

Gamma-glutamyltransferase activity in patients with calcific aortic stenosis

Kalsifik aort darlığı bulunan hastalarda gama-glutamiltransferaz aktivitesi

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Objectives: We evaluated gamma-glutamyltransferase (GGT) activity in patients with calcific aortic stenosis (AS) and investigated the association between GGT levels and the maximum and mean aortic gradients.

Study design: The study included 34 patients (5 women, 29 men; mean age 63±13 years) with calcific AS. Thirty-eight subjects (8 women, 30 men; mean age 57±10 years) with echocardiographically normal aortic valves constituted the control group. Echocardiographic evaluation was performed in all the subjects and venous blood samples were obtained to determine plasma glucose, fibrinogen, total cholesterol, LDL and HDL cholesterol, triglyceride, and GGT levels. The activity of GGT was determined by the kinetic method. Associations were sought between GGT levels and the maximum and mean aortic gradients.

Results: In the AS group, the mean maximum and mean gradients of the aortic valve were 74±15 mmHg and 39±9 mmHg, respectively. Fibrinogen concentrations differed significantly between the patient and control groups (3.9±1.7 mg/dl and 2.9±0.9 mg/dl, respectively; $p<0.02$). Activity of GGT was not influenced by gender in both groups ($p>0.05$). Compared to controls (21±14 U/l), the mean GGT level was significantly higher in the AS group (39±13 U/l; $p=0.005$). In linear regression analysis, weak but significant sex- and age-adjusted correlations were found between the GGT level and the maximum ($r=0.20$, $p<0.001$) and mean ($r=0.17$, $p<0.001$) aortic gradients.

Conclusion: Patients with calcific AS have higher GGT levels compared to controls, suggesting the presence of a common etiologic mechanism for both calcific AS and coronary artery disease.

Key words: Aortic valve stenosis/blood; calcinosis/complications; coronary arteriosclerosis; gamma-glutamyltransferase.

Amaç: Kalsifik aort darlığı (AD) bulunan hastalarda gama-glutamiltransferaz (GGT) aktivitesi ve GGT düzeyleri ile maksimum ve ortalama aortik gradiyentler arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya kalsifik AD olan 34 hasta (5 kadın, 29 erkek; ort. yaş 63±13) alındı. Ekokardiyografi ile aort kapağı normal bulunan 38 kişiden (8 kadın, 30 erkek; ort. yaş 57±10) kontrol grubu oluşturuldu. Tüm olgularda ekokardiyografik inceleme yapıldı ve venöz kan örnekleri alınarak plazma glukozu, fibrinojen, total kolesterol, LDL ve HDL kolesterol, trigliserid ve GGT düzeyleri belirlendi. Gama-glutamiltransferaz aktivitesi kinetik yöntemle belirlendi. Maksimum ve ortalama aortik gradiyentler ile GGT aktivitesi arasında olası ilişkiler araştırıldı.

Bulgular: Kalsifik AD grubunda aort kapağı maksimum ve ortalama aortik gradiyentler sırasıyla 74±15 mmHg ve 39±9 mmHg ölçüldü. Hasta ve kontrol grupları arasında fibrinojen konsantrasyonu açısından anlamlı farklılık görüldü (sırasıyla, 3.9±1.7 mg/dl ve 2.9±0.9 mg/dl; $p<0.02$). Her iki grupta da cinsiyetin GGT aktivitesini etkilemediği görüldü ($p>0.05$). Kontrol grubuyla (21±14 U/l) karşılaştırıldığında, ortalama GGT düzeyi AD'li grupta anlamlı derecede yüksek bulundu (39±13 U/l; $p=0.005$). Cinsiyet ve yaşa göre düzeltilmiş doğrusal regresyon analizinde, GGT aktivitesi maksimum ($r=0.20$, $p<0.001$) ve ortalama ($r=0.17$, $p<0.001$) aortik gradiyentler ile zayıf, ama anlamlı korelasyon gösterdi.

Sonuç: Kalsifik AD'li hastalarda GGT düzeyi kontrole göre daha yüksek seyretmektedir. Bu durum, kalsifik AD ve koroner arter hastalığında benzer etyolojik mekanizmanın rol oynayabileceğini düşündürmektedir.

