# Elevated serum gamma-glutamyltransferase levels in patients with dilated ascending aorta

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## Abstract

**Objective:** This study aimed to evaluate the serum gamma-glutamyltransferase (GGT) levels as an indirect marker of elevated oxidative stress in patients with dilated ascending aorta.

**Methods:** The study was designed as an observational cross-sectional controlled study. One hundred consecutive patients with dilated ascending aorta and 50 consecutive controls with normal ascending aorta diameter were selected for the study by comprehensive transthoracic echocardiography (TTE). The aortic dilatation group was divided into two subgroups, according to the literature as the ectasia group (3.8-4.3 cm, 53 patients, 24 male and 29 female, mean age: 62.9±10.9 years) and the aneurysm group (≥4.4 cm, 47 patients, 18 male and 29 female, mean age: 65.5±11.1 years). The control group consisted of patients demonstrating no ascending aorta dilatation (≤3.7 cm, 50 patients, 24 male and 26 female, mean age: 62.7±9.2 years). ANOVA, Mann-Whitney U test, Pearson's correlation analysis, multivariate logistic regression analysis, and receiver-operator curve analysis were used for statistical analysis.

**Results:** Regarding the comparison of laboratory parameters between the patient and control groups, serum gamma-glutamyltransferase (GGT) levels were found to be statistically significantly higher in both of the aortic dilatation subgroups than in the control group ($p<0.001$). In the correlation analysis between the ascending aorta diameter and GGT, a statistically significant positive correlation was found ($r=0.282$, $p<0.001$). The multivariate regression analysis revealed a significant relationship between GGT and the proximal ascending aorta diameter ($\beta=0.131$, odds ratio: 1.140, 95% CI: 1.060-1.225, $p<0.001$).

**Conclusion:** GGT as a marker of oxidative stress may play a role in the pathogenesis of aneurysm of the ascending aorta.

*(Anadolu Kardiyol Derg 2014; 14: 106-14)*

**Key words:** aortic aneurysm, gamma-glutamyltransferase, oxidative stress, hypertension, regression analysis, sensitivity, specificity

## Introduction

Aneurysms of the ascending aorta (AAA) are a disease that can be lethal (1). Contrary to aneurysms of the descending and abdominal aorta, the role of atherosclerosis in the etiology of AAA is lower, and most AAAs are classified as idiopathic, as the disease cause cannot be identified in most cases (2, 3). The destructive reshaping of the extracellular matrix, and exposure of the aortic wall to long-term hemodynamic force (e.g. in case of high blood pressure) are some of the possible mechanisms that can lead to ascending aorta dilation (4, 5). Especially the disequilibrium between the matrix metalloproteinases and their inhibitors plays a major role in the reshaping of aortic wall, and the development of aortic aneurysms (6). Likewise, infiltration of inflammatory cells into the aortic wall, and the cytokines secreted by these cells (thus, inflammation), are believed to have a significant contribution to these processes (7). Increased oxidative stress is known to play a role in the development various diseases. Several studies support the hypothesis that oxidative stress especially plays a role in the development of aneurysms of the abdominal aorta (8, 9). Moreover, recent findings indicate that increased oxidative stress plays a role in the development of aorta dilations, which are believed to have complicated development processes (10).

Gamma-glutamyltransferase (GGT) is an enzyme located on the extracellular side of various cells, and plays a role in resynthesis of glutathione, which is a major component of intracellular protective antioxidant mechanisms (11). In recent years, the

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**Accepted Date:** 27.03.2013 **Available Online Date:** 14.01.2014



*DOI:10.5152/akd.2014.4646*

understanding of the physiological roles and cellular effects of GGT, an enzyme which is considered as an important marker for hepatic and biliary diseases, have advanced. Different studies have shown that this enzyme is not only a simple marker for evaluating liver functions, but is also associated with increased oxidative stress (12). Some researchers consider GGT as a direct marker for increased oxidative stress (12). Serum GGT levels have been evaluated in various cardiovascular and metabolic diseases. A comprehensive prospective health study in the general public has shown that the risk of coronary artery disease increases with increasing serum GGT level (13). In addition, diseases with increasing prevalence and which carry high cardiovascular risk, such as metabolic syndrome and type 2 diabetes mellitus (DM), have been associated with high serum GGT levels (14, 15). When the oxidative equilibrium shifts to the prooxidant side, the cellular need for glutathione increases. Since GGT plays an important role in glutathione synthesis, its levels increase as a response to increased oxidative stress.

