Relationship between elevated levels of serum uric acid and saphenous vein graft disease

Yüksek serum ürik asit düzeyleri ile safen ven grefti hastalığı arasındaki ilişki

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Objectives: Several studies have shown an association between elevated serum uric acid (SUA) levels and coronary heart disease and cardiovascular mortality. We investigated the relationship between SUA levels and the patency of saphenous vein grafts (SVG) after coronary artery bypass graft (CABG) surgery.

Study design: The study included 192 patients (152 men, 40 women) who underwent elective coronary angiography after a mean of 5.6 years following CABG surgery, which involved the use of at least one SVG. The patients were divided into two groups depending on the extent of SVG patency. Stenosis of 50% or greater within the SVG was accepted as hemodynamically significant. Serum uric acid levels were determined with the enzymatic colorimetric method.

Results: Ninety patients (71 men, 19 women; mean age 62±8 years) were found to have patent SVG. Stenotic SVGs were detected in 102 patients (81 men, 21 women; mean age 62±10 years). The time interval between surgery and angiography was significantly longer in the stenotic group (p<0.001). Compared to patients without SVG disease, the mean SUA level was significantly higher in patients with SVG disease (4.9±1.2 mg/dl *vs* 5.8±1.4 mg/dl; p=0.02). Serum uric acid levels were similar in patients having stenosis in a single vein graft or multiple vein grafts (p=0.224). In multiple regression analysis, SVG disease was independently associated with SUA (p<0.001), diabetes mellitus (p=0.028), and smoking (p=0.039).

Conclusion: Our results show that there is a significant association between increased SUA levels and SVG disease in patients undergoing CABG, which may justify the need for early screening for hyperuricemia and antiuricemic treatment.

Key words: Coronary angiography; coronary artery bypass; graft occlusion, vascular; hyperuricemia; saphenous vein/transplantation; uric acid/blood.

Amaç: Serum ürik asit (SÜA) yüksekliğinin koroner arter hastalığı ve kardiyovasküler ölümle ilişkisi birçok çalışmada gösterilmiştir. Bu çalışmada, koroner arter baypas ameliyatı geçiren hastalarda, uzun dönem safen ven grefti (SVG) açıklığının SÜA düzeyleri ile ilişkisi araştırıldı.

Çalışma planı: Çalışmaya, en az bir adet SVG kullanılarak yapılan koroner arter baypas cerrahisinden ortalama 5.6 yıl sonra elektif koroner anjiyografi ile değerlendirilen 192 hasta (152 erkek, 40 kadın) alındı. Hastalar SVG açıklığının derecesine göre iki grupta değerlendirildi; ven greftinde %50 veya daha fazla darlık olması hemodinamik olarak önemli kabul edildi. Serum ürik asit düzeyleri enzimatik kolorimetrik yöntemle belirlendi.

Bulgular: Safen ven greftleri 90 hastada (71 erkek, 19 kadın; ort. yaş 62±8) açık bulunurken, 102 hastada (81 erkek, 21 kadın; ort. yaş 62±10) darlık saptandı. Cerrahi ile anjiyografi arasındaki süre darlık saptanan grupta anlamlı derecede uzun bulundu (p<0.001). Greftin açık olduğu grupla karşılaştırıldığında, ortalama SÜA düzeyi darlık grubunda anlamlı derecede yüksek idi (4.9±1.2 mg/dl ve 5.8±1.4 mg/dl; p=0.02). Serum ürik asit düzeyleri, tek veya birden çok greftte darlık gelişen hastalar arasında anlamlı farklılık göstermedi (p=0.224). Çoklu regresyon analizinde, SVG hastalığının bağımsız belirleyicilerinin SÜA düzeyi (p<0.001), diyabetes mellitus (p=0.028) ve sigara içme (p=0.039) olduğu görüldü.

Sonuç: Bulgularımız, koroner arter baypas ameliyatı geçiren hastalarda artmış SÜA düzeyi ile SVG hastalığı arasında anlamlı ilişki olduğunu göstermektedir. Bu durum hiperürisemi için erken tarama ve antiürisemik tedavi gerektiğini düşündürmektedir.

