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Could uric acid to high-density lipoprotein cholesterol ratio be used to predict late-stage saphenous vein graft disease after coronary artery bypass graft surgery?

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ABSTRACT

Objectives: Various vascular grafts are used in coronary artery bypass graft (CABG) surgeries, however, the most commonly used one is the saphenous vein graft (SVG). Various studies conducted on this topic have found a relationship between uric acid to HDL-C (UHR) and cardiovascular diseases. In this current study, we aimed to investigate the predictive importance of UHR value in predicting long-term SVG disease in patients who underwent CABG surgery.

Methods: Patients who had a history of CABG surgery at least one year prior, had stable angina pectoris, and underwent coronary angiography between January 01, 2016 and January 01, 2020, were included in the study retrospectively. Patients with open saphenous veins were defined as Group 1, and patients who had 50% or more stenosis in at least one SVG after coronary angiography, were defined as Group 2.

Results: The median age of the 204 patients included in Group 1 and 292 patients in Group 2 were 65 (38-77) years and 66 (45-79) years, respectively (p = 0.251). The two groups were similar in terms of gender, hypertension, chronic obstructive pulmonary disease rates, history of cerebrovascular events, ejection fraction, body mass index, and current medical treatments. In univariate analysis, SVG disease was found to significantly correlate with diabeter mellitus (odds ratio [OR]: 1.644, 95% confidence interval [CI]: 1.190-1.985, p = 0.008), current smoking (OR: 0.875, 95% CI: 0.669-0.940, p = 0.030), number of patients with target artery diameter < 1.5 mm (OR: 1.945, 95% CI: 1.221-2.398, p < 0.001), age of SVG (OR: 2.960, 95% CI: 1.980-4.168, p < 0.001), uric acid (OR: 1.241, 95% CI: 1.078-1.592, p = 0.004), triglyceride (OR: 0.780, 95% CI: 0.569-0.935, p = 0.044) and UHR (OR: 1.894, 95% CI: 1.384-2.896, p < 0.001).

Conclusions: In this study, we showed that we can predict saphenous vein graft occlusion with serum UHR value.

Keywords: Coronary artery bypass graft, inflammation, cholesterol, saphenous vein, occlusion

Today, coronary artery bypass graft (CABG) surgery is an indispensable treatment method for some patient groups despite advances in endovascular technology. Various vascular grafts are used in these

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surgeries, however, the most commonly used one is the saphenous vein graft (SVG) [1]. Although SVGs are widely preferred by surgeons due to their ease of preparation and practicality, patency difficulties do arise. About half of these vessels can be occluded in the 10th year after CABG operations. Surgical problems play a role in early occlusion but the main occlusion mechanism after the first year is atherosclerotic processes that begin with intimal hyperplasia. Inflammation also plays an important role in these processes [2, 3].

It has been shown that high uric acid blood levels decrease nitric oxide release and are associated with diseases such as endothelial dysfunction, atherosclerosis, and hypertension [4]. On the contrary, high-density lipoprotein cholesterol (HDL-C) is known for its anti-inflammatory and vasorelaxant properties and has protective properties from atherosclerosis [5]. It has been shown that there is a relationship between coronary artery plaque load and HDL-C [6]. Various studies conducted on this topic have found a relationship between uric acid to HDL-C (UHR) and metabolic syndrome and atherosclerotic diseases [7, 8].

The purpose of the current study was to look at the predictive importance of UHR value in predicting long-term SVG disease in patients who underwent CABG surgery.

METHODS

Patients who had a history of CABG surgery at least one year prior had stable angina pectoris and underwent coronary angiography between January 01, 2016, and January 01, 2020, were included in the study retrospectively. The information on the patients was obtained from the data system of the coronary angiography unit and the hospital data recording system. Demographic data of the patients and hemogram (white blood cell, platelet, hematocrit, etc.) and biochemical parameters [urea, creatinine, low-density lipoprotein-cholesterol (LDL-C), HDL-C collected at the time of admission were recorded. Patients with the acute coronary syndrome, heart failure, severe heart valve disease, malignancy, renal failure (creatinine > 1.5 mg/dL), gout disease, familial hyperlipidemia, and autoimmune disease, were all excluded from the study. Following the application of the exclusion criteria, 496 patients were included in the study.

Following a study of baseline clinical demographic variables, the following were identified: Chronic obstructive pulmonary disease was defined as having a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity of less than 70%. Use of at least one antihypertensive medication and/or arterial blood pressure greater than 140/90 mmHg were considered to be symptoms of hypertension. Diabetes mellitus was defined as the use of antidiabetic medications, and fasting blood glucose levels over 126 mg/dL or 200 mg/dL while being examined regularly. Finally, a neurological disability that has existed for at least 24 hours was considered a sign of a preoperative cerebrovascular event.

