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## Gamma-glutamyl transferase activity increases in prehypertensive patients

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**Aim:** To investigate the association between serum gamma-glutamyl transferase (gamma-glutamyl transpeptidase, GGT) levels and prehypertension in a nationally representative sample of Turkish adults. GGT is an enzyme present in serum and most cell surfaces. It is used as an oxidative stress marker. Increased serum GGT levels are implicated in increased blood pressure and the progression of hypertension. GGT may also have a role in the pathogenesis of cardiovascular disease, diabetes mellitus, obstructive sleep apnea syndrome, and metabolic syndrome.

**Materials and methods:** Prehypertension was identified as systolic blood pressure ranging from 120 to 139 mmHg or diastolic blood pressure ranging from 80 to 89 mmHg. Enrolled in this study were 23 female and 45 male patients in the prehypertensive group (Group 1; mean age of  $44.6 \pm 11.2$  years) and 25 female and 43 male patients in the normotensive group (Group 2; mean age of  $43.3 \pm 7.0$  years). The serum GGT activity of these patients was measured.

**Results:** The mean GGT activities were significantly higher in the prehypertension group than in the control group (24.33 and 18.85 U/L, respectively;  $P < 0.001$ ).

**Conclusion:** Elevated GGT levels in prehypertensive individuals support the idea that these patients are under increased oxidative stress. Even in the prehypertensive stage, it is essential to manage strict cardiovascular risk factor modifications.

**Key words:** GGT, prehypertension, cardiovascular

### Gama-glutamyl transferaz aktivitesi prehipertansif hastalarda artar

**Amaç:** Türk yetişkinleri temsil eden bir ulusal örneklemede serum GGT düzeyleri ile prehipertansiyon arasındaki ilişkiyi araştırmaktır. Gama-glutamyl transferaz (gama-glutamyl transpeptidaz, GGT) serum ve bir çok hücre yüzeyinde bulunan bir enzimdir. GGT bir oksidatif stress belirteci olarak kullanılmaktadır. Artmış serum GGT düzeyleri artmış kan basıncı ve hipertansiyonun ilerlemesiyle ilişkili bulunmuştur. GGT aynı zamanda kardiyovasküler hastalıkların patogeneğinde, diyabetes mellitusta, obstruktif uyku apnesi sendromunda ve metabolic sendromda rol oynuyor olabilir.

**Yöntem ve gereç:** Prehipertansiyonu sistolik kan basıncının 120-139 mmHg ya da diyastolik kan basıncının 80-89 mmHg aralığında olması olarak tanımlamıştır. 23 kadın ve 45 erkek prehipertansif hasta (Grup 1, ortalama yaş  $44,6 \pm 11,2$  yıl), 25 kadın ve 43 erkek normotansif hasta (Grup 2, ortalama yaş  $43,3 \pm 7,0$  yıl) çalışmaya alındı. Bu hastalarda serum GGT aktivitesi ölçüldü.

**Bulgular:** Prehipertansif grupta kontrol grubuna göre ortalama GGT aktivitesi anlamlı olarak yüksekti (24,33 karşın 18,85 U/L,  $P < 0,001$ , sırasıyla).

**Sonuç:** Prehipertansif bireylerdeki artmış GGT düzeyi bu hastaların artmış oksidatif stress altında olduğu düşüncesini desteklemektedir. Prehipertansif evrede bile sıkı kardiyovasküler risk faktörü kontrolü sağlamak çok önemli görünmektedir.

**Anahtar sözcükler:** GGT, prehipertansiyon, kardiyovasküler

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## Introduction

Glutathione (L-g-glutamyl-L-cysteinylglycine) is the main antioxidant in mammalian cells and is a ubiquitous thiol-containing tripeptide, which plays a central role in cell biology (1). Gamma-glutamyl transferase (gamma-glutamyl transpeptidase, GGT) is an enzyme present in serum and most cell surfaces (2). It is involved in glutathione metabolism by transferring the glutamyl moiety to a variety of acceptor molecules including water, some of the L-amino acids, and peptides. This reaction produces cysteinyl-glycine moieties, which are usually taken within the intracellular milieu by the action of membrane dipeptidases as precursors for glutathione resynthesis (1). GGT is used as an oxidative stress marker (3). One of the suggested mechanisms for this association is increased transport of glutathione into cells by increased GGT activity, to maintain high intracellular antioxidant glutathione levels in order to compensate for the oxidative stress (4,5). Increased serum GGT levels are implicated in increased blood pressure and the progression of hypertension (4-7). Lee et al. demonstrated that serum GGT is a strong predictor of incident diabetes and hypertension, even within a range regarded as physiologically normal, in the CARDIA study (4). GGT may also have a role in the pathogenesis of cardiovascular disease, diabetes mellitus, obstructive sleep apnea syndrome, and metabolic syndrome (8-14).