Anahtar sözcükler: Koroner anjiyografi; koroner arter baypas; greft tıkanıklığı, vasküler; hiperürisemi; safen ven, transplantasyon; ürik asit/kan.

Received: July 15, 2007 *Accepted:* December 25, 2007

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Coronary artery bypass graft (CABG) surgery is effective in relieving angina symptoms and prolongs survival. Unlike arterial grafts, saphenous vein grafts (SVG) show poorer patency because of greater susceptibility to early and late atherosclerotic degeneration. In this respect, SVG disease has a key role as the major determinant of long-term graft viability in patients undergoing CABG surgery.[1,2] During the first-year after bypass surgery, up to 15% of venous grafts become occluded, by 10 years after surgery only 50% of vein grafts are patent, and nearly one-half of the patent grafts show angiographic evidence for atherosclerosis.[1,3]

In addition to smoking, high cholesterol levels, and diabetes mellitus as well-known cardiovascular risk factors, hyperhomocysteinemia and metabolic syndrome have been identified as risk factors for SVG disease.[4,5] Moreover, elevated serum uric acid (SUA) level is a known independent risk factor for cardiovascular disease. Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death. To the best of our knowledge, the association of SUA concentrations with SVG disease has not been examined.[6] The purpose of this study was to determine whether there was an association between plasma uric acid levels and SVG disease after CABG surgery.

PATIENTS AND METHODS

Study population. The study consisted of 192 patients (152 men, 40 women) who underwent elective coronary angiography more than one year (mean 5.6 years) after CABG surgery, which involved the use of at least one SVG for bypass (Table 1). The patients were divided into two groups depending on the extent of SVG patency. Stenosis of 50% or greater within the SVG was accepted as hemodynamically significant. Clinical indications for coronary angiography were recurrent postoperative stable angina pectoris and preoperative evaluation for noncardiac surgery. Before angiography, a complete medical history was obtained from each patient, including risk factors for coronary heart disease. Exclusion criteria were the presence of unstable ischemic conditions (unstable angina pectoris and myocardial infarction), severe valvular heart disease, uncontrolled hypertension, renal or hepatic dysfunction (creatinine >2.5 mg/dl, AST and ALT >2 times upper normal limits, respectively), and acute or chronic infections. Patients with a history of alcohol use or diuretics containing thiazide were also excluded. Body mass index (weight in kilograms divided by the square of the height in meters) was calculated for each patient. Patients who had been smoking within one year of angiography were considered current smokers. Hypertension was defined as a systolic/diastolic blood pressure of ≥140/90 mmHg on one or more occasions or if the patient was on antihypertensive medication.[7] Diabetes mellitus was diagnosed by a fasting serum glucose level of >126 mg/dl or an arbitrary serum glucose level of >200 mg/dl or if the patient was receiving insulin or oral hypoglycemic agents.

Fasting blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride levels were recorded. Blood samples were drawn by venipuncture for routine blood chemistry. Serum uric acid levels were determined with the enzymatic colorimetric method by a clinical chemistry autoanalyzer (Aeroset, Abbott Laboratories, Chicago, IL, USA). The study was approved by the local ethics committee.

Coronary angiography. Coronary angiography was routinely performed by the Judkins technique using 6-French right and left heart catheters. Angiograms were recorded on a DICOM digital media at 25 squares/msec and were reviewed by two experienced angiographers who had no knowledge of the patients' clinical status. Saphenous vein grafts were visualized from at least two angles after selective injection of contrast material. Aortic root angiography was per-

Table 1. The number and localization of saphenous vein grafts (SVG)

	Patients without SVG stenosis (n=90)		Patients with SVG stenosis (n=102)		
	n	%	n	%	*p*
One vein graft	38	42.2	45	44.1	0.345
Two vein grafts	26	28.9	30	29.4	0.675
Three or more vein grafts	26	28.9	27	26.5	0.576
SVG to left anterior descending coronary artery	6	6.7	8	7.8	0.457
SVG to diagonal	26	28.9	25	24.5	0.687
SVG to left circumflex coronary artery	44	48.9	42	41.2	0.124
SVG to right coronary artery	51	56.7	58	56.9	0.344

Table 2. Characteristics of the patients with and without saphenous vein graft (SVG) stenosis

