The relationship between saphenous coronary bypass graft occlusion and serum gamma-glutamyltransferase activity

Serum gama-glutamiltransferaz aktivitesinin safen koroner baypas greft tıkanıklığı ile ilişkisi

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Objectives: Serum gamma-glutamyltransferase (GGT) activity has been shown to be associated with progression of atherosclerosis. We evaluated the relationship between serum GGT levels and saphenous vein bypass graft disease at least one year after coronary artery bypass graft (CABG) surgery.

Study design: The study included 125 consecutive patients who had undergone CABG surgery with at least one saphenous vein graft (SVG) and were referred to cardiac catheterization for stable anginal symptoms or positive stress test results at least one year after CABG surgery. Laboratory parameters including serum GGT levels were measured before angiography. Occluded grafts were defined as a luminal stenosis of ≥70% or absence of distal TIMI 3 flow. Thus, SVGs were found to be patent in 53 patients (42.4%; 40 males, 13 females; mean age 65±8 years) and occluded in 72 patients (57.6%; 62 males, 10 females; mean age 64±9 years).

Results: The two groups were similar with regard to age, gender, hypertension, diabetes mellitus, family history of coronary artery disease, smoking, and alcohol consumption. The mean time from CABG to angiography was similar in patients with a patent and occluded SVG (6.8±4.3 *vs.* 8.1±3.7 years; p>0.05). Waist circumference was greater (p=0.02) and serum levels of total cholesterol (p=0.001), triglyceride (p=0.02), uric acid (p<0.001), hs-CRP (p<0.001), GGT (p<0.001) and fibrinogen (p<0.001) were significantly higher in patients with occluded veins. Serum GGT level was moderately but significantly correlated with waist circumference (r=0.2, p=0.04), uric acid (r=0.3, p=0.008), and hs-CRP (r=0.3, p=0.002). In logistic regression analysis, total cholesterol (OR=1.012, 95% CI 1.002-1.023, p=0.03), hs-CRP (OR=1.968, 95% CI 1.17-3.311, 0.01), uric acid (OR=1.57, 95% CI 1.1-2.208, p=0.01), and GGT (OR=1.047, 95% CI 1.002-1.1, p=0.04) were found to be significant predictors of SVG occlusion.

Conclusion: Our results suggest that serum GGT activity is associated with higher occlusion rates of venous bypass grafts.

Key words: Coronary artery bypass; gamma-glutamyltransferase; graft occlusion, vascular; saphenous vein/transplantation.

Amaç: Serum gama-glutamiltransferaz (GGT) aktivitesinin ateroskleroz gelişimi ile ilişkili olduğu gösterilmiştir. Bu çalışmada, koroner arter baypas greft (KABG) ameliyatından en az bir yıl sonra serum GGT düzeyleri ile safen ven baypas greft hastalığı arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya, en az bir safen ven greftiyle (SVG) KABG ameliyatı geçiren ve ameliyattan en az bir yıl sonra kararlı angina semptomları veya pozitif efor testi nedeniyle kardiyak kateterizasyon uygulanan ardışık 125 hasta alındı. Koroner anjiyografiden önce, tüm hastalarda serum GGT düzeyleri de dahil laboratuvar değerleri ölçüldü. Greftin tıkalı olması ≥%70 lüminal darlık bulunması veya distal TIMI 3 akım olmaması şeklinde tanımlandı. Kardiyak kateterizasyonda, SVG 53 hastada (%42.4; 40 erkek, 13 kadın; ortalama yaş 65±8) açık, 72 hastada (%57.6; 62 erkek, 10 kadın; ortalama yaş 64±9) tıkalı bulundu.