All coronary angiographies were performed after obtaining informed consent from the patients and were performed using the Judkin method via the femoral, radial, or brachial arteries. Selective images of all grafts were obtained with appropriate catheters. If the SVG did not display selectively, aortography was performed. All saphenous vein grafts were evaluated in at least two view planes. As a result of the evaluations made by two experienced cardiologists, patients with 50% or more stenosis in at least one SVG were defined as the SVG disease group. The patients were divided into 2 groups according to the presence of saphenous vein disease. Patients with open saphenous veins were defined as Group 1, and patients who had 50% or more stenosis in at least one SVG after coronary angiography, were defined as Group 2.

The blood parameters of all patients were evaluated from blood samples taken from peripheral venous vascular structures during hospitalization. These evaluations were performed by blood counts in EDTA-coated tubes. An automatic analyzer was used for the measurement of hematological parameters. Biochemical parameters were calculated using a molecular analyzer. In the measurements made, the UHR value was calculated as follows: UHR= Uric acid (mg/dL) / HDL- C (mg/dL).

Statistical Analysis

The Statistical Package for the Social Sciences was used to examine statistical data (IBM SPSS Statistic Inc. version 21.0, Chicago, IL). Nominal variables were expressed as frequency and percentage, whereas continuous and ordinal variables were ex-

pressed as mean standard deviation or median (minimum-maximum). Data distribution was determined using the Shapiro-Wilk and Kolmogorov-Smirnov tests for normalcy. When comparing two groups of continuous variables with a normal distribution, the Student's t-test was used. When there was no normal distribution for the continuous variables, the Mann-Whitney U test was used to compare the two groups. For nominal variables, the Chi-square test was employed to compare two groups. Binary logistic regression analysis was used to evaluate the predictors of SVG disease. For all tests, a p value of < .05 was accepted as statistically significant. The area under the curve (AUC) for UHR was computed using a receiver-operating characteristic (ROC) curve for the prediction of SVG disease.

RESULTS

The median age of the 204 patients included in Group 1 and 292 patients in Group 2 were 65 (38-77) years and 66 (45-79) years, respectively (p = 0.251). The two groups were similar in terms of gender, hypertension, chronic obstructive pulmonary disease rates, history of cerebrovascular events, ejection fraction, body mass index, and current medical treatments (Table 1). The rates of diabetes mellitus, current smoking rates, and number of patients with target diameter artery < 1.5 mm were higher in Group 2 (p = 0.007, p = 0.024, and p < 0.001 respectively). The age of SVGs was significantly higher in Group 2 (p < 0.001) (Table 1).

Table 2 lists the patient's entrance laboratory results. White blood cell, hematocrit, platelet, creatinine,

Table 1. Demographic and preoperative features of the patients

Variables	Group 1 (n = 204)	Group 2 (n = 292)	*p* value
Age (years)	65 (38-77)	66 (45-79)	0.251‡
Female gender, n (%)	38 (18.6)	61 (20.9)	0.535*
Hypertension, n (%)	165 (80.9)	226 (77.4)	0.348*
Diabetes mellitus, n (%)	37 (18.1)	84 (28.8)	**0.007***
Current smoker, n (%)	29 (14.2)	65 (22.3)	0.024*
COPD, n (%)	21 (10.3)	33 (11.3)	0.723*
Previous CVA, n (%)	17 (8.3)	29 (9.9)	0.546*
BMI (kg/m^2)	27.3 (24-40)	27.6 (25-39.8)	0.294‡
Ejection fraction (%)	45 (35- 5)	40 (30-55)	0.078‡
β- Blocker therapy, n (%)	178 (87.3)	260 (89)	0.542*
ARB/ACE-I therapy, n (%)	162 (79.4)	218 (74.7)	0.216*
DAPT, n (%)	32 (16.7)	35 (12)	0.236*
Acetylsalicylic acid, n (%)	133 (65.2)	185 (63.4)	0.674*
Clopidogrel, n (%)	19 (6.3)	21 (7.2)	0.393*
Oral anticoagulant, n (%)	17 (8.3)	19 (6.5)	0.440*
Statin use, n (%)	172 (84.3)	233 (79.8)	0.245*
LITA usage, n (%)	200 (98)	289 (99)	0.631*
Target artery diameter <1.5 mm, n (%)	27 (13.2)	79 (27.1)	**< 0.001***
Number of SVG, n (range)	3 (1-5)	3 (1-4)	0.217‡
Age of SVG (years)	3 (1-11)	7 (1-16)	**< 0.001‡**