To our knowledge, while various studies have shown the correlation between serum GGT levels and different cardiovascular diseases, there is no information about the correlation between ascending aorta dilation and GGT. In this context, the aim of this study was to compare serum GGT levels (as an indicator of increased oxidative stress), between patients with ascending aorta dilation and a control group.

## Methods

### Study design

The study was designed as an observational, cross-sectional, controlled study.

### Study population

One hundred consecutive patients who were admitted to the hospital between March 2011 and August 2012, and who were diagnosed with ascending aorta dilation using transthoracic echocardiography (TTE), and 50 consecutive patients with normal aorta dimensions (control group) were included in the study.

Exclusion criteria were as follows: congestive heart failure, documented coronary artery disease, atrial fibrillation, congenital heart disease, Marfan's syndrome, bicuspid aortic valve, valvular heart disease, myocarditis, pericarditis, cardiomyopathies, DM or impaired fasting glucose, metabolic syndrome, alcohol consumption over 30 g/day, acute and chronic hepatitis, gallbladder or biliary tract diseases, renal dysfunction, creatinine >1.5 mg/dL, hepatotoxic medication use, tumors, chronic inflammatory disease, active infection, chronic liver disease, known hepatis lipidosis, using medications that induce microsomal enzymes, and antioxidant vitamin use. In addition, patients with secondary hypertension were also excluded from the study.

The study was approved by the hospital's Ethics Committee. Informed consent forms were obtained from all patients.

### Study protocol

Patients who were included in the study were divided into the following groups. The aorta dilation group was divided into 2 subgroups according to the literature (16): the ectasia group (aorta diameter between 3.8-4.3 cm; 53 patients, 24 males and 29 females, mean age 62.9±10.9 years) and the aneurysm group (aorta diameter ≥4.4 cm, 47 patients, 18 males and 29 females, mean age 65.5±11.1 years) (16). The control group consisted of patients who did not have aorta dilation (≤3.7 cm, 50 patients: 24 males and 26 females, mean age: 62.7±9.2 years).

A comprehensive anamnesis was obtained from all patients, and all patients underwent detailed physical examination. Each patient was evaluated using 12-channel electrocardiography. Hypertension was defined as having a systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher in at least 3 independent measurements, or antihypertensive medication use. DM was defined as having a fasting glucose level of 126 mgr/dL or higher, ongoing antidiabetic treatment or following a diet. Patients with a fasting plasma glucose between 100 and 126 mg/dL were said to have impaired fasting glucose. The National Cholesterol Education Program-Adult Treatment Panel (NCEP ATP) III diagnostic criteria were followed for metabolic syndrome (17). At the time of diagnosis, patients who were actively smoking (independent from the amount of smoking) were considered smokers. Patients with a total cholesterol level over 200 mg/dL and/or triglyceride level over 150 mg/dL were considered to have hyperlipidemia (17). Body-mass index (BMI) was calculated by using the formula: *weight (kg)/height($m^2$)*.

Following a 12-hour fasting period, blood samples were collected in the morning between 8:00-10:00 a.m., by performing a careful venous puncture from a vein of the forearm by using a 21-G sterile syringe without stasis. The hemogram analysis was performed at the latest 1 hour after the venous puncture, on an automated hematology analyzer (Beckman Coulter, USA). Fasting blood glucose was analyzed using the hexokinase method, total cholesterol was analyzed using the enzymatic method, HDL was analyzed using the accelerator selective detergent method, triglycerides were analyzed using the triglyceride glycerol phosphate oxidase method, and LDL was analyzed using the Friedewald formula on a Abbott Architect autoanalyzer by using their respective original kits (18).