Bulgular: İki grup yaş, cinsiyet, hipertansiyon, diabetes mellitus, koroner arter hastalığı için aile öyküsü, sigara ve alkol alımı açısından benzer bulundu. Grefti açık ve tıkalı olan hastalarda ameliyattan koroner anjiyografiye kadar geçen ortalama süre benzerdi (sırasıyla 6.8±4.3 ve 8.1±3.7 yıl; p>0.05). Grefti tıkalı olan hastalarda bel çevresi daha büyük (p=0.02), total kolesterol (p=0.001), trigliserit (p=0.02), ürik asit (p<0.001), hs-CRP (p<0.001), GGT (p<0.001) ve fibrinojen (p<0.001) düzeyleri anlamlı derecede yüksek bulundu. Serum GGT düzeyleri, bel çevresi (r=0.2, p=0.04), serum ürik asit (r=0.3, p=0.008) ve hs-CRP (r=0.3, p=0.002) düzeyleriyle orta düzeyde ancak anlamlı ilişki gösterdi. Lojistik regresyon analizinde, total kolesterol (OO=1.012, %95 GA 1.002-1.023, p=0.03), hs-CRP (OO=1.968, %95 GA 1.17-3.311, p=0.01), ürik asit (OO=1.57, %95 GA 1.1-2.208, p=0.01) ve serum GGT (OO=1.047, %95 GA 1.002-1.1, p=0.04) SVG tıkanıklığıyla anlamlı ilişki gösterdi.

Sonuç: Bulgularımız, serum GGT aktivitesinin safen ven greftlerinde yüksek tıkanma oranlarıyla ilişkili olduğunu düşündürmektedir.

Anahtar sözcükler: Koroner arter baypas; gama-glutamiltransferaz; greft tıkanıklığı, vasküler; safen ven/transplantasyon.

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Gamma-glutamyltransferase (GGT) is an enzyme located on the cell membrane and is also available in the serum and contributes to the extracellular catabolism of glutathione, which is one of the main antioxidants of the mammalian cells.[1] The measurement of serum GGT levels has long been used for the diagnosis of hepatobiliary disease and as a marker of alcohol consumption.[2] Recently, high GGT levels were reported to be associated with various atherosclerotic risk factors such as diabetes mellitus, hyperlipidemia, and hypertension, independent of alcohol consumption and liver dysfunction. Baseline GGT levels were also found to be related to both cardiovascular and all-cause morbidity and mortality.[3-5] Moreover, some evidence exists suggesting a direct link between increased GGT activity and occurrence or progression of atherosclerosis.[6,7]

Coronary artery bypass graft (CABG) surgery is an effective revascularization method for the treatment of coronary artery disease. The patency rate of grafts mainly predicts the benefit from CABG surgery both on short- and long-term. Since the saphenous veins can be harvested and grafted more rapidly and easily with a sufficient length, they are used frequently for coronary grafting. However, venous grafts have a relatively higher occlusion rate compared with the arterial grafts.[8] Early occlusions are mostly due to technical factors, but the main cause of occlusion beyond one year is newly developed atherosclerosis in grafted saphenous veins.[9,10] So far, no study has examined the relationship between serum GGT activity and graft patency in post-CABG patients. We aimed to investigate whether there was a relationship between saphenous vein graft disease and serum GGT levels in CABG patients examined at least one year after the index operation.

PATIENTS AND METHODS

The study included 125 consecutive patients who had undergone CABG surgery with at least one saphenous vein graft (SVG) between July and December 2006, followed by cardiac catheterization at least one year after CABG. All patients underwent coronary angiography for stable anginal symptoms or positive stress test results. Patients who underwent coronary angiography within one year of CABG, and patients who had acute coronary syndrome, hepatobiliary disease, pancreatic disease, and acute and chronic inflammatory diseases were excluded from the study. The following data were recorded at hospitalization: age, gender, atherosclerotic risk factors such as hypertension, diabetes mellitus, and family history for premature coronary artery disease, smoking habit, alcohol consumption, and current medications. Plasma glucose, lipid profile, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, alkaline phosphatase (ALP), total bilirubin, and direct bilirubin levels were measured in the morning fasting blood samples before angiography. Serum GGT levels were measured by the enzymatic colorimetric assay at 37° C using L-gamma-glutamyl-3-carboxy-4-nitroanilide as a substrate. In our laboratory, the normal reference range of GGT level is 8-61 U/l. Serum high-sensitivity C-reactive protein (hs-CRP) levels were measured by the immunonephelometric method with a normal reference range of 0.00-0.744 mg/dl for healthy individuals. Complete blood counts were analyzed by standard methods and fibrinogen levels were measured with the Clauss method.