*Chi-square test, ‡Mann Whitney U test (Data is expressed as median (minimum-maximum)) ACE-I = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BMI = Body mass index, CVA = Cerebrovascular accident, COPD = Chronic obstructive pulmonary disease, DAPT = Dual antiplatelet therapy, LITA = Left internal thoracic artery, SVG = Saphenous vein graft

Table 2. Admission laboratory variables of the patients

Variables	Group 1 (n = 204)	Group 2 (n = 292)	*p* value‡
White blood Cell (10^3/μL)	7.8 (4.9-16.3)	8.1 (4.5- 5.1)	0.101
Hematocrit (%)	37 (33-47)	40 (34-46)	0.287
Platelet (10^3/μL)	234 (140-440)	241 (132-424)	0.446
Creatinine (mg/dL)	0.92 (0.8-1.5)	0.94 (0.7-1.5)	0.667
Urea (mg/dL)	18 (14-29)	16 (18-33)	0.192
Albumin (g/L)	37 (35-54)	39 (35-51)	0.794
Uric acid (mg/dL)	5.4 (3.2-8.1)	7.9 (3.5-9.8)	**0.002**
HDL-C (mg/dL)	37 (29-58)	34 (26-60)	0.076
LDL-C, mg/dL	114 (80- 226)	121 (85-210)	0.269
Total cholesterol (mg/dL)	187 (134-210)	191 (128-224)	0.118
Triglyceride (mg/dL)	161 (104-189)	169 (110-194)	**0.042**
UHR	0.15 (0.07-0.26)	0.24 (0.09-0.37)	**< 0.001**

‡Mann Whitney U test, LDL-C = Low density lipoprotein-cholesterol, HDL-C = High density lipoprotein-cholesterol, UHR = Uric acid to high density lipoprotein cholesterol ratio

urea, albumin, LDL-C, and HDL-C values did not significantly differ across the groups. Triglyceride levels, uric acid levels, and UHR levels were all significantly higher in Group 2 ($p = 0.042$, $p = 0.002$, and $p < 0.001$, respectively).

To determine the variables influencing SVG disease-occurring CABG surgeries, logistic regression analysis was carried out (Table 3). In univariate analysis, SVG disease was found to significantly correlate with diabetes mellitus (odds ratio [OR]: 1.644, 95% confidence interval [CI]: 1.190-1.985, $p = 0.008$), current smoking (OR: 0.875, 95% CI: 0.669-0.940, p =

Table 3. Logistic regression analysis to identify factors affecting development of saphenous vein graft disease

	Univariate analysis			Multivariate analysis		
Variables	***p value***	**Exp(B) Odds Ratio**	**95% CI Lower-Upper**	***p value***	**Exp(B) Odds Ratio**	**95% CI Lower-Upper**
Age	0.254	1.209	0.882-1.790	--	--	--
Hypertension	0.350	1.420	0.956-2.114	--	--	--
Diabetes mellitus	**0.008**	1.644	1.190-1.985	**0.035**	1.120	1.070-1.436
Current smoker	**0.030**	0.875	0.669-0.940	0.378	1.060	0.892-1.338
TAD < 1.5 mm, n (%)	**< 0.001**	1.945	1.221-2.398	**0.012**	1.344	1.110-1.742
Age of SVG	**< 0.001**	2.960	1.980-4.168	**< 0.001**	1.910	1.375-2.364
Uric acid (mg/dL)	**0.004**	1.241	1.078-1.592	--	--	--
HDL-C (mg/dL)	**0.081**	0.894	0.745-1.190	--	--	--
Triglyceride (mg/dL)	**0.044**	0.780	0.569-0.935	0.536	0.794	0.691- 1.010
UHR	**< 0.001**	1.894	1.384-2.896	**0.008**	1.290	1.060- 1.897

COPD = Chronic obstructive pulmonary disease, SVG = Saphenous vein graft, HDL-C = High density lipoprotein-cholesterol, UHR = Uric acid to high density lipoprotein cholesterol ratio, TAD = Target artery diameter

0.030), number of patients with target artery diameter < 1.5 mm (OR: 1.945, 95% CI: 1.221-2.398, p < 0.001), age of SVG (OR: 2.960, 95% CI: 1.980-4.168, p < 0.001), uric acid (OR: 1.241, 95% CI: 1.078-1.592, p = 0.004), triglyceride (OR: 0.780, 95% CI: 0.569-0.935, p = 0.044) and UHR (OR: 1.894, 95% CI: 1.384-2.896, p < 0.001). In multivariate analysis, diabetes mellitus (OR: 1.120, 95% CI: 1.070-1.436, p = 0.035), target artery diameter 1.5 mm (OR: 1.344, 95% CI: 1.110-1.742, p = 0.012), age of SVG (OR: 1.910, 95% CI: 1.375-2.364, p < 0.001) and UHR (OR: 1.290, 95% CI: 1.060-1.897, p = 0.008) were determined as independent predictors for SVG disease development.