	Patients without SVG stenosis (n=90)			Patients with SVG stenosis (n=102)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age			62±8			62±10	0.65
Sex (male/female)	71 / 19			81 / 21			0.54
Time interval after surgery (years)			4.9±1.9			6.4±2.2	<0.001
Hypertension	58	64.4		54	52.9		0.124
Diabetes mellitus	25	27.8		35	34.3		0.156
Body mass index (kg/m^2)			25.6±4.5			26.1±4.8	0.721
Current smokers	5	5.6		12	11.8		0.118
Serum glucose (mg/dl)			117±35			124±50	0.270
Total cholesterol (mg/dl)			186.2±44.3			209.7±43.35	<0.001
LDL-cholesterol (mg/dl)			112.1±38.9			127.3±36.8	0.005
HDL-cholesterol (mg/dl)			44.6±8.6			42.9±7.8	0.235
Triglyceride (mg/dl)			149.9±83.4			160.5±79.7	0.119
Myocardial infarction	32	35.6		37	36.3		0.436
Ejection fraction (%)			54.2±11.7			52.8±12.1	0.523
Aspirin	80	88.9		86	84.3		0.912
Beta-blocker	39	43.3		37	36.3		0.623
ACE inhibitors	34	37.8		33	32.4		0.548
Statins	33	36.7		36	35.3		0.854
Internal mammary artery graft	75	83.3		84	82.4		0.533
Creatinine (mg/dl)			1.19±0.9			1.07±0.4	0.931
Hemoglobin (g/dl)			14.1±1.5			15.9±1.3	0.684
Serum uric acid (mg/dl)			4.9±1.2			5.8±1.4	0.02

LDL: Low-density lipoprotein; HDL: High-density lipoprotein; ACE: Angiotensin converting enzyme.

formed to assess graft patency when needed. Vein graft disease was defined as stenosis of ≥50% of the vessel diameter in any SVG.[8] Anastomotic lesions between an SVG and a native artery were excluded from the study.

Statistical analysis. Continuous variables were given as mean ± SD; categorical variables were expressed as percentages. Differences between groups were analyzed using the Student's t-test for unpaired data and chi-square test when appropriate. Odds ratios and 95% confidence intervals were estimated with a multiple logistic regression model, which included age, diabetes, and hypertension. The time interval between bypass surgery and coronary angiography, serum cholesterol level, and SUA were included as confounding variables. Statistical significance was defined as a *p* value of less than 0.05. All statistical calculations were performed using the SPSS statistical software (SPSS for Windows 10.0, Chicago, IL, USA).

RESULTS

Ninety patients (71 men, 19 women; mean age 62±8 years) were found to have patent SVG. Stenotic SVGs were detected in 102 patients (81 men, 21 women; mean age 62±10 years). The main characteristics of the patient groups are summarized in Table 2. There were no significant differences between the two groups with respect to age, sex, body mass index, smoking status, diabetes mellitus, previous myocardial infarction, or left ventricular ejection fraction. The time interval between bypass surgery and coronary angiography was significantly longer in the stenotic group (p<0.001). The use of salicylate, lipid-lowering drugs, beta-blockers, and angiotensin converting enzyme inhibitors were similar in both groups. Creatinine and hemoglobin levels were also comparable in both groups.

Although high-density lipoprotein cholesterol and triglyceride levels were not different, patients with stenosis exhibited significantly higher total cholesterol and low-density lipoprotein cholesterol levels.

Compared to patients without graft disease, the mean SUA level was significantly higher in patients with SVG disease (4.9±1.2 mg/dl *vs* 5.8±1.4 mg/dl; p=0.02).

Of 102 patients having SVG disease, stenosis developed in a single vein graft in 67 patients (65.7%), in two vein grafts in 30 patients (29.4%), and in three or more vein grafts in five patients (4.9%), with no significant difference in the mean SUA levels (5.9±1.2 mg/dl, 5.8±1.1, mg/dl, and 5.6±1.3 mg/dl, respectively; p=0.224).