After getting local ethics committee approval for the study and written informed consent from each patient, all patients underwent routine coronary angiography using the Judkins technique on a digital angiography equipment. Selective angiograms were obtained to evaluate the patency of SVG with appropriate catheters. Aortography was performed in case the SVG could not be visualized. All angiograms were assessed by interventional cardiologists blinded to the patient's laboratory data. Occluded grafts were defined as a luminal stenosis of ≥70% or absence of distal TIMI (Thrombosis In Myocardial Infarction) 3 flow. Patients were divided into two groups based on the patency of SVGs. Patients with a patent or occluded SVG were included in group A and group B, respectively.

Statistical analysis. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Student's t-test was used to compare continuous variables and chi-square test was used for categorical variables. In the whole group, Pearson correlation coefficient was used to

Table 1. Localizations of saphenous vein grafts in 125 patients

	n	%
Circumflex artery	39	31.2
Right coronary artery	17	13.6
Circumflex and right coronary artery (sequential)	53	42.4
Diagonal artery	6	4.8
Circumflex and diagonal artery (sequential)	4	3.2
Left anterior descending artery	5	4.0
Left anterior descending and circumflex (sequential)	1	0.8

Table 2. Demographic, clinical, and laboratory findings of the patients having a patent (group A) or occluded (group B) saphenous vein graft

	Group A (n=53)			Group B (n=72)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			65±8			64±9	0.5
Sex							0.16
Male	40	75.5		62	86.1		
Female	13	24.5		10	13.9		
Hypertension	36	67.9		48	66.7		0.8
Diabetes mellitus	27	50.9		39	54.2		0.8
Smoking	11	20.8		19	26.4		0.5
Family history	20	37.7		30	41.7		0.7
Alcohol	1	1.9		5	6.9		0.2
Waist circumference (cm)			99±8			103±14	**0.02**
Time after CABG surgery (years)			6.8±4.3			8.1±3.7	0.8
Medications							
Aspirin	46	86.8		68	94.4		0.2
ACE inhibitor	23	43.4		39	54.2		0.3
Angiotensin II receptor blocker	7	13.2		9	12.5		0.9
Beta-blocker	42	79.3		58	80.6		0.8
Calcium channel blocker	6	11.3		11	15.3		0.6
Antihyperlipidemic drugs	34	64.2		48	66.7		0.9
Laboratory findings							
Glucose (mg/dl)			121±45			129±58	0.4
Total cholesterol (mg/dl)			171±45			199±51	**0.001**
HDL-cholesterol (mg/dl)			48±14			44±19	0.2
Triglyceride (mg/dl)			133±54			162±84	**0.02**
Aspartate aminotransferase (U/l)			22±5			23±5	0.2
Alanine aminotransferase (U/l)			22±7			23±7	0.5
Gamma-glutamyltransferase (U/l)			24±10			32±11	**<0.001**
Alkaline phosphatase (U/l)			169±45			166±38	0.7
Total bilirubin (mg/dl)			0.80±0.30			0.86±0.27	0.2
Direct bilirubin (mg/dl)			0.27±0.19			0.31±0.16	0.1
Uric acid (mg/dl)			5.1±1.4			6.3±1.6	**<0.001**
Fibrinogen (g/l)			2.7±0.8			3.3±1.0	**<0.001**
High-sensitivity CRP (mg/dl)			0.64±0.66			1.60±1.32	**<0.001**
White blood cell count (x10^3/mm^3)			7.9±1.7			7.7±1.7	0.5

assess correlations between serum GGT levels and other continuous variables. A two-tailed *p* value of <0.05 was considered to be statistically significant. Multiple logistic regression analysis was used to evaluate the independent predictors of occluded SVGs. Parameters with a *p* value of <0.1 in univariate analysis were included in the model. All computations were performed using the SPSS 10.0 statistical software package.

