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Original Article / Özgün Makale

Evaluation of the relationship between the levels of high-sensitivity C-reactive protein and saphenous vein graft disease

Yüksek duyarlıklı C-reaktif protein düzeyleri ve safen ven greft hastalığı arasındaki ilişkinin değerlendirilmesi

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Background: In this study, we aimed to evaluate the relationship between the levels of high-sensitivity C-reactive protein (hs-CRP) and saphenous venous graft disease (SVGD).

Methods: A total of 78 patients (54 males, 24 females; mean age 60.4±9.4 years; range 37 to 78 years) with previous history of coronary artery bypass graft (CABG) surgery who underwent coronary angiography based on predetermined objective clinical criteria were included. Risk factors leading to atherosclerosis were questioned and biochemical tests were studied in all patients. A 50% or more stenosis in at least one of the saphenous vein grafts was defined as SVGD. The patients were divided in two groups according to the presence of SVGD (group 1), and the absence of SVGD (group 2).

Results: When we compared the demographic characteristics and laboratory findings of both groups, body mass index (BMI), total cholesterol/high-density lipoprotein (HDL) cholesterol ratio, uric acid (UA) and hs-CRP levels were significantly higher, while HDL cholesterol level was significantly lower in group 1. Multivariate logistic regression analysis showed that BMI, UA and hs-CRP levels were independent predictors of SVGD (hs-CRP OR: 1.522, p<0.01, UA OR: 1.48, p=0.01, BMI OR: 1.31, p=0.04). The ROC analysis demonstrated that a 0.8 mg/dL hs-CRP cut-off value indicated SVGH with a 80% sensitivity and 85% specificity rate.

Conclusion: In our study, hs-CRP was found to be the most powerful predictor of SVGD. High-sensitivity-C-reactive protein is a noninvasive, reliable and useful parameter in the prediction and monitoring of SVGD.

Key words: Atherosclerosis; high-sensitivity C-reactive protein; saphenous venous graft disease.

Amaç: Bu çalışmada safen ven greft hastalığı (SVGH) ile yüksek duyarlıklı C-reaktif protein (hs-CRP) seviyeleri arasındaki ilişki değerlendirildi.

Çalışma planı: Çalışmaya koroner arter baypas greft ameliyatı öyküsü olan, önceden belirlenen objektif kriterlere göre koroner anjiyografi yapılan toplam 78 hasta (54 erkek, 24 kadın; ort. yaş 60.4±9.4 yıl; dağılım 37-78 yıl) dahil edildi. Ateroskleroza neden olan risk faktörleri sorgulandı ve tüm hastaların biyokimyasal testleri çalışıldı. Safen ven greftlerden herhangi birinde %50 ve daha fazla darlık olması SVGH olarak tanımlandı. Hastalar SVGH olan (grup 1) ve SVGH olmayanlar (grup 2) olmak üzere iki gruba ayrıldı.

Bulgular: Her iki grubun demografik özellikleri ve laboratuvar değerleri karşılaştırıldığında, grup 1'de vücut kütle indeksi (VKİ), total kolesterol/yüksek yoğunluklu lipoprotein (HDL) kolesterol, ürik asit (ÜA) ve hs-CRP düzeyleri anlamlı oranda yüksek olup, HDL kolesterol düzeyi anlamlı oranda düşüktü. Yapılan çok değişkenli lojistik regresyon analizinde VKİ, ÜA ve hs-CRP düzeylerinin SVGH'yi öngörmede bağımsız belirteçler olduğu tespit edildi (hs-CRP OR: 1.522, p<0.01, ÜA OR: 1.48, p=0.01, VKİ OR: 1.31, p=0.04). Yapılan ROC analizinde hs-CRP düzeyi 0.8 mg/dL "kesim değeri" olarak alındığında %80 duyarlılık ve %85 özgüllük oranı ile SVGH'yi belirlediği bulundu.

Sonuç: Çalışmamızda SVGH'yi öngördüren en güçlü belirtecin hs-CRP olduğu saptandı. Yüksek duyarlıklı C-reaktif protein, SVGH varlığını öngörme ve izleminde noninvaziv, güvenilir ve yararlı bir belirteçtir.