ROC curve analysis revealed that the cutoff value for UHR was 0.19 (AUC: 0.790, 95% CI: 0.751-0.829, p < 0.001, sensitivity of 75.2% and specificity of 69.4%) (Fig. 1).

DISCUSSION

The incidence of coronary artery disease (CAD), which occupies a prominent place among atherosclerotic cardiovascular diseases, is increasing day by day. CABG surgery is one of the most important treatment methods of CAD and although the most important graft used in CABG operations is the left internal thoracic artery, SVG is also valuable because of its various advantages. A variety of blood parameters have been investigated in the literature to predict late (after one year) saphenous vein disease [9]. In this study, we are the first to reveal in the literature that serum UHR is associated with late SVG disease. In our multivariate analysis, in addition to known risk factors such as coronary artery structure and diabetes mellitus, we detected UHR as an independent predictor of SVG disease development.

Purine metabolism produces uric acid (UA), which is linked to poor metabolic health [10]. Uric acid penetrates the cell membrane, causing oxidation and inflammation. It also reduces nitric oxide release in the endothelium and inhibits cell proliferation and migration. In addition to these, aside from direct damage to vascular smooth muscle structures, the expression of proinflammatory cytokines also triggers the development of atherosclerosis [7].

In a recent study that included 15,843 (73.90% male) participants, a significant correlation was found between high UA values and carotid intima-media thickness [11]. In another recent study that included 369 people, a significant relationship was found between high UA values and metabolic syndrome [12]. In a study in which 814,804 (415,779 males and

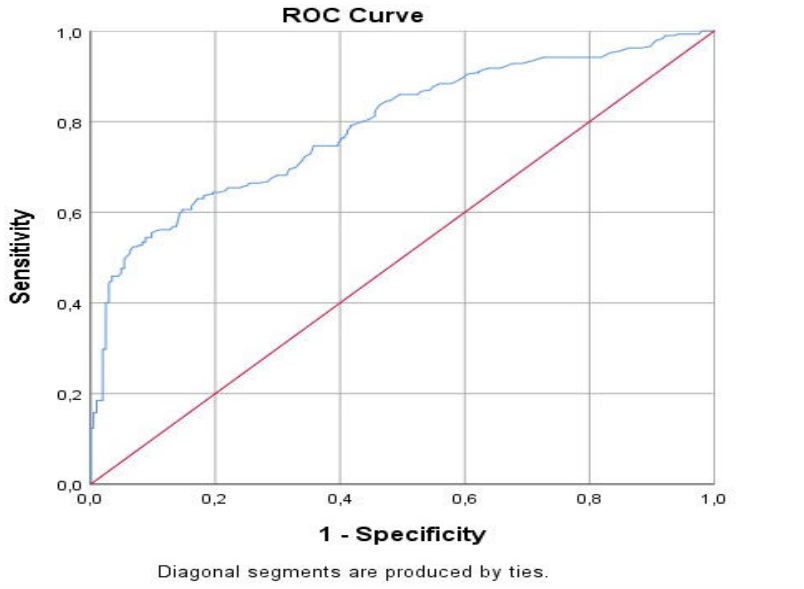

Fig. 1. ROC (Receiver operation characteristic) curve and AUC (Area under the curve) for admission uric acid to high-density lipoprotein cholesterol ratio for predicting saphenous vein graft disease. (Cut-off: 0.19, AUC: 0.790, 95% CI: 0.751- 0.829, p < 0.001, sensitivity of 75.2% and specificity of 69.4%).

399,025 females) volunteers were included, a linear relationship was revealed between serum UA values and atrial fibrillation [13]. In a study conducted by Tavil *et al*. [14], the relationship between serum UA levels and SVG disease was investigated in 192 patients, followed for an average of 5.6 years after CABG operation. At the conclusion of the study, a significant correlation was found between high serum UA values and SVG disease [14]. In our study, serum UA values were significantly higher in our patient group with SVG disease.