### Study parameters

Basic variables such as age, gender, smoking status, hypertension, and hyperlipidemia were determined for all patients. In addition, basic laboratory variables including fasting plasma glucose level, serum total cholesterol level, serum triglyceride level, serum creatinine level, serum uric acid level, and serum GGT level were determined. Proximal ascending aortic diameter was set as the predictive variable and GGT was set as the outcome variable.

**Echocardiography**

All patients underwent detailed, two-dimensional, M-mode and Doppler echocardiographic examination by two echocardiographer, who had no information about the biochemical data. A Vivid S-5 echocardiography instrument (GE Vingmed, Horten, Norway) was used with a 2.5-3.5 MHz probe. Left atrium, left ventricle dimensions, right atrium, right atrium dimensions, and wall thicknesses were individually measured. Left ventricle ejection fraction (LVEF) was measured by using the American Society for Echocardiography M-mode technique and M-mode echocardiography in the parasternal long axis view (19). The morphology of the aortic valve was examined in detail in the long- and short-axis view. The annulus diameter of the aortic was measured. In addition, the diameter of the aortic was measured individually at the sinus Valsalva level and at the sinotubular junction. The diameter of the proximal ascending aortic was measured according to the American Society for Echocardiography guidelines, by using M-mode echocardiography, in the parasternal long-axis view, which indicates the largest aortic diameter, by using the leading-edge technique in a perpendicular plane to the long-axis of the aortic (20). The final aortic diameter was calculated by taking the average of 5 consecutive measurements. Aortic dilation values were divided into two subgroups according to the literature (16). Patients with an ascending aortic diameter between 3.8-4.3 cm were classified as the ectasia group. Patients with an ascending aortic diameter ≥4.4 cm were classified as the aneurysm group. Patients with an ascending aortic diameter ≤3.7 cm were classified as the control group (normal aortic diameter).

In addition to minimal aortic regurgitation, patients with mild, moderate, and severe aortic regurgitation and patients who had dilation only in the aortic root were excluded from the study.

**GGT measurement**

GGT levels were measured on an Abbott Architect C 16000 (USA) biochemical autoanalyzer, by using its original kit and the enzymatic calorimetric method. In the laboratory, the normal reference range for serum GGT level is 9-55 U/L.

**Statistical analysis**

Data were analyzed using SPSS 20.0 for Windows software (SPSS Inc, Chicago, IL, USA). Frequency, ratio, mean, minimum, maximum, and standard deviation values were used in the descriptive statistics. The Kolmogorov-Smirnov test was used to control the data distribution. ANOVA was used for the analysis of parametric, discontinuous variables, whereas the Tukey test was used for further subanalysis. The Kruskal-Wallis test was used for the analysis of nonparametric variables, while the Mann-Whitney U test was used for further subanalysis. The chi-square test was used to analyze rational data; when the assumptions of the chi-square test were not met, Fischer's exact test was used. Pearson's correlation analysis was used to assess the correlation. Multivariate logistic regression analysis was used to determine the effect levels of the parameters. Standard beta coefficients and 95% confidence intervals (CI) were calculated. Receiver operating curve (ROC) analysis was used to calculate the required GGT cut-off values to distinguish patients with dilated proximal aortic diameter with maximum sensitivity and specificity. P values <0.05 were considered as statistically significant.

## Results

**Basic features**

Patients' personal information, and clinical and laboratory findings are summarized in Table 1. There was no significant difference in age, gender, hyperlipidemia, smoking, family history, and BMI between the ectasia, aneurysm, and control groups. However, the number of patients who had high blood pressure was higher in the patients with dilated ascending aortic (Ectasia: 66%, Aneurysm: 76%, Control: 34%, respectively; p<0.01) (Table 1).