RESULTS

Table 1 shows the localizations of SVGs used in CABG surgery. Only five patients (4%) had SVG for grafting of the left anterior descending artery (LAD), in the remaining, the left internal mammary artery was grafted to the LAD. Saphenous vein grafts were found to be patent in 53 patients (42.4%) and occluded in 72 patients (57.6%). Table 2 demonstrates clinical and laboratory characteristics of the two groups. There were no significant differences between the two groups with regard to age, gender, presence of hypertension, diabetes mellitus, family history of coronary artery disease, smoking habit, and alcohol consumption. The mean time from CABG to coronary angiography was similar. Waist circumference was greater in patients with occluded veins (p=0.02). Serum levels of total cholesterol, triglyceride, uric acid, hs-CRP, and fibrinogen were significantly higher in group B. The two groups had similar levels of serum AST, ALT, ALP, total and direct bilirubin, but the mean serum GGT level was significantly higher in patients with occluded SVG. In the whole group, serum GGT level was moderately but significantly correlated with waist circumference (r=0.2, p=0.04), serum uric acid (r=0.3, p=0.008), and hs-CRP (r=0.3, p=0.002).

Table 3. The predictors of saphenous vein graft occlusion

	Odds ratio	95% confidence interval	*p*
Total cholesterol	1.012	1.002 - 1.023	**0.03**
Triglyceride	1.0	0.993 - 1.006	0.9
Waist circumference	1.018	0.984 - 1.054	0.3
Gamma-glutamyltransferase	1.047	1.002 - 1.1	**0.04**
High-sensitivity CRP	1.968	1.17 - 3.311	**0.01**
Fibrinogen	1.235	0.737 - 2.071	0.4
Uric acid	1.57	1.1 - 2.208	**0.01**
Time after CABG surgery	1.017	0.906 - 1.143	0.8

In logistic regression analysis, taking the vein graft occlusion as the dependent variable, total cholesterol (OR=1.012, 95% CI 1.002-1.023, p=0.03), hs-CRP (OR=1.968, 95% CI 1.17-3.311, p=0.01), uric acid (OR=1.57, 95% CI 1.1-2.208, p=0.01), and serum GGT (OR=1.047, 95% CI 1.002-1.1, p=0.04) levels were found to be significant predictors of SVG occlusion (Table 3).

DISCUSSION

In selected patients, CABG surgery is an effective revascularization method, improving cardiac mortality and morbidity. The benefit of CABG is mainly drawn by the patency of grafts on both short- and long terms. Despite higher early and late occlusion rates, autologous SVGs are widely used in CABG surgery. Occlusion of SVGs due to atherosclerosis is expected after a period of one year.[10] Therefore, only patients who had symptoms one year after the index operation were included in our study in order to determine the relationship between GGT levels and atherosclerotic process of SVG. As expected, patients with occluded grafts had a more atherothrombotic risk profile as compared with those with patent vein grafts. In addition, serum GGT levels were also significantly higher in patients with occluded vein grafts despite similar levels of hepatic transaminase and ALP. Moreover, GGT levels were independently associated with SVG disease.

In clinical practice, determination of serum GGT levels is routinely used as a basic biochemical test for the evaluation of liver function and alcohol consumption. Serum GGT level has been found to be an independent predictor of mortality from all causes.[11] High serum GGT levels have also been associated with an increased risk for myocardial infarction and stroke.[11,12] These associations were partly explained by the demonstrated correlations of GGT with various risk factors in the pathogenesis of cardiovascular diseases, such as hypertension, hyperlipidemia, increased body mass index, hypertension, insulin resistance, and type 2 diabetes mellitus.[13-18] Despite small sample size of our study group, significant correlations were noted between serum levels of GGT and various metabolic risk parameters including waist circumference, uric acid, and hs-CRP levels.

