± 12	0.33
BMI (kg/m²)	29 ± 5	28 ± 4	0.62
Male/female	44/66	58/46	0.12
Hypertension (%)	53 (48%)	57 (55%)	0.24
Smoking (%)	22 (20%)	32 (30%)	0.07
Family history (%)	16 (15%)	22 (21%)	0.20
Diabetes mellitus (%)	19 (17%)	25 (24%)	0.15
Acetylsalicylate use (%)	31 (28%)	37 (35%)	0.08
ACE inhibitor use (%)	15 (14%)	20 (19%)	0.16
B-blocker use (%)	31 (28%)	34 (33%)	0.47
ARB use (%)	19 (17%)	16 (15%)	0.71

ACE: Angiotensin-Converting Enzyme; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CAE: Coronary Artery Ectasia; SD: Standard Deviation

The distribution results of coronary ectasia in coronary angiography were as follows: %5 in the left main coronary artery, %53 in the left anterior descending artery, %32 in the circumflex artery, and %52 in the right coronary artery (Table 3).

Table 2. Laboratory data of the study group

Variables	Control group (N=110)	CAE group (N=104)	p value
Creatinine (mg/dl)	0.87 ± 0.15	0.90 ± 0.18	0.23
Fasting plasma glucose (mg/dl)	113 ± 55	113 ± 37	0.33
LDL-cholesterol (mg/dl)	113 ± 33	122 ± 30	0.22
HDL-cholesterol (mg/dl)	51 ± 15	47 ± 12	< 0.001*
Triglyceride (mg/dl)	184 ± 119	173 ± 89	0.36
Total cholesterol (mg/dl)	190 ± 39	210 ± 78	0.27
Uric acid (mg/dl)	5.37 ± 1.12	6.48 ± 1.62	< 0.001*
UHR (%)	0.11 ± 0.05	0.15 ± 0.05	< 0.001*
Hemoglobin (gr/dl)	13.3 ± 1.4	13.6 ± 1.2	0.22
MPV (fl)	8.19 ± 1.52	8.06 ± 1.06	0.55
Platelet counts (k/mm^3)	237 ± 56	234 ± 63	0.19
WBC (x10^{3}µl)	7.1 ± 2.2	7.40 ± 2.3	0.12
Hematocrit	40 ± 4	42 ± 6	0.22

LDL: Low Density Lipoprotein Cholesterol; HDL: High Density Lipoprotein Cholesterol; UHR: Uric Acid to HDL-Cholesterol Ratio; MPV: Mean Platelet Volume; WBC: White Blood Cell
x= Statistically significant

Table 3. The distribution of coronary ectasia in coronary arteries

Coronary artery	Coronary artery ectasia (%)
LMCA	5 (5%)
LAD	55 (53%)
CX	33 (32%)
RCA	54 (52%)

LMCA: Left Main Coronary Artery; LAD: Left Anterior Descending Artery; CX: Circumflex Artery; RCA: Right Coronary Artery

Spearman's correlation test showed a significant association of uric acid and UHR values with CAE (r=0.40, p<0.001 and r=0.51, p<0.001, respectively). However, a negative correlation was found between HDL and the presence of CAE (r=0.44, p<0.001).

Multiple logistic regression analysis was also performed to define the predictive value of variables for the presence of CAE. Smoking, uric acid, HDL, UHR, and using acetylsalicylate values were included in this model. Only UHR was found to be independently associated with CEA (Table 4).

A receiver operating curve (ROC) analysis revealed that a cut-off>0.120 UHR values had a sensitivity of 72% and specificity of 68% for determination of CEA (AUC = 0.737, 95% CI, 0.670-0.804).

Table 4. Multiple logistic regression analysis for independent predictors of coronary artery ectasia

	OR	95% CI	p value
Smoking	0.231	(0.098 - 0.502)	0.074
Acetylsalicylate	0.782	(0.716 - 1.013)	0.435
HDL	0.951	(0.891 - 1.014)	0.172
Uric acid	1.460	(0.850 - 2.508)	0.171
UHR (%)	1.331	(1.150 - 1.535)	< 0.001*

CI: Confidence Interval, OR: Odds Ratio,
HDL= High Density Lipoprotein Cholesterol, UHR: Uric Acid to HDL -Cholesterol Ratio

DISCUSSION

The principal finding of the present study is that uric acid level and UHR were higher in patients with coronary ectasia than normal coronary artery group.

Although the underlying mechanism of coronary ectasia remains unclear, several studies reported that the atherosclerotic process and inflammation were associated with CAE (11,12). In the literature, elevated inflammatory markers such as C-reactive protein, interleukin-6, tumor necrosis factor-alfa, matrix metalloproteinases, and white blood cell counts are associated with the presence and severity of CAE (3).

The pathogenesis of CAE includes inflammation in the arterial wall and expansive remodeling by enzymatic degradation of the extracellular matrix by metalloproteinases and other lytic enzymes (13). Histopathological examination of the ectatic segment revealed atherosclerotic changes and thinner tunica media of the artery (14).

As the final product in purine metabolism, uric acid is synthesized by xanthine oxidase. Multiple studies have associated hyperuricemia with cardiovascular disease, coronary artery ectasia, hypertension, metabolic syndrome, coronary artery disease, vascular diseases such as cerebrovascular disease, vascular dementia, preeclampsia, and kidney disease (15,16). Studies emphasizing the pathogenic mechanisms of uric acid refer to an inflammatory response as the primary mechanism for these vascular and cardiovascular diseases (15).

HDL cholesterol has antioxidant and anti-inflammatory mechanisms (16). The mechanism by which inflammation increases atherosclerosis and CAE is probably multifactorial, but changes in the amount and structure of HDL during inflammation may also involve in this process. HDL levels decrease with inflammation and there are significant changes in HDL-associated proteins (17). A study in familial hypercholesterolemia patients demonstrated that there is an increased prevalence of coronary ectasia related to lower levels of HDL cholesterol (18). Jafari et al. found that patients with CAE had significantly lower HDL cholesterol and a higher LDL/HDL ratio compared to the control group with normal coronary angiograms (19).

In a recent study, UHR was found to be a predictor of metabolic syndrome in type 2 DM patients and suggested as a marker for the control of diabetes with high sensitivity and specificity (7). In another study, UHR was found to be a strong predictor of diabetes control in men with type 2 diabetes mellitus (20).

UHR is a new marker consisting of two values, namely the uric acid and HDL cholesterol. Using UHR, we can determine the degree of inflammation that may also be involved in ectasia formation, which necessitates a higher level of uric acid or a lower level of HDL cholesterol, or both.

We assume that UHR should be the first parameter to investigate in patients with CAE. Providing advantages such as being inexpensive, simple, and widely used, uric acid and UHR are easily available parameters in the evaluation of the inflammatory process in CAE patients.

Single-center and retrospective design are important limitations of this study. In addition, cellular studies are required for the mechanism leading to CAE in individuals with high UHR.

CONCLUSION

Elevated uric acid and UHR values were individually associated with the presence of CAE. Prospective and multicenter studies with large sample size are needed to understand the importance of these findings in the diagnosis and follow-up of CAE patients.

Conflict of interest : The authors declare that they have no competing interest.

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