Patient's laboratory and echocardiographic features are summarized in Table 2. When the laboratory parameters were compared between the patient group and the control group, serum GTT levels were significantly higher in both aortic dilation groups compared to the control group (Ectasia: 27.1±12.8 U/L, Aneurysm: 34.3±25.0 U/L, Control: 19.8±5.4 U/L, respectively, p<0.001) (Fig. 1) (Table 2). Similarly, serum uric acid levels were significantly higher in both aortic dilation groups compared to the control group (Ectasia: 5.2±1.4 mg/dL, Aneurysm: 5.8±1.5 mg/dL, Control: 4.7±1.6 mg/dL, respectively; p<0.05) (Table 2). There was no significant difference in other standard laboratory parameters between the groups. Similarly, there was no significant difference in the type of antihypertensive medications used between the aortic dilation group and the control group.

**Correlation between serum GGT level and the diameter of ascending aortic**

Pearson's correlation analysis showed a significant positive correlation between the diameter of the ascending aortic and the serum GGT level (r=0.282, p<0.001) (Fig.2).

Multivariate regression analysis (ascending aortic diameter set as the dependent variable) revealed a significant correlation between the serum GGT levels and proximal ascending aortic diameter (β=0.131, odds ratio: 1.140, 95% CI: 1.060-1.225, p<0.001) (Table 3). In addition, there was a significant correlation between the high blood pressure and proximal ascending aortic diameter (β=-2.824, odds ratio: 0.06, 95% CI: 0.02-0.21, p<0.001) (Table 3).

**Predictive value of serum GGT level for proximal ascending aortic width**

The ROC curve for GGT revealed that cut-off values over 19 U/L were correlated with dilation of the ascending aortic (77% sensitivity, 60% specificity, positive predictive value: 79.4%, negative predictive value: 56.6%) (area under the curve: 0.731, 95% CI: 0.649-0.786, p<0.001) (Fig. 3).

**Table 1. Comparison of personal information and clinical features between patients with dilated ascending aorta and the control group**

| Paramaters | Aortic diameter moderately dilated (Ectasia) n=53 | Aorta diameter severely dilated (Aneurysm) n=47 | Control n=50 | F values for ANOVA | $X^2$ values for chi-square test | *P* value |
|---|---|---|---|---|---|---|
| Age, years | 62.9±10.9 | 65.5±11.1 | 62.7±9.2 | 1.069 | - | 0.537 |
| Gender (male/female), n, % | 24 (45)/ 29 (54) | 19 (40) / 28 (59) | 24 (48)/ 26 (52) | - | 0.575 | 0.750 |
| High blood pressure, n, % | 41 (75) | 33 (70) | 17 (34) | - | 12.44 | <0.01 |
| Hyperlipidemia, n, % | 21 (39) | 19 (40) | 27 (54) | - | 2.650 | 0.266 |
| Smoking, n, %, | 21 (39.6) | 17 (36) | 18 (36) | - | 0.184 | 0.912 |
| Family history, n, % | 11 (20) | 9 (19) | 15 (30) | - | 3.550 | 0.169 |
| BMI, kg/m$^2$ | 24.9±2.8 | 24.3±2.5 | 24.1±2.8 | 1.211 | - | 0.301 |
| Systolic blood pressure, mm Hg | 133±12 | 132±13 | 132±13 | 0.096 | - | 0.909 |
| Diastolic blood pressure, mm Hg | 73±10 | 73±9 | 73±10 | 0.036 | - | 0.965 |
| Aspirin, n, % | 14 (26) | 13 (27) | 14 (28) | - | 0.036 | 0.982 |
| Beta blocker, n, % | 19 (35) | 23 (48) | 18 (36) | - | 2.447 | 0.294 |
| Calcium channel blocker, n, % | 17 (32) | 16 (34) | 18 (36) | - | 0.177 | 0.915 |
| ACEI/ARB, n, % | 22 (41) | 20 (42) | 25 (50) | - | 1.356 | 0.508 |
| Statin, n, % | 10 (18) | 9 (19) | 13 (26) | - | 0.974 | 0.614 |