At the cellular level, GGT activity is crucial to maintain intracellular presence of glutathione (GSH), which is an important antioxidant for mammalian cells. Since GSH itself cannot be transported across the cell membranes, GGT which is a membrane-bound enzyme, degrades extracellular GSH to its thiol metabolites such as cysteinyl-glycine and glutamate. These degradation products can be transported across the membrane to the cytoplasm where they are involved in the GSH synthesis pathway.[19] Despite this role of intracellular antioxidant mechanisms, thiol metabolites may cause prooxidant effects by generating superoxide anion radicals through their interaction with free iron[20] and may promote LDL oxidation in the atherosclerotic process. This hypothesis is supported with the demonstration of dense GGT activity in foam cells within atherosclerotic plagues.[7] It has also been shown that serum GGT forms complexes with several plasma proteins including lipoproteins. Thus, GGT adsorbed to circulating LDL may easily diffuse inside the atherosclerotic plaques.[6,21] Therefore, the oxidative stress caused by GGT might in part contribute to the evolution and instabilization process of atherosclerotic plaques. Demonstration of strong GGT activity within human atherosclerotic plaques supports this assumption.[6,22] Interestingly, it has been indicated that history of coronary artery disease further strengthens the prognostic value of serum GGT activity. Emdin et al.[23] demonstrated an association between high serum GGT levels and increased risk for cardiovascular death and nonfatal myocardial infarction in patients with angiographically documented coronary artery disease. It seems that serum GGT levels could be helpful in further stratifying patients with established coronary artery disease in addition to common atherosclerotic risk factors.[24] Recent evidence suggests

that serum GGT activity is also related to neointimal proliferation of coronary arteries after percutaneous coronary artery intervention. Ulus et al.[25] have shown a strong association between serum GGT activity and coronary stent restenosis independent of alcohol consumption. Although the mechanism of stent restenosis is different, in our study serum GGT activity was also a significant predictor of SVG occlusion, in addition to hs-CRP, total cholesterol, and uric acid levels. All these findings suggest that GGT activity is involved in various processes of arterial injury and stenosis.

High-sensitivity CRP is a principal inflammatory risk marker of atherosclerosis. It was found to be an independent predictor of SVG occlusion in our study. Besides, there was a significant correlation between serum levels of GGT and hs-CRP. Recent studies showed an association between serum GGT activity of normal range and CRP concentrations in healthy adults.[24,26] Although these cross-sectional studies have not yielded a casual consequence of this relationship, oxidative stress is known to play a crucial role in chronic inflammatory processes such as atherosclerosis.[27,28] Therefore, it is plausible to suggest that, as a mediator of oxidative stress, GGT activity might directly participate in inflammatory reactions occurring in the evolution of atherosclerotic plaques.

There are some limitations that must be taken into account in evaluating our results. Firstly, since baseline GGT levels of most patients were not available before CABG surgery, it could not be possible to compare baseline and follow-up GGT levels. Such a comparison might be more valuable. Secondly, we included only patients with stable anginal symptoms and/or a positive stress test at least one year after CABG surgery. Therefore, our results might not be applicable to all CABG patients. Finally, there are so many factors which may significantly affect serum GGT levels including age, gender, alcohol consumption, etc. Due to insufficient number of patients, these factors could not be analyzed in detail.

In conclusion, our study showed that elevated GGT levels in patients with CABG, even in normal limits, were associated with SVG disease and might be a predictor of SVG occlusion. Based on current data from our study and epidemiological studies, serum GGT activity may be included in multifactorial risk algorithms of these post-CABG patients in the future. To better clarify this issue, randomized studies with high numbers of patients are required to determine the universal cut-off values of this parameter.

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