Anahtar sözcükler: Ateroskleroz; yüksek duyarlıklı C-reaktif protein; safen ven greft hastalığı.

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Coronary artery bypass graft (CABG) surgery has long been a treatment modality to alleviate anginal episodes, improve quality of life, and prolong life expectancy in patients with coronary artery disease (CAD). On the basis of the nature of the obstructed vessel, arterial or venous grafts can be used, and saphenous bypass grafts are preferred over arterial grafts in cases with an earlier and more profound obstruction.[1] Fifteen percent of the saphenous vein grafts (SVGs) become obstructed within the first postoperative year, and this ratio may increase to 50-60% at the end of the 10th postoperative year.[2] Therefore, identification of the presence of a possible saphenous vein graft disease (SVGD) in patients with CABG is very important so as to anticipate long-term myocardial nourishment and assess myocardial viability.

The clear elucidation of the relationship between atherosclerosis and inflammation in recent years has given rise to the idea that some of the inflammatory markers may be utilized to predict the risk of future cardiovascular events. The most robust evidence regarding these markers is associated with high-sensitivity C-reactive protein (hs-CPR). Recent studies have proven the usefulness of hs-CRP in anticipating the prognosis in healthy subjects as well as those with cardiovascular disease.[3-4]

Although various factors such as the native vessel diameter, the nature of the vessel to which the grafting was performed, the severity of the proximal obstruction of the bypass graft, age of the graft, the use of tobacco, increased serum cholesterol levels, diabetes mellitus (DM), hypertension (HT), hyperhomocysteinemia, hyperfibrinogenemia, and the amount of elapsed time after CABG affect the relationship between hs-CRP and SVGD, the amount of information regarding this topic is very limited in the literature.[1,5,6]

In our study, we investigated the relationship between hs-CRP and SVGD in patients with CABG.

PATIENTS AND METHODS

Patient groups

A total of 78 patients (54 males; 24 females; mean age 60.4±9.4 years; range 37 to 78 years) who were admitted to Adana Numune Education and Research Hospital between May 2011 and October 2011 with a previous history of CABG identified via coronary angiography (CAG) based on objective clinical indications were included in our study (Table 1). The patients were divided into two groups. Group 1 was comprised of those patients with SVGD, and group 2 was made up of those without SVGD. Patients experiencing recurrent chest pain episodes despite optimal medical treatment, those with a positive treadmill test, or those with findings compatible with new ischemia discovered by electrocardiogram (ECG) or myocardial perfusion scintigraphy underwent CAG. However, patients with a history of acute coronary syndrome, severe valvular heart disease, uncontrolled hypertension, renal or hepatic dysfunction [alanine aminotransferase (ALT)-aspartate aminotransferase (AST) >3 time, creatinine >2.5 mg/dL], acute/chronic infective or inflammatory disease, or symptomatic heart disease were excluded from the study along with those currently using statins or those who had undergone CABG in the past three months.

All the patients were hospitalized 12 hours prior to the operation. An intense scrutiny of each participant was conducted which involved patient histories and physical examinations. The dates of the CABG, the type and number of grafts used, and the type of technique utilized in the preparation of the SVGs were recorded after a retrospective evaluation of the patient files. In addition, the presence of risk factors like HT, DM, and hyperlipidemia along with the use of tobacco, a positive family history of cardiac diseases, a previous history of myocardial infarction (MI) or cerebrovascular event, and the medicines currently being used by the patients were also noted. The weight, height, blood pressure,

Table 1. The number and localization of saphenous vein grafts

	Group 1 (n=38)		Group 2 (n=40)		
	n	%	n	%	*p*
One vein graft	19	50.0	12	30.0	0.1
Two vein grafts	15	39.5	18	45.0	0.8
Three or more vein grafts	4	10.5	10	25.0	0.07
SVG to left anterior descending coronary artery	7	18.4	7	17.5	0.9
SVG to diagonal artery	8	21.0	12	30.0	0.3
SVG to left circumflex coronary artery	29	76.3	28	70.0	0.8
SVG to right coronary artery	18	47.3	23	57.5	0.2

SVG: Saphenous vein grafts.

heart rate, and body mass index (BMI) were also determined for each patient. According to our records, conventional harvesting techniques had been performed on all patients.