*Personal information and clinical feature data are expressed as mean±SD and median (minimum-maximum). ANOVA and chi-square test were used for data comparison.
ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index

**Table 2. Comparison of laboratory findings and echocardiographic features between patients with dilated ascending aorta and the control group**

| Paramaters | Aortic diameter moderately dilated (Ectasia) n=53 | Aorta diameter severely dilated (Aneurysm) n=47 | Control n=50 | Fa values for ANOVA | *P* value |
|---|---|---|---|---|---|
| Glucose, mg/dL | 87.3±7.1 | 87.9±8.4 | 88.8±6.0 | 0.576 | 0.564 |
| Urea, mg/dL | 30.0±7. 5 | 29.6±7.7 | 29.9±9.6 | 0.174 | 0.841 |
| Creatinine, mg/dL | 0.76±0.16 | 0.8±0.17 | 0.77±0.15 | 0.985 | 0.824 |
| TCHOL, mg/dL | 186.0±30. 4 | 184.7±28. 2 | 134.8±62.1 | 1.347 | 0.263 |
| LDL, mg/dL | 117.8±27.9 | 113.5±30.8 | 119.4±30.0 | 0.513 | 0.600 |
| HDL, mg/dL | 41.9±11.1 | 43. 7±11.5 | 45.8±10.3 | 1.627 | 0.200 |
| TG, mg/dL | 136.8±82.9 | 122.2±69.4 | 137.4±63. 6 | 0.624 | 0.537 |
| AST, U/L | 19.9±5.3 | 21.6±7.1 | 20.2±6.1 | 0.401 | 0.670 |
| ALT, U/L | 18.9±6.7 | 18.7±6.9 | 21.0±9.1 | 1.392 | 0.252 |
| GGT, U/L | 27.1±12.8 | 34.3±25.0 | 19.8±5.4 | 9.608 | <0.001 |
| Uric acid, mg/dL | 5.2±1.4 | 5.8±1.5 | 4.7±1.6 | 6.509 | <0.05 |
| Hemoglobin, g/dL | 13.3±1.4 | 13.7±1.9 | 13.3±1.4 | 1.105 | 0.334 |
| LVEF, % | 61.7±3.7 | 60.8±3.6 | 61.8±3.2 | 1.089 | 0.339 |
| Diameter of proximal ascending aorta, mm | 41.9±2.5 | 47.5±4.4 | 33.9±2.8 | 204.140 | <0.001 |

*Laboratory findings and echocardiographic features were represented as mean±SD and median (minimum-maximum). Kruskal-Wallis, Mann-Whitney U test, and ANOVA-Tukey's test were used for comparison.
AST - aspartate transaminase; ALT - alanine transaminase; AP - alkalene phosphatase; GGT - gamma-glutamyltransferase; HDL - high-density lipoprotein; LDL - low-density lipoprotein; LVEF - left ventricle ejection fraction; mm-millimeter; TCHOL - total cholesterol; TG - triglyceride

**Table 3. Results of multivariate logistic regression analysis (proximal ascending aorta as the dependent variable**

| Multivariate model | β | OR | 95% confidence interval | | *P* value |
|---|---|---|---|---|---|
| | | | Minimum | Maximum | |
| Glucose | -0.045 | 0.956 | 0.883 | 1.036 | 0.273 |
| TCHOL | -0.013 | 0.987 | 0.946 | 1.030 | 0.560 |
| TG | 0.000 | 1.000 | 0.990 | 1.010 | 0.973 |
| HDL | 0.003 | 1.003 | 0.948 | 1.062 | 0.906 |
| Creatinine | 3.440 | 31.202 | 0.484 | 2.011 | 0.106 |
| GGT | 0.131 | 1.140 | 1.06 | 1.22 | <0.001 |
| Uric acid | 0.284 | 1.328 | 0.980 | 1.80 | 0.067 |
| Age | -0.418 | 1.658 | 0.919 | 1.023 | 0.985 |
| Smoking | 0.174 | 1.228 | 0.345 | 5.446 | 0.879 |
| Male gender | 0.256 | 1.015 | 0.421 | 6.632 | 0.794 |
| Hyperlipidemia | -1.345 | 1.362 | 0.165 | 2.489 | 0.556 |
| High blood pressure | -2.824 | 0.060 | 0.020 | 0.210 | <0.001 |

*Multivariate logistic regression analysis
GGT - Gamma-glutamyltransferase; HDL - high-density lipoprotein; TG - triglyceride; TCHOL - total cholesterol

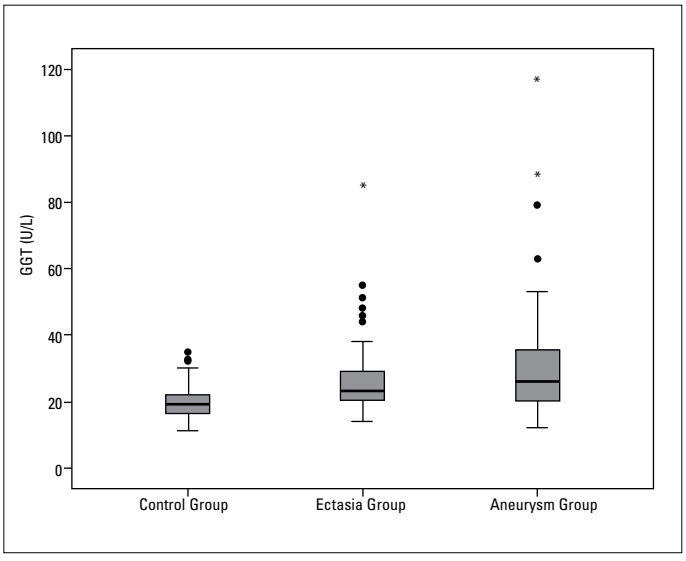


**Figure 1. Serum GGT levels in the patient and control groups**
GGT - gamma-glutamyltransferase

## Discussion

The major finding of this study is the elevated serum GGT levels in patients with ascending aorta dilation compared to the control group. Another important finding is the positive correlation between serum GGT levels and the diameter of ascending aorta. To our knowledge, this is the first study to evaluate serum GGT levels in patients with dilated ascending aorta.

Despite being rare, aneurysms of the ascending aorta are serious disease conditions, which may result in mortality (21). A couple of major risk factors, including age, high blood pressure, and smoking, have been defined for aneurysms of the aorta (21). However, various studies have been unable to fully elucidate the disease mechanism and progression. In histopathological examinations of aneurysms of the ascending aorta, medial degeneration is observed to a great extent (22). Cystic medial degeneration is defined as the severe form of medial degeneration, which is expressed as the loss of smooth muscles and elastic lamina degradation (23). Smooth muscles in the medial layer of the aorta and elastic fibers are lost to a great extent in the histopathological examination of cystic medial degeneration (23). The accumulation of basophilic material in the degenerated area in the media layer results in a cystic appearance (24). Matrix metalloproteinases play a major role in the cystic medial degeneration and reshaping of the aortic wall (6). This is due to the degradation of extracellular matrix proteins elastin and collagen by matrix metalloproteinases, and these enzymes play important roles in vascular biology (25). In particular, matrix metalloproteinases 2 and 9 have been correlated with the development of thoracic aortic aneurysms (25). In vitro studies have shown that the rate of matrix metalloproteinases increases during conditions such as increased oxidative stress (26). Reactive oxygen species scavengers, which are known as antioxidants, have been shown to decrease MMP-9 expression in macrophage foam cells in aortic plaques (27). Therefore, in addition to increased oxidative stress, decreased antioxidant activity (i.e. shift in the prooxidant-antioxidant equilibrium to the prooxidant side) may play a role in the development of aneurysms. Moreover, the local environment, which is generated by the inflammatory cells and smooth muscle cells within the aortic wall structure, various growth factors released from these cells, and lipid intermediates, has