HDL-C is known for its protective effects from atherosclerosis. It has a composite structure consisting of lipid composites of different sizes. HDL-C has anti-inflammatory, anti-diabetic and antithrombotic effects along with cholesterol-mobilizing effects in tissues [15]. In a study conducted on these effects, it was shown that every 16 mg/dL increase in HDL-C levels leads to a decrease in CAD rates (OR of 0.95, 95% CI: 0.85-1.06) and diabetes mellitus rates (OR of 0.83 95% CI: 0.76-0.90) [16]. CAD was found in 60% of individuals with low HDL-C levels in cohort studies [17]. In a multicenter study by Jerzevski *et al*. [18], including 113 patients who underwent CABG and were evaluated at 12 months, the relationship between HDL-C and SVG disease was investigated. In their study, the HDL-C cut-off value was determined as 40 mg/dL, and low HDL-C values were shown to be mostly associated with SVG occlusion and increased intimal hyperplasia [18].

Considering this information available regarding uric acid and HDL-C, UHR values emerge as an important cardiovascular risk indicator. In a study conducted on the general population, UHR values were found to be significantly higher in patients with non-alcoholic fatty liver disease, compared to the control group [19]. In another study, the prognostic significance of UHR values in peritoneal dialysis patients was investigated. In their study, in which 1953 patients were included and followed up for an average of 61.3 months, high UHR values were found to be associated with cardiovascular and all-cause mortality [20]. In a retrospective cross-sectional cohort study conducted in the cardiovascular field, the effect of UHR values on hypertension control was investigated in 535 hypertension patients. Here, UHR values were significantly correlated with systolic ($r = 0.33$, $p < 0.001$) and diastolic ($r = 0.28$, $p < 0.001$) blood pressure. In addition, UHR value has been shown as an independent predictor of poor blood pressure control, and it has been determined that a unit increase in UHR value affects poor blood pressure control 7.3 times ($p < 0.001$, 95% CI: 3.9-13.63) [21]. In our study, high UHR values were also shown as an independent predictor of SVG disease.

After CABG surgery, SVGs can become occluded for several reasons. The cause of SVG disease occurring in the first month is thrombosis, and intimal hyperplasia for up to one year, followed by atherosclerosis [22]. In our study, at least 1 year had passed after CABG surgeries for all patients. Therefore, it is inevitable that atherosclerotic risk factors play a role in the development of the disease. Lipid-lowering therapies and antiplatelet therapy algorithms used by patients may play a role in the development of SVG disease. It has been shown that medical treatment strategies may affect the development of SVG disease [2, 23]. In our study, there was no significant difference between the postoperative medical treatments applied between the groups.

The age of the SVG and the coronary vascular structure and the diameter of the target vessel bypassed, are other important factors that may affect the development of SVG disease [24]. In a retrospective study by Bayam *et al*. [25] including 398 patients, SVG age was shown as an independent predictor of SVGD development (OR:1.18, 95% CI: 1.02-1.35, $p = 0.020$). In another recent study [26], the severity of coronary artery disease, calculated by the SYNTAX score, was shown as an independent predictor of SVG disease (OR: 0.978, 95% CI: 0.957-0.999, $p = 0.045$). And in a study in which SVGs were prepared with the no-touch technique in all patients, a target vessel diameter of less than 1.5 mm was shown as an independent predictor of SVG disease [26].

Limitations

There are some limitations in our study. Primarily, our study was a single-center retrospective study, therefore the number of patients was limited. In addition, only the diameter was taken as a variable for the coronary artery structure before CABG in our study group. It should be noted that the general disease status of the vessel, apart from the diameter, may also affect the development of SVG disease. In addition, a detailed lesion analysis of all saphenous veins could not

be performed. There is a need for multicenter prospective studies in which these analyzes are also carried out.

CONCLUSION

Although CABG surgeries constitute the prominent treatment option for atherosclerotic heart diseases, the atherosclerotic process continues as long as the patients are alive. Beyond the first year following CABG surgeries, atherosclerosis plays a leading role in the development of SVG disease. Therefore, clinical follow-up of these patients is particularly imperative. In this study, we showed that we can predict saphenous vein graft occlusion with serum UHR values; to the best of our knowledge, this is the first time this was done in the literature.

Authors' Contribution

Study Conception: OG, ME; Study Design: OG, ME; Supervision: OG, ME, ŞY; Funding: OG, FA, ÖFD; Materials: OG, ME; Data Collection and/or Processing: OG, ME, ÖFD; Statistical Analysis and/or Data Interpretation: OG, ME; Literature Review: OG, ME, ÖFD, FA, ŞY; Manuscript Preparation: OG, ME,ÖFD and Critical Review: OG, ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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