Blood samples were drawn from the patients following at least 12 hours of fasting after they were admitted to the coronary angiography clinic. A hemogram was then performed, and tests were done to determine the levels of fasting blood glucose, urea, creatinine, ALT, AST, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and uric acid (UA). A thyroid function test was also performed for each patient.

Laboratory examination for high-sensitivity C-reactive protein

Following the 12-hour fast and a 20-minute rest period, 10 ml blood samples were drawn into test tubes that contained ethylenediaminetetraacetic acid (EDTA) for hs-CRP measurement in the morning. The samples were then centrifuged for five minutes at 1500 rpm and +4 °C, and the supernatant plasma was transferred into another test tube for hs-CRP analysis. An immunoassay analysis method (IMMAGE® Immunochemistry Systems, Beckman Coulter, Inc., Brea, California) was then used to measure the level of hs-CRP in the supernatant serum.

Evaluation of the coronary angiography

Coronary angiography was undertaken according to the Judkins technique using routine standard projections. The SVGs were subjected to an evaluation based on at least two distinct angles. If needed, an aortic root evaluation was also conducted. The presence of ≥50% obstruction in any one of the SVGs was accepted as SVGD. Three different cardiologists who were blinded to the study determined the treatment approach following the CAG.

Statistical analysis

All the analyses were implemented using the SPSS (SPSS Inc., Chicago, Illinois, USA) version 17.0 for Windows statistical software package. Continuous variables for the data related to the groups were expressed as mean ± standard deviation (mean±SD) while categorical variables were indicated using numbers and percentages. Comparisons between the continuous variables of the two groups were fulfilled utilizing Student's t-test, and a chi-square test was used to compare categorical variables. In order to specify the independent variables that had an impact on the presence of SVGD, multivariate logistic regression analysis was performed. Any rise or fall stemming from each unit increase in the variables that proved to be significant was determined using

Table 2. Comparison of the clinical and demographic properties of the patients

	Group 1 (n=38)			Group 2 (n=40)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			60.8±9.1			60.0±9.7	0.8
Gender							
Male	27			27			
Female	11			13			0.8
Diabetes mellitus	19	50.0		12	30.0		0.1
Hypertension	26	68.4		25	62.5		0.6
Hyperlipidemia	33	86.8		25	62.5		0.02
Number of smokers	16	42.1		14	35.0		0.6
Body mass index (kg/m^2)			27.9±2.7			25.9±3.2	0.004
Systolic blood pressure (mmHg)			128.6±18.3			122.1±16.3	0.1
Diastolic blood pressure (mmHg)			80.1±10.8			76.2±15.9	0.2
Heart rate			77.7±11.9			71.6±8.5	0.01
Time interval after bypass surgery (months)			82.0±36.6			66.4±40.0	0.07
Medical therapy							
Aspirin	37	97.4		35	87.5		0.2
Beta blocker	33	86.8		31	77.5		0.4
ACE/ARB	28	73.7		28	70.0		0.8
Clopidogrel	7	18.4		5	12.5		0.5
Nitrate	24	63.2		16	40.0		0.04
Calcium channel blocker	10	26.3		8	20.0		0.8

SD: Standard deviation; BP: Blood pressure; ACE: Angiotensin-converting enzyme; ARB: Aldosterone receptor antagonist.

Table 3. Comparison of laboratory properties of the patients

	Group 1 (n=38)	Group 2 (n=40)	
	Mean±SD	Mean±SD	*p*
Hematocrit (%)	41.2±4.0	40.6±3.9	0.5
Platelet (x10^3 /uL)	275±74	274±68	0.9
Fasting blood glucose (mg/dL)	143.4±71.3	116.7±52	0.06
Creatinine (mg/dL)	1.1±0.2	1.0±0.2	0.1
Total cholesterol (mg/dL)	187.0±56.8	169.9±30.5	0.1
LDL cholesterol (mg/dL)	117.4±42.1	104.8±25.0	0.1
HDL cholesterol (mg/dL)	38.2±7.1	41.7±6.8	0.03
Triglycerides (mg/dL)	167.9±95.4	141.3±47.3	0.1
Total cholesterol/HDL ratio	5.0±1.6	4.1±0.9	0.006
Uric acid (mg/dL)	6.0±1.2	4.9±1.1	<0.001
hs-CRP (mg/dL)	1.1±0.6	0.5±0.3	<0.001

