Increased serum gamma-glutamyltransferase activity in patients with metabolic syndrome

Metabolik sendromu olan hastalarda artmış serum gama-glutamiltransferaz düzeyi

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ABSTRACT

Objectives: Accumulating data indicate that serum gamma-glutamyltransferase (GGT) activity represents a true marker of atherosclerotic cardiovascular disease and has prognostic importance. In this study, we sought to evaluate serum GGT activity in patients with metabolic syndrome (MetS).

Study design: We enrolled 232 patients (mean age 60.4 years) from our outpatient cardiology clinic, 117 with and 115 without MetS (control group) as defined by the ATP-III criteria. The results of serum liver function tests including serum GGT and C-reactive protein (CRP) levels were compared between the two groups.

Results: The two groups were similar with regard to age, sex, smoking, and family history of coronary artery disease (p>0.05). The prevalences of hypertension and dyslipidemia were significantly higher in patients with MetS. Compared with controls, patients with MetS had significantly higher serum GGT [(median 21, interquartile range (16-33) *vs.* 19 (14-26) U/l; p=0.008] and C-reactive protein levels [6.2 (3.6-9.4) *vs.* 5.0 (3.1-7.0) U/l; p=0.044]. A high GGT activity (>40 U/l) was determined in 14.5% of the patients with MetS and in 4.4% of the control subjects (p=0.012). Serum GGT level showed significant correlations with MetS (r=0.24, p=0.001), CRP (r=0.20, p=0.003), triglyceride (r=0.18, p=0.006), HDL cholesterol (r=-0.19, p=0.004), aspartate aminotransferase (r=0.15, p=0.02), alanine aminotransferase (r=0.32, p=0.001), and alkaline phosphatase (r=0.16, p=0.01). This significant association continued only for MetS (β=-0.25, p=0.03), HDL cholesterol (β=-0.18, p=0.03), and alkaline phosphatase (β=0.17, p=0.01) in multivariate regression analysis.

Conclusion: Our findings suggest that patients with MetS have higher serum GGT and CRP levels compared with controls. This increased GGT level might be a marker of increased oxidative stress and premature atherosclerosis.

ÖZET

Amaç: Giderek artan veriler serum gama-glutamiltransferaz (GGT) düzeyinin aterosklerotik kardiyovasküler hastalık için gerçek bir belirteç olduğunu ve prognostik değer taşıdığını göstermektedir. Bu çalışmada metabolik sendromu (MetS) olan hastalarda GGT düzeyinin incelenmesi amaçlandı.

Çalışma planı: Kardiyoloji polikliniğine başvuran 232 hasta (117 MetS, 115 kontrol; ort. yaş 60.4) çalışmaya alındı. Metabolik sendrom tanısı ATP III ölçütlerine göre kondu. Hasta ve kontrol grubunun GGT dahil karaciğer fonksiyon testleri sonuçları ve C-reaktif protein (CRP) düzeyleri karşılaştırıldı.

Bulgular: İki grup yaş, cinsiyet, sigara içme ve ailede koroner arter hastalığı öyküsü açısından benzerdi (p>0.05). Hipertansiyon ve hiperlipidemi sıklığı MetS grubunda daha yüksek idi. Kontrol grubuyla karşılaştırıldığında, MetS olan hastalarda serum GGT [medyan 21, çeyreklerarası aralık (16-33) ve 19 (14-26) U/l; p=0.008] ve C-reaktif protein [6.2 (3.6-9.4) ve 5.0 (3.1-7.0) U/l; p=0.044] düzeyleri anlamlı derecede yüksek saptandı. Yüksek GGT aktivitesi (>40 U/l) MetS grubunda %14.5 oranında, kontrol grubunda %4.4 oranında görüldü (p=0.012). Serum GGT düzeyi şu parametrelerle anlamlı ilişki gösterdi: MetS (r=0.24, p=0.001), CRP (r=0.20, p=0.003), trigliserit (r=0.18, p=0.006), HDL-kolesterol (r=-0.19, p=0.004), aspartat aminotransferaz (r=0.15, p=0.02), alanin aminotransferaz (r=0.32, p=0.001) ve alkalin fosfataz (r=0.16, p=0.01). Çokdeğişkenli regresyon analizinde bu anlamlılık sadece MetS (β=-0.25, p=0.03), HDL-kolesterol (β=-0.18, p=0.03) ve alkalin fosfataz (β=0.17, p=0.01) için vardı.