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) identified prehypertension as systolic blood pressure ranging from 120 to 139 mmHg or diastolic blood pressure ranging from 80 to 89 mmHg, and also as a predictor for developing hypertension (15). Shankar et al. adduced that higher serum GGT levels are associated with prehypertension in the US adult population (5). In this context, we examined the association between serum GGT levels and prehypertension in a nationally representative sample of Turkish adults.

## Materials and methods

### Patients

This case-control study was performed at the Ministry of Health Dışkapı Yıldırım Beyazıt Research

and Educational Hospital Cardiology Clinic from January 2007 to August 2008. The participants enrolled in the study were selected from among the patients admitted to the cardiology polyclinic. Enrolled in the study were 23 female and 45 male patients in the prehypertensive group (Group 1; mean age of  $44.6 \pm 11.2$  years) and 25 female and 43 male patients in the normotensive group (Group 2; mean age of  $43.3 \pm 7.0$  years). Exclusion criteria were hypertension history, use of antihypertensive medication, renal failure, thyroid disorders, congestive heart failure, cirrhosis of the liver, liver tumors, hepatitis, use of hepatotoxic drugs or oral contraceptives, previous myocardial infarction or coronary artery bypass graft operation, coronary artery disease history, obstructive sleep apnea syndrome, biliary obstruction, alcohol abuse, and serum levels more than 2-fold the upper limit of the reference range of hepatic enzymes. For each subject, seated systolic and diastolic blood pressures were measured 3 times using a mercury sphygmomanometer according to the American Heart Association and JNC7 recommendations, and the 3 measurements were averaged. Prehypertension was defined as systolic blood pressure 120-139 mmHg or diastolic blood pressure 80-89 mmHg, based on JNC7 criteria. The hospital's ethics committee approved the study and all patients gave informed written consent.

### Echocardiographic evaluation

All patients underwent complete 2-dimensional transthoracic echocardiographic and Doppler studies in the left lateral decubitus position, from multiple windows, to exclude valvular pathologies and heart failure. A GE Vivid 3 echocardiograph was used. Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography and studies were recorded on compact disks for storage. Left ventricle volumes and ejection fractions were obtained by the modified biplane Simpson method. The left atrium, left ventricle end-diastolic and end-systolic, and aortic root dimensions were measured from the parasternal long axis view, and the mitral early diastolic flow (E) velocity and late diastolic flow (A) velocity, deceleration time, ejection time, isovolumetric relaxation time, and isovolumetric

contraction time were measured from the apical 4-chamber view.

### Blood tests

Venous blood samples were obtained from an antecubital vein after a 12-h overnight fast.

Serum GGT, fasting glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, and creatinine concentrations were measured at 37 °C with an automatic analyzer.

### Statistical analysis

The statistical analysis was performed using SPSS for Windows. Categorical data were presented as absolute values and percentages, whereas continuous data were summarized as mean values  $\pm$  SD. Chi-square and Fisher's exact tests were used for comparison of categorical variables, as appropriate. Comparison of continuous variables was performed by means of Student's t-test or the Wilcoxon rank-sum test, as appropriate.  $P < 0.05$  was considered statistically significant.

## Results

The baseline clinical characteristics of 156 patients are summarized in Table 1. There was no statistically significant difference for age, sex, smoking, familial coronary artery disease history, heart rate, or body mass index between the groups. Group 2 normotensive patients had lower systolic and diastolic blood pressure than Group 1 prehypertensive patients (systolic blood pressure:  $112.9 \pm 7.0$  vs.  $130.8 \pm 1.8$  mmHg consecutively,  $P < 0.001$ ; diastolic blood pressure:  $75.5 \pm 6.1$  vs.  $81.9 \pm 3.2$  mmHg consecutively;  $P < 0.001$ ).