SD: Standard deviation; LDL: Low density lipoprotein; HDL: High-density lipoprotein, hs-CRP: High-sensitivity C-reactive protein.

the odds ratio (OR). The "cut-off'' values of the parameters which independently predicted the SVGD were specified according to the receiver operating characteristic (ROC) analysis. As for the group comparisons, a one-way analysis of variance (ANOVA) test was used for the normally distributed parameters. A p value <0.05 was accepted as being statistically significant.

RESULTS

Findings associated with saphenous vein graft disease development

The number of patients with a history of hyperlipidemia and increases in heart rates, BMI and nitrate usage were significantly higher in group 1 (Table 2). Furthermore, the total cholesterol/HDL ratio and levels of hs-CPR and UA were significantly higher in group 1 and the HDL levels were lower than in group 2 (Table 3). The other biochemical, demographic, and clinical parameters were similar between two groups. A comparison between the number of patients with SVGD and the levels of hs-CRP are given in Table 4. The levels of hs-CRP were significantly higher in the participants with three or more vein graft diseases, and these are defined as group 3 in Table 4 (p=0.02).

The independent markers in the prediction of saphenous vein graft disease

The variables that were found to be statistically significant in univariate analysis between groups 1 and 2 were entered into multivariate logistic regression analysis, and this indicated that hs-CRP, UA, and BMI were independent predictors of SVGD (Table 5). Increases of 0.1 mg/dL in hs-CRP, 0.5 mg/dL in UA, and one unit in BMI revealed a respective 52%, 48% and 32% increase in the risk for development of SVGD (hs-CRP OR: 1.522, 95% CI: 1.23-1.87, p<0.01; UA OR: 1.48, 95% CI: 1.08-2.02, p=0.01; BMI OR: 1.31, 95% CI: 1.01-1.70, p=0.04) (Table 5).

The use of the receiver operating characteristic analysis in the prediction of saphenous vein graft disease development

A ROC analysis was implemented for any variable exhibiting an independent correlation with SVGD development (Table 6). A significant correlation was observed in the area under the ROC (AUROC) curves for hs-CRP, UA, and BMI with regard to SVGD development. These levels were calculated as 0.875, 0.766 and 0.688, respectively. After accepting 0.8 mg/dL as the "cut-off'' value for the hs-CRP level, it

Table 4. The number of saphenous vein graft diseases and levels of high-sensitivity C-reactive protein

	Group 1 (n=24)		Group 2 (n=10)		Group 3 (n=4)			
	n	Mean±SD	n	Mean±SD	n	Mean±SD	p1	p2
Saphenous vein grafts	19	–	30	–	12	–	–	–
hs-CRP	19	0.95±0.33	15	1.30±0.94	4	1.68±0.49	0.1	0.02

SD: Standard deviation; hs-CRP: High-sensitivity C-reactive protein; Group 1: One vein graft disease; Group 2: Two vein graft diseases; Group 3: Three or more vein graft diseases; p1: Comparison between groups 1 and 2; p2: Comparison between group 1 and 3

Table 5. Independent predictors of saphenous vein graft disease

	Odds ratio	95% Confidence interval	*p*
hs-CRP (each 0.1 mg/dL)	1.522	1.238-1.871	<0.001
Uric acid (each 0.5 mg/dL)	1.483	1.088-2.022	0.013
BMI (each 1 kg/m^2)	1.315	1.015-1.704	0.04
HDL (each 1 mg/dL)	0.937	0.845-1.039	0.216
Total cholesterol/HDL ratio	0.974	0.503-1.887	0.939

hs-CRP: High-sensitivity C-reactive protein; BMI: Body mass index; HDL: High density lipoprotein.

corresponded to 80% sensitivity and 85% specificity in the prediction of SVGD development.