Sonuç: Bulgularımız MetS olan hastalarda serum GGT ve CRP düzeylerinin yüksek olduğunu göstermektedir. Artmış GGT düzeyi MetS'li olgularda artmış oksidatif stresin ve erken aterosklerozun bir belirteci olabilir.

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Serum gamma-glutamyltransferase is a marker of hepatobiliary disease and alcohol consumption. It is a plasma membrane enzyme with a central role in glutathione homeostasis which is important in maintaining adequate concentrations of intracellular glutathione to protect cells against oxidants.

It has been shown in rat lung epithelial cells that GGT expression becomes more apparent by oxidants, suggesting that increased GGT activity may be a marker for oxidative stress.[1] These findings have been supported by other research, demonstrating that serum concentrations of GGT could be used as a marker for increased oxidative stress in humans.[2] Accumulating data indicate that there is an association between serum GGT levels (within the normal range) and cardiovascular diseases.[3,4] An association has been shown between elevated GGT and obesity.[5] Nonalcoholic fatty liver disease, a manifestation of obesity, has been reported to be associated with GGT elevation.[6] Several studies have revealed that elevated serum GGT is a predictor for the development of diabetes mellitus.[3,7,8] A population-based study demonstrated a significant association between serum GGT levels and type 2 DM.[9]

Factors responsible for elevated liver enzymes, especially GGT, have been shown to include increasing age, obesity, DM, physical inactivity, insulin resistance, hypertension, and dyslipidemia.[4] Metabolic syndrome is a constellation of atherosclerotic risk factors and identifies patients who are at high risk for DM and cardiovascular disease.

Considering these associations between GGT and cardiovascular disease, we evaluated the possible relationship between serum GGT activity and MetS. We also investigated potential associations between serum GGT levels and cardiac risk factors, and the levels of other liver enzymes and C-reactive protein.

PATIENTS AND METHODS

We enrolled 232 patients from our outpatient cardiology clinic, 117 with and 115 without MetS (control group). The diagnosis of MetS was based on the National Cholesterol Education Program, ATP III criteria.[10] Patients having at least three of the following five criteria were considered to have MetS: *(i)* fasting blood glucose ≥110 mg/dl; *(ii)* serum triglyceride ≥150 mg/dl or being on lipid lowering therapy; *(iii)* serum HDL <40 mg/dl in men and <50 mg/dl in women or being on antilipidemic therapy; *(iv)* blood pressure ≥130 mmHg systolic and/or ≥85 mmHg diastolic or being on antihypertensive therapy; and *(v)* waist circumference >102 cm in men and >88 cm in women.

Abbreviations:

ALT	*Alanine aminotransferase*
AP	*Alkaline phosphatase*
AST	*Aspartate aminotransferase*
CRP	*C-reactive protein*
DM	*Diabetes mellitus*
GGT	*Gamma-glutamyltransferase*
MetS	*Metabolic syndrome*
NAFLD	*Nonalcoholic fatty liver disease*

Exclusion criteria involved the presence of the following: alcohol intake more than 30 g/day, hepatitis B or C infection or other known liver diseases, liver enzymes exceeding three times the upper reference range, use of hepatotoxic drugs, acute infectious/inflammatory conditions, familial hyperlipidemia, or New York Heart Association class 3-4 heart failure.

Dyslipidemia was defined as a total cholesterol level >200 mg/dl, LDL cholesterol level >130 mg/dl, HDL cholesterol level <40 mg/dl, or a triglyceride level >150 mg/dl or being on lipid lowering treatment (ATP III). Body mass index was calculated as weight (kg)/[height (m)]^2. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest with the patient in the standing position and at the end of a normal expiration. A measuring tape was placed around the abdomen parallel to the floor, taking care not to compress the skin while reading. Hypertension was defined as blood pressure ≥140/90 mmHg on two or more measurements or being on antihypertensive medication. Smoking was defined as current cigarette smoking or abstinence ≤2 years.