Anahtar sözcükler: Aort kapak darlığı/kan; kalsinozis/kompikasyon; koroner arterioskleroz; gama-glutamiltransferaz.

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Gamma-glutamyltransferase (GGT) is a routinely used biochemical marker for the evaluation of liver function, with low-cost and high sensitivity. In addition, it has been found that GGT is associated with adverse cardiovascular events, especially atherosclerosis.^[1-4] It is found on the outer layer of cells and in serum, and is responsible for extracellular degradation of glutathione, which is an antioxidant molecule in mammalian cells.

Calcific aortic stenosis (AS) is common in older ages and is one of the most commonly encountered valvular pathologies requiring surgery in developed countries.^[5] Pathological and epidemiological studies have shown similar mechanisms for atherosclerosis and aortic stenosis. Infiltration of lipid-laden foam cells and proliferation of smooth muscle cells have been shown to cause subendothelial thickening of aortic leaflets.^[6,7] In addition, it has been shown that high serum cholesterol levels are associated with both the development^[8] and rapid progression of AS.^[9]

The aim of this study was to evaluate GGT activity in patients with calcific AS and to determine whether the degree of AS was correlated with GGT levels.

PATIENTS AND METHODS

Study population. The study was conducted in Türkiye Yüksek İhtisas Training and Research Hospital from April 2005 to July 2005 and included 34 patients (5 women, 29 men; mean age 63±13 years) in whom a systolic ejection murmur was elicited during auscultation and the presence of AS was confirmed by echocardiographic evaluation. The control group was comprised of 38 subjects (8 women, 30 men; mean age 57±10 years) with echocardiographically normal aortic valves.

Exclusion criteria included the following: aortic stenosis with a mean gradient of less than 20 mmHg (mild disease); congestive heart failure; other valvular diseases exceeding a mild degree in severity; rheumatic or congenital valvular diseases; all forms of diabetes mellitus; alcohol intake; treatment for hyperlipidemia; renal or hepatic dysfunction (creatinine >2.5 mg/dl, AST and ALT 2 times higher than the upper normal limit, respectively).

Diagnosis of AS. Transthoracic Doppler echocardiography was used for the diagnosis of AS. The peak aortic gradient was calculated using continuous wave Doppler ultrasound scans obtained along the aortic valve from a range of peak velocities, and the mean gradient was calculated using the time-velocity integrals.

The control subjects had echocardiographically normal aortic valve leaflets.

Laboratory data. Fasting peripheral venous blood samples were obtained from all the patients and controls for the measurement of fasting plasma glucose, fibrinogen, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, and GGT levels. Blood samples were centrifuged and plasma was obtained. Fasting blood glucose, fibrinogen, GGT, total cholesterol, HDL cholesterol, and triglyceride levels were measured by standard laboratory techniques. Serum total cholesterol and triglyceride levels were measured enzymatically. HDL cholesterol was determined after precipitation of apolipoprotein B-containing lipoproteins with manganese chloride and dextran sulphate. Measurement of LDL cholesterol was made using the formula described by Friedewald et al.^[10] Plasma glucose was measured with the glucose oxidase technique. Plasma fibrinogen concentration was determined by the Clauss' method. The activity of GGT was determined by the kinetic method.

Anthropometric measurements. Height and weight were measured and body mass index (BMI) was calculated from height and weight data (kg/m²).

Statistical analysis. Data were analyzed with the SPSS software (version 10.0) for Windows. Continuous variables were given as mean±standard deviation, and categorical variables as percentages. Differences in baseline characteristics of the patient and control groups were assessed with the t-test for continuous variables and chi-square test for binary variables. Temporal change in the parametric data was evaluated by paired sample's t-test. Correlations between the baseline characteristics and the presence of AS were sought by the Pearson correlation test. Linear regression analysis was used to evaluate the relationship between GGT activity and aortic gradients. All the tests were two-sided with a 0.05 significance level.