DISCUSSION

The paramount finding in this study was that the high levels of hs-CRP, UA, and BMI were found to be significant, independent markers for predicting SVGD development. Additionally, the levels of hs-CRP were significantly associated number of patients with SVGDs in our study.

Several risk factors have been described in studies that have been conducted regarding demographic, laboratory, and treatment findings and their relationship to their ability to predict SVGD development. Female gender, DM, HT, the use of tobacco, elevated total and LDL cholesterol levels, decreased HDL cholesterol levels, increased total cholesterol/HDL ratios, hyperhomocysteinemia, increased levels of fibrinogen, the age of the graft, the diameter of the native vessel, the vessel to which the SVG was connected, and the severity of the proximal obstruction of the bypass graft have all been identified as having a connection with SVGD. The patency of vein grafts can also be affected by the harvesting technique. Investigators have suggested that the no-touch technique can decrease early graft failure caused by thrombosis and intimal hyperplasia.[7] In our study, a correlation was found between SVGD development and a positive history for hyperlipidemia, the use of nitrates, heart rate, BMI, hs-CRP and UA levels, total cholesterol/HDL ratios, and low levels of HDL cholesterol. However, in contrast to previous studies, we found no significant correlation between female gender, DM, HT, the use of tobacco, and elevated total cholesterol and LDL cholesterol levels and SVGD development.[2,6,8] Our study population was small, and this could have affected our results. However, we did not evaluate the patients' medication history, especially their use of statins, since that can influence cholesterol levels. Our evaluations were based solely on the medications that were currently being used.

Although the annual restenosis rates in SVGs one and six years after bypass surgery is 1-2%, this ratio increases by 4% for each year between the postoperative sixth and 10th years, with only 60% of the SVGs remaining patent in the 10th postoperative year.[2] Hence, the age of the graft has been considered to be one of the risk factors for SVGD. There appeared to be a significant correlation between the age of the graft and SVGD in our study, and this was consistent with the findings of previous studies. However, our study was unique in that we were able to document that the age of the graft did not independently affect the development of SVGD.

No precise data exists in the literature concerning the correlation between DM and SVGD. However, five-year survival rates have been shown to be significantly lower in diabetic patients.[9] In our study, the incidence of DM was higher in group 1, but it did not reach the level of statistical significance.

Hyperlipidemia is a strong indicator of atherosclerosis occurring in both native coronary arteries and SVGs.[2,10] In a study by Campeau et al.[11] the elevated total cholesterol, very low-density lipoprotein (VLDL)

Table 6. Receiver-operating characteristic curve analysis for serum high sensitive C-reactive protein, uric acid levels, and body mass index in predicting saphenous vein graft disease

Variable	AUROC (95% CI)	p	Cut-off	Sensitivity	Specificity
				%	%
hs-CRP (mg/dL)	0.875 (0.797-954)	<0.001	0.8 mg/dL	80	85
Uric acid (mg/dL)	0.766 (673-882)	<0.001	5.5 mg/dL	74	75
Body mass index (kg/m^2)	0.688 (570-806)	0.004	27 kg/m^2	71	65

AUROC: Area under receiver operating characteristic; CI: Confidence interval; hs-CRP: High-sensitive C-reactive protein.

and LDL levels along with lower HDL levels proved to be primary indicators for predicting the development of new angiographic lesions 10 years after bypass surgery. They suggested that the increased LDL and decreased HDL cholesterol levels were significant predictors of the development of new lesions. Likewise, there was a significant correlation between elevated the total cholesterol/HDL and LDL/HDL ratios associated with late SVG thrombosis.[12] This condition was proposed to result from the increased risk for rupture of the lipid-rich plaques as well as a boost in the procoagulant effect. In concordance with previous studies, we found lower HDL cholesterol levels and significantly higher total cholesterol/HDL ratios in group 1.