Venous blood samples were obtained after overnight fasting. Serum liver enzymes, CRP levels, and other hematochemical variables were determined and compared between the groups. Serum GGT levels were measured by the enzymatic calorimetric test at 37 ºC on a Roche/Hitachi analyzer (Mannheim, Germany), using L-gamma-glutamyl-3-carboxy-4-nitroanilide as a substrate. Using this method, the normal reference range of the GGT level was 8 to 61 U/l. Serum CRP levels were determined by the immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany) with a normal reference value of <10 mg/l. Enzymatic measurements of total cholesterol, triglyceride, and HDL levels were performed on a Hitachi 912 autoanalyzer using commercial kits. LDL was calculated using the Friedewald formula.

The study protocol was approved by the local ethics committee and informed consent was obtained from each subject.

Table 1. Demographic and clinical characteristics of the study and control groups

	Metabolic syndrome (n=117)			Control (n=115)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			60.8±9.7			60.1±9.7	0.5
Gender							0.4
Female	86	73.5		79	68.7		
Male	31	26.5		36	31.3		
History of myocardial infarction	15	12.8		8	7.0		0.1
Atrial fibrillation	3	2.6		5	4.4		0.7
Body mass index (kg/m^2)			30.2±4.6			27.6±4.9	**<0.001**
Waist circumference (cm)			101.1±9.9			94.5±11.3	**<0.001**
Risk factors							
Hypertension	104	88.9		67	58.3		**<0.001**
Dyslipidemia	93	79.5		69	60.0		**0.001**
Smoking	30	25.6		27	23.5		0.07
Menopause (females)	68	79.1		60	76.0		0.7
Family history of early CAD	51	43.6		50	43.5		1.0
Medications							
ACE inhibitor/angiotensin receptor blocker	53	45.3		34	29.6		0.001
Calcium channel blocker	28	23.9		18	15.7		0.009
Beta-blocker	28	23.9		26	22.6		0.1
Diuretics	38	32.5		30	26.1		0.02
Statin	43	36.8		17	14.8		<0.0001
Fibrates	6	5.1		2	1.7		0.2

Statistical analyses were performed using the SPSS software (ver. 9.0). Data were expressed as means ± standard deviation (SD) or median and interquartile ranges, or as frequencies and group percentages, where appropriate. Distribution of continuous variables for normality was tested with the one-sample Kolmogorov-Smirnov test. Differences between patients with MetS and controls for variables with or without normal distribution were evaluated using the unpaired t-test and Mann-Whitney U-test, respectively. Categorical variables were analyzed with the chi-square test. Correlations were sought by the Pearson correlation analysis. Multivariate linear regression analysis was used to assess the independent associations with GGT. All *p* values were two-sided, and a *p* value of <0.05 was considered significant.

RESULTS

The mean age of the study population was 60.4±9.7 years, and 165 (71.1%) were females. Table 1 shows demographic and clinical characteristics and laboratory results for both groups. The two groups with and without MetS were homogenous with regard to age and sex (p>0.05).

As expected, the prevalences of hypertension and dyslipidemia were significantly higher in patients with MetS, whereas the two groups were similar with respect to smoking and family history of coronary artery disease. The mean values for body mass index and waist circumference were significantly higher in the MetS group. Concerning the medications, the use of an ACE inhibitor/angiotensin receptor blocker, calcium channel blocker, and diuretics was higher in patients with MetS (p<0.05), while beta blocker use was similar in both groups (p>0.05). As expected, statin use was significantly higher in the MetS group (p<0.05). Eight patients were on fibrate therapy, six in the MetS group and two in the control group.

Compared with the controls, patients with MetS had a significantly higher median serum GGT level (p=0.008, Table 2). This association was also observed after exclusion of patients with a history of

Table 2. Laboratory results of the study and control groups

	Metabolic syndrome (n=117)		Control (n=115)		
	Mean±SD	Median (Range)	Mean±SD	Median (Range)	*p*
Fasting blood glucose (mg/dl)	105±19		94±14		**<0.001**
Total cholesterol (mg/dl)	211±38		204±53		0.2
HDL cholesterol (mg/dl)	45±10		55±13		**<0.001**
LDL cholesterol (mg/dl)	132±32		119±32		**0.003**
Triglyceride (mg/dl)		193 (153-259)		115 (84-158)	**<0.001**
Uric acid (mg/dl)	5.6±1.3		5.6±1.3		0.1
C-reactive protein (mg/l)		6.2 (3.6-9.4)		5.0 (3.1-7.0)	**0.044**
Gamma-glutamyltransferase (U/l)		21 (16-33)		19 (14-26)	**0.008**
Aspartate aminotransferase (U/l)	22.3±6.2		24.0±9.8		0.1
Alanine aminotransferase (U/l)	22.8±11.5		22.6±13.6		0.6
Alkaline phosphatase (U/l)	190.4±51.6		198.1±56.8		0.3
Total bilirubin (mg/dl)	0.61±0.32		0.69±0.30		0.1
Direct bilirubin (mg/dl)	0.16±0.13		0.17±0.10		0.7
Hemoglobin (g/dl)	13.8±1.2		13.8±1.2		0.9
Leukocyte (K/mm^3)	6.9±1.6		6.8±2.3		0.8
Platelets (K/mm^3)	256±74		259±70		0.7

alcohol consumption of less than 30 g/day (p<0.001). When the patients were divided into two groups as in previous studies based on serum GGT levels of ≤40 U/l (low GGT activity) and >40 U/l (high GGT activity), a high GGT activity was identified in 14.5% of the patients with MetS and in 4.4% of the control subjects (p=0.012). Further evaluation of the two groups based on the median GGT values showed that 53.9% of MetS patients had a GGT concentration above the median value, compared to 41.7% in the control group (p=0.043).

The median serum CRP level was significantly higher in patients with MetS than in controls (p=0.044). Patients with MetS had significantly higher LDL cholesterol (p=0.003) and triglyceride (p<0.001) concentrations, and lower HDL cholesterol levels (p<0.001), whereas total cholesterol levels were similar in the two groups (p>0.05). Serum levels of other liver enzymes including alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase, and total and direct bilirubin concentrations did not differ between the two groups (p>0.05). The two groups were also comparable with regard to complete blood count results (p>0.05).

In correlation analysis, serum GGT level showed significant correlations with MetS (r=0.24, p=0.001), and CRP (r=0.20, p=0.003), triglyceride (r=0.18, p=0.006), and HDL cholesterol (r=-0.19, p=0.004) levels, and with liver enzymes AST (r=0.15, p=0.02), ALT (r=0.32, p=0.001), and AP (r=0.16, p=0.01). Leucocyte count was not correlated with serum GGT (r=0.07, p=0.28). This significant association continued only for MetS (β=-0.25, p=0.03), HDL cholesterol (β=-0.18, p=0.03), and alkaline phosphatase (β=0.17, p=0.01) in multivariate regression analysis. (Table 3).

DISCUSSION

The present study demonstrates that patients with MetS have increased GGT activity, a marker of oxidative stress, and serum CRP, a marker of systemic inflammation.

It has been clearly demonstrated that serum GGT levels even within normal range are associated with some atherosclerotic risk factors and are predictors of future heart disease, hypertension, stroke, and type 2 DM.[4,7,11] Although the exact mechanism responsible for this association is unknown, several possible mechanisms have been proposed for the role of serum GGT in increasing cardiovascular risk. The most widely accepted mechanism is oxidative stress, followed by hepatic insulin resistance and subclinical inflammation.

Table 3. Multivariate predictors of serum GGT activity adjusted for other liver enzymes

	Coefficient	95% CI	*p*
Metabolic syndrome (MetS)	-0.259	-16.0, -0.84	**0.03**
Number of MetS components	-0.20	-6.92, 1.27	0.17
Age	0.013	-0.23, 0.28	0.86
Fasting glucose	0.049	-0.11, 0.20	0.55
HDL cholesterol	-0.182	-0.42, -0.02	**0.03**
Triglyceride	-0.003	-0.02, 0.01	0.96
Waist circumference	0.08	-0.11, 0.36	0.30
Systolic blood pressure	0.06	-0.12, 0.20	0.61
Diastolic blood pressure	-0.14	-0.49, 0.12	0.24
Alkaline phosphatase	0.17	0.01, 0.09	**0.01**

Through these mechanisms, elevated GGT is thought to play a role in the initiation and progression of atherosclerosis.

Second, elevated serum GGT might be a marker of NAFLD, which is thought to cause hepatic insulin resistance. Although serum ALT and GGT levels have also been found to be associated with fatty liver, only GGT activity has been reported to be related to oxidative stress. An association between GGT and systemic inflammation has also been demonstrated.[3,7,12,13] Studies have shown that NAFLD, in which liver enzymes (including GGT) are usually elevated, is associated with insulin resistance, and patients with this condition are at high risk for cardiovascular diseases.[5,14] Conversely, a study in Pima Indians found that ALT concentration but not serum GGT or AST was related to hepatic insulin action.[15]

The third possible mechanism implicated is subclinical chronic inflammation. Evidence indicates that serum GGT elevation might be due to inflammation, an important mechanism in all stages of atherosclerotic cardiovascular disease.[16] C-reactive protein synthesized by the liver as a marker of systemic inflammation has been shown to be associated with MetS, DM, and cardiovascular disease.[17] Indeed, oxidative processes are components of chronic inflammation acting on different pathways and stimulating the inflammatory response. It has been shown that an association exists between serum GGT and CRP levels, while no such association has been reported between ALT and CRP.[18] This finding is important in that increased GGT activity is associated with an inflammation marker, CRP. Recent data have shown that, in the presence of Fe^{3+} and Cu^{2+}, GGT is involved in generating free oxygen radicals, which in turn, induce oxidative stress to cells.[19] Thus, subclinical inflammation and oxidative stress are implicated as important mechanisms in the development of atherosclerosis and MetS. In the CARDIA study (Coronary Artery Risk Development in Young Adults), serum GGT levels within normal limits were found to predict CRP levels, a marker of inflammation, and F_2-isoprostanes, a marker of oxidative activity.[20]

Nakanishi et al.[8] reported that GGT activity was related to the development of impaired fasting glucose or type 2 DM. These authors also found an association between serum GGT and white blood cell count and stated that this finding could provide evidence for subclinical inflammation as an underlying mechanism. In our study, we found a significant association between serum CRP levels and GGT activity, suggesting that subclinical inflammation might act as an underlying mechanism.

Data on serum GGT levels and MetS are limited. In a cross-sectional study, Onat et al.[20] reported that waist circumference was a major determinant of serum GGT activity. Analysis of the Mexico City Diabetes Study revealed that all four liver enzymes –serum ALT, AST, GGT, and AP– were associated with multiple features of MetS, with GGT being associated with the largest number of features.[21] Bo et al.[18] reported that serum levels of GGT in healthy adult subjects with no measurable metabolic abnormalities were associated with fasting glucose levels of normal range, providing evidence for oxidative stress (increased nitrotyrosine levels) and inflammation (elevated CRP levels).

In sum, it may be said that GGT levels seem to be elevated in patients with MetS, a condition that

poses a high risk for atherosclerotic cardiovascular disease. Our findings suggest that GGT might act as an intervening factor in the association between obesity, MetS, and DM. We speculate that the association between GGT levels and MetS might be due to the adverse oxidative pattern of this patient population.

Limitations

Patients in the MetS group had, by definition, 3, 4, or 5 components of the syndrome, while some subjects in the control group had 1 or 2 components. A control group having none of these components would yield better results. The probability of NAFLD is expected to be higher in patients with MetS, a factor that should be taken into account when interpreting our findings. If high-sensitivity CRP, instead of conventional CRP, had been studied, it could have provided us more valuable data.

In conclusion, patients with MetS have a higher serum GGT activity than those without this syndrome. Since GGT can be determined easily, this inexpensive and eligible marker might have important use in clinical practice. Details regarding the underlying link between elevated GGT and multiple coronary risk factors remain unclear. Further research is required to elucidate the exact role of GGT and how the activity of this enzyme is related to MetS or its components.

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Key words: Biological markers/blood; gamma-glutamyltransferase/blood; inflammation; metabolic syndrome X; oxidative stress.

Anahtar sözcükler: Biyolojik belirteç/kan; gama-glutamiltransferaz/kan; enflamasyon; metabolik sendrom X; oksidatif stres.