Regarding the echocardiographic evaluations, results were similar between the groups for the left atrium diameter, left ventricle ejection fraction, and E and A velocity of mitral inflow with pulsed-wave Doppler and isovolumetric relaxation time (Table 2).

Serum total cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride, blood glucose, and creatinine levels were similar between the groups (Table 3). Mean GGT activities were significantly higher in the prehypertension group than in the

Table 1. Demographic characteristics of the study participants.

	Group 1 (N = 78)	Group 2 (N = 78)	P-value
Age (years)	44.6 $\pm$ 11.2	43.3 $\pm$ 7.0	0.382
Male gender	45 (57.7%)	43 (55.1%)	0.747
Smoking	29 (37.2%)	27 (34.6%)	0.739
Dyslipidemia	9 (11.5%)	8 (10.3%)	0.797
Family history of cardiovascular disease	14 (17.9%)	12 (15.4%)	0.667
Systolic blood pressure (mmHg)	130.8 $\pm$ 1.8	112.9 $\pm$ 7.0	<0.001
Diastolic blood pressure (mmHg)	81.9 $\pm$ 3.2	75.5 $\pm$ 6.1	<0.001
Height (cm)	166.8 $\pm$ 9.0	167.4 $\pm$ 8.5	0.668
Weight (kg)	76.7 $\pm$ 10.7	74.4 $\pm$ 12.8	0.227
Body mass index	27.9 $\pm$ 4.0	27.0 $\pm$ 4.3	0.148
Heart rate (beats/min)	79.0 $\pm$ 10.4	80.2 $\pm$ 10.0	0.483

Table 2. Echocardiographic parameters of the study participants.

	Group 1	Group 2	P-value
LVEF (%)	64.9 ± 3.5	65.7 ± 4.5	0.204
LAD (cm)	3.52 ± 0.25	3.46 ± 0.32	0.196
E (cm/s)	0.80 ± 0.1	0.82 ± 0.2	0.304
A (cm/s)	0.64 ± 0.1	0.66 ± 0.2	0.409
DT (ms)	191.9 ± 25.2	188.9 ± 16.8	0.382
IVRT (ms)	87.4 ± 9.9	85.6 ± 9.4	0.243

LVEF: Left ventricular ejection fraction, LAD: left atrial dimension, E: early diastolic flow, A: atrial contraction signal, DT: deceleration time, IVRT: isovolumic relaxation time.

Table 3. Comparison of laboratory parameters between groups.

	Group 1 (N = 78)	Group 2 (N = 78)	P-value
Total cholesterol (mg/dL)	185.7 ± 19.9	182.8 ± 35.4	0.526
Triglyceride (mg/dL)	154.5 ± 69.0	153.2 ± 104.5	0.924
High-density lipoprotein (mg/dL)	43.4 ± 8.9	44.7 ± 12.9	0.442
Low-density lipoprotein (mg/dL)	112.7 ± 30.2	107.8 ± 23.5	0.258
Fasting blood glucose (mg/dL)	92.9 ± 20.0	93.8 ± 18.2	0.766
Creatinine (mg/dL)	0.9 ± 0.1	0.8 ± 0.2	0.090
Uric acid (mg/dL)	4.7 ± 1.1	4.5 ± 1.2	0.197
GGT	24.3 ± 6.1	18.8 ± 3.7	<0.001

control group (24.33 and 18.85 U/L, respectively;  $P < 0.001$ ) (Figure). The GGT level was not correlated with any clinical or laboratory parameters.

## Discussion

This study demonstrated an increased serum GGT activity in prehypertensive patients compared to normotensive subjects. In recent years, GGT activity has been accepted as a valuable marker of oxidative stress status. Glutathione (L-g-glutamyl-L-cysteinylglycine) is a ubiquitous thiol-containing tripeptide, which plays a central role in cell biology and is the main antioxidant in mammalian cells. It is implicated in the cellular defense against xenobiotics

and naturally occurring deleterious compounds, such as free radicals and hydroperoxides. Glutathione status is a highly sensitive indicator of cell functionality and viability (1). In humans, glutathione depletion is linked to a number of disease states, including cancer and neurodegenerative and cardiovascular diseases (16).