The inflammatory process plays an important role in each step of atherosclerosis.[13] One of the most investigated inflammatory markers in patients with CAD is hs-CRP,[14,15] and this has been shown to be a stronger indicator than the level of LDL cholesterol for cardiovascular events.[16,17] For this reason, CRP was cited as one of the major cardiovascular risk factors and a secondary target for statin therapy in the 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular diseases in the adult---2009 recommendations.[18]

Although several studies have reported an association between hs-CRP and CAD, the relationship between hs-CRP and SVGD remains unclear.[14,15] A study by Jabs et al.[19] demonstrated that CRP-messenger ribonucleic acid (mRNA) and protein expression increased in patients with SVGD. Christiansen et al.,[20] found that more inflammatory cytokines were secreted from diseased SVGs than from the atherosclerotic coronary artery, and these increased cytokines were thought to be associated with accelerated atherosclerosis that is evident in SVGD. Owen et al.[21,22] reported that hs-CRP was significantly associated with venous graft failure in patients with peripheral artery disease and the effect of hs-CRP levels on the remodeling of venous vessels. In our study, we detected an independent correlation between hs-CRP levels and the presence of SVGD. This result points to the importance of the chronic inflammatory process in SVGD, which is similar to that found in native vessel disease, and supports the studies that have demonstrated that hs-CRP is a significant predictor of vascular risk. Moreover, by dividing the patients with SVGD into two subgroups according to whether they had complete obstruction or partial obstruction, the measured hs-CRP levels were much greater in those with complete obstruction. This suggests that hs-CRP might possibly be secreted from the calcified plaques rather than the vulnerable plaques.

Numerous studies have investigated the correlation between the serum levels of UA and CAD in the literature.[23] The pro-inflammatory effect, oxidative metabolism, and procoagulant effect of the urate crystals have been suggested as underlying mechanisms for an association between serum UA and CAD.[23] In a study conducted on 192 bypass patients which investigated the probable relationship between UA levels and SVGD, the UA levels were significantly higher in patients with this disease.[23] In our study, the elevated serum UA level was an another independent predictor of SVGD, and a "cut-off'' value of 5.5 mg/dL was proposed, with 74% sensitivity and 75% specificity, to indicate SVGD. This result supports the findings from a previous study by Tavil et al.[23] We concluded on the basis of the aforementioned results that monitorization of the serum UA level was justified in the routine follow-up of patients undergoing CABG.

Besides it being an independent risk factor for the development of CAD, obesity is also related to other cardiac risk factors such as DM, HT, and hyperlipidemia.[24] The ability of obesity to increase the risk for CAD has especially been associated with its metabolic effects (metabolic syndrome, DM, dyslipidemia, inclination to thrombosis). In a study which followed up 54,783 patients without CAD for 7.7 years who had been recruited for the Danish Prospective Diet, Cancer and Health Trial, BMI was closely associated with the risk for CAD; moreover, a one unit drop in the BMI was directly related to a 5% decrease in CAD in women and a 7% decrease in CAD in men ($p<0.0001$).[25] In our study, a significant correlation was documented between BMI and SVGD. A ''cut-off'' BMI value of 27 was identified, with 71% sensitivity and 65% specificity, to predict SVGD. An evaluation of BMI together with waist circumference measurements would provide additional beneficial results regarding the risk management of patients undergoing CABG.

Study limitations

Among all of the inflammatory markers, we were only able to base our study on the hs-CRP level due to financial shortcomings. Accordingly, our study would have been more meaningful if other inflammatory parameters such as white blood cell count, IL-1, IL-2, IL-6, tumor necrosis factor-alpha (TNF-α), serum amyloid A, procalcitonin, and serum adhesion molecules had been included so that their roles in the prediction of SVGD could also have been evaluated. We examined the levels of hs-CRP at one point in time. Further evaluation of hs-CRP levels at regular intervals could provide

further valuable information regarding the prediction of SVGD. Statin therapy has also been shown by previous studies to have an impact on hs-CRP levels.[16,26] The patients included in our study had been using either different medications or similar medications at various doses, so the effects of these drugs on the hs-CRP levels and SVGD development could not be assessed. The presence and degree of SVGD was determined in our study on the basis of diagnostic coronary angiography. However, we think that depicting the changes created by the ongoing inflammatory process in SVGD by more sophisticated imaging techniques, such as intravascular ultrasound (IVUS) and other advanced diagnostic methods, would contribute more to the grading and follow-up of the disease. The major limitation of our study was the relatively small patient population; therefore, studies involving larger numbers of participants should be conducted to verify and further advance our findings.

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