RESULTS

Baseline demographic and laboratory characteristics of the patients are outlined in Table 1. In the AS group, the mean maximum and mean gradients of the aortic valve were 74±15 mmHg and 39±9 mmHg, respectively. There were no significant differences between the study and control groups with respect to baseline demographic and laboratory characteristics except for fibrinogen concentrations, which were 3.9±1.7 mg/dl and 2.9±0.9 mg/dl (p<0.02), respectively (Table 1).

Table 1. Baseline characteristics of the patient and control groups

	Control group (n=38)			Aortic stenosis (n=34)			p
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			57±10			63±13	0.1
Sex							0.6
Male	30	79.0		29	85.3		
Female	8	21.1		5	14.7		
Hypertension	6	15.8		8	23.5		0.5
Hyperlipidemia	10	26.3		13	38.2		0.4
Body mass index (kg/m ²)			25.4±5.4			25.1±4.9	0.8
Cholesterol (mg/dl)							
Total			188±38			187±46	0.9
HDL			48±13			43±12	0.2
LDL			113±32			118±39	0.6
Triglyceride (mg/dl)			126±52			125±59	0.9
Blood pressure (mmHg)							
Systolic			121±18			122±16	0.8
Diastolic			75±8			76±8	0.6
Heart rate (beat/min)			73±5			74±9	0.6
Fibrinogen (mg/dl)			2.9±0.9			3.9±1.7	0.02

Activity of GGT was not influenced by gender in both groups ($p>0.05$). Compared to controls (21 ± 14 U/l), the mean GGT level significantly differed in the AS group (39 ± 13 U/l; $p=0.005$). In linear regression analysis, weak but significant sex- and age-adjusted correlations were found between the GGT level and the maximum ($r=0.20$, $p<0.001$) and mean ($r=0.17$, $p<0.001$) aortic gradients.

DISCUSSION

In our study, we found that patients with calcific AS had significantly increased GGT levels compared to controls. In addition, age- and sex-adjusted regression analysis within the patient group showed a correlation between the GGT activity and the peak and mean aortic gradients. Despite relatively low correlation coefficients, this is a hitherto unreported association.

Although GGT, a catalytic enzyme, is routinely used for the evaluation of liver function, it has been demonstrated that it is also associated with cardiovascular diseases.^[1-4] It catabolizes glutathione which is an antioxidant found on the plasma surface of various cell types and in serum. Catalytically-active GGT is influenced by genetic^[11] and environmental^[12] factors. A positive correlation has been shown between catalytically-active serum GGT and body mass index, plasma glucose, total cholesterol, LDL and HDL cholesterol, triglyceride, heart rate, and systolic/diastolic blood pressures.^[12] Immunohistochemical studies demonstrated catalytically-active GGT within human atherosclerotic plaques.^[2] It has been postulated that active

GGT is conveyed to atherosclerotic plaques via LDL lipoproteins.^[13] This catalytically-active enzyme degrades glutathione resulting in the formation of cysteinyl-glycine which reduces Fe^{+3} to Fe^{+2} and subsequently mediates free radical formation such as superoxide anion and hydrogen peroxide.^[1] These free radicals catalyze the oxidation of LDL lipoproteins^[14] which further promote plaque formation and destabilization that result in plaque rupture and myocardial infarction.

Calcific AS is considered to be the consequence of degeneration of the aortic valve leaflets in older ages. However, AS has an active rather than a passive progression. A strong association has been demonstrated between the presence of calcific AS and risk factors for atherosclerosis, especially high cholesterol levels,^[15,16] suggesting that a similar mechanism might be involved in these two diseases. Mautner and Roberts^[17] reported that the incidence of coronary heart disease was 37% in patients with calcific AS, suggesting the possibility of a common etiologic mechanism. In addition, treatment with hydroxymethylglutaryl coenzyme-A reductase inhibitors and statins was associated with a slower progression of calcific AS.^[18]

Study limitations. Our sample size was small, affecting the strength of our findings. In addition, several confounding factors were not studied including inflammatory markers (high-sensitive C-reactive protein, interleukins), life style behaviors (physical activity, diet) and genetic factors.

In conclusion, patients with calcific AS have higher GGT concentrations compared to control subjects, suggesting the presence of a common etiologic mechanism for both calcific AS and coronary artery disease.

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