Table 3. Logistic regression analysis for predictors of saphenous vein graft disease

	Odds ratio	95% confidence interval	*p*
Age	1.032	0.986 – 1.081	0.177
Diabetes mellitus	2.469	1.049 – 5.811	0.028
Smoking	1.948	1.036 – 3.662	0.039
Hypertension	0.469	0.210 – 1.050	0.066
Body mass index	0.788	0.654 – 1.011	0.158
Fasting glucose level	0.996	0.985 – 1.006	0.996
LDL-cholesterol	1.002	0.991 – 1013	0.727
HDL-cholesterol	0.980	0.931 – 1.031	0.442
Triglycerides	1.002	0.996 – 1.007	0.562
Creatinine	0.408	0.122 – 1.366	0.146
Time interval after bypass surgery	0.934	0.848 – 1.029	0.166
Serum uric acid	2.147	1.456 – 3.166	<0.001

In multiple regression analysis, SVG disease was independently associated with SUA (β=0.76; p<0.001) along with diabetes mellitus (β=0.94; p=0.028) and smoking (β=0.61; p=0.039). The adjusted odds ratios for the development of SVG disease are presented in Table 2.

DISCUSSION

Coronary artery bypass graft surgery has become widely accepted and established as an effective treatment for coronary artery disease. However, its long-term efficacy is limited by SVG disease.[1,2] Many risk factors have been identified for SVG disease, including smoking, elevated cholesterol levels, diabetes, and longer intervals after CABG.[5,6,9,10]

In the present study, we found that patients with SVG disease had significantly higher SUA levels compared to patients without SVG disease, and that the number of stenotic SVGs was not correlated with SUA levels.

Many factors have been found to predispose to reduced vein graft patency including hypertension, diabetes mellitus, smoking, hyperlipidemia, native vessel diameter, gender, grafted vessel, age of graft, severity of bypassed proximal stenosis, plasma levels of lipoprotein (a), homocysteine, and fibrinogen.[10,11] These risk factors are also associated with native coronary artery disease. In addition, the technique by which venous conduits are harvested may also contribute to SVG disease, resulting in focal endothelial disruption during and after surgery.[3,10] Unlike arterial grafts, vein grafts are more susceptible to intimal hyperplasia, arteriosclerosis, progressive stenosis, and occlusion.[10]

Although hyperuricemia is a well-recognized risk factor for atherosclerotic diseases such as myocardial infarction and stroke, the independence of this association from other risk factors has remained controversial. This is mostly because SUA is associated with other cardiovascular risk factors such as hypertension and dyslipidemia.[12-15] For this reason, the effect of hyperuricemia on atherosclerotic progress is still debatable. In accordance with findings of previous studies,[14,15] we found that higher levels of SUA were significantly associated with diabetes and smoking. After appropriate adjustment, SUA was found to be independently associated with SVG disease, with an odds ratio of 2.147 (95% CI, 1.456 to 3.166; p<0.001). Our finding that SUA levels did not differ depending on the number of stenotic SVGs showed that SUA levels were mainly associated with atherosclerotic or thrombotic process rather than the severity of SVG disease.

Several possible mechanisms linking SUA to cardiovascular disease have been proposed, including deleterious effects of urate crystals on endothelial function, oxidative metabolism, platelet adhesiveness and aggregation. It has been demonstrated that urate crystals are associated with proinflammatory effects, activation of the complement pathway, stimulation of neutrophils to release proteases and oxidants, stimulation of macrophages, and activation of platelets and the coagulation cascade.[16-18]

The main limitation of this study was exclusion of patients who underwent elective angiography for miscellaneous reasons. Therefore, SUA levels were not studied in patients who had acute coronary syndrome or died after CABG surgery. Further prospective studies investigating this relation from the beginning of CABG surgery are needed to elucidate the role of SUA in SVG disease. Secondly, SVG disease may

also be associated with metabolic syndrome, which is characterized by a cluster of atherosclerotic risk factors including insulin resistance, high blood pressure, low HDL-cholesterol level, high triglyceride level, high plasma glucose concentration, and obesity.[19] To eliminate this relationship, we performed regression analysis and showed the independent effect of SUA on SVG disease.

In conclusion, to the best of our knowledge, this study is the first to show a significant association between increased SUA levels and SVG disease. Our findings may justify the need for early screening for hyperuricemia and clinical trials to elucidate the potential benefit of antiuricemic treatment in slowing down the progression of SVG disease in patients undergoing CABG with SVG.

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