GGT is an enzyme present in serum and most cell surfaces. It is found in the epithelia of tissues that are extensively involved in transport, for example the liver, bile ducts, nephron, choroid plexus, jejunum, epididymis, and ciliary bodies (2). Although GGT can be produced by every tissue, because glucose moieties linked to the enzyme display differences between tissues, only GGT produced by the liver

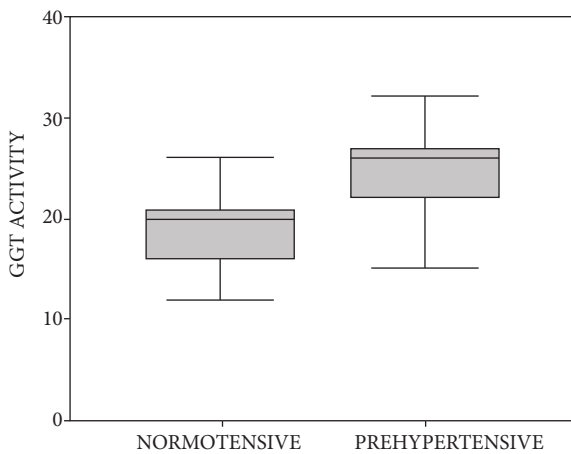


Figure. GGT levels in normotensive and prehypertensive patients.

can be detected in serum (17). GGT is responsible for initiating extracellular catabolism of glutathione, the main antioxidant in mammalian cells, and for the transfer of amino acids across the cellular membrane. It is involved in glutathione metabolism by transferring the glutamyl moiety to a variety of acceptor molecules including water, some of the L-amino acids, and peptides. This reaction produces cysteinyl-glycine moieties, which are usually taken within the intracellular milieu by the action of membrane dipeptidases as precursors for glutathione resynthesis (1). Since serum GGT mainly comes from the biliary system, it is a sensitive test for liver function, especially in biliary obstruction and alcohol abuse. However, there are many other reasons for an increased serum GGT level, such as congestive heart failure, cirrhosis of the liver, restricted blood flow to the liver, restricted venous outflow from the liver (like Budd-Chiari syndrome), necrosis of the liver, liver tumors, hepatitis, and hepatotoxic drugs. GGT is also used as an oxidative stress marker (3). One of the suggested mechanisms for this association is the increased transport of glutathione into cells by increased GGT activity, to maintain a high intracellular antioxidant glutathione level in order to be able to compensate for the oxidative stress (4, 5). Lee et al. demonstrated that serum C-reactive protein levels, a marker of inflammation, positively correlated with GGT levels (18). Increased

serum GGT levels are implicated in increased blood pressure and the progression of hypertension (4-7). Lee et al. demonstrated that serum GGT is a strong predictor of incident diabetes and hypertension, even within a range regarded as physiologically normal, in the CARDIA study (2). GGT may have a role in the pathogenesis of cardiovascular disease, diabetes mellitus, obstructive sleep apnea syndrome, and metabolic syndrome (8-14). Strong positive associations between serum GGT level and body mass index, smoking, total lipoprotein and high-density lipoprotein, serum cholesterol, uric acid, serum triglycerides, heart rate, antihypertensive medication, use of oral contraceptives, and menopause have been shown (6,19,20). Active GGT has been found within atherosclerotic cerebral, carotid, and coronary plaques from autopsic studies and surgical endarterectomy materials. GGT was colocalized with oxidized density lipoproteins and CD68+ foam cells in these lesions (21-23). To explain the possible association between GGT and the inflammatory process, it should also be considered that GGT has a key role in the interconversion of the glutathione-containing inflammatory mediator leukotriene C4 into leukotriene D4 (24).

### Conclusion and limitations

The main limitation of this study was the small number of patients. Results should be confirmed with larger studies.

We demonstrated that the GGT level in prehypertensive patients was higher than that of normotensive individuals (24.33 vs. 18.85 U/L, respectively;  $P < 0.001$ ), pointing to the prehypertension-GGT relationship. Elevated GGT levels in prehypertensive individuals support the idea that these patients are under increased oxidative stress. These findings confirm the need for strict monitoring and follow-up of cardiovascular diseases and diabetes in these patients. Even before people are diagnosed as hypertensive, oxidative damage progresses rapidly and begins to harm many of the organs. Even in the prehypertensive stage, it is essential to manage strict cardiovascular risk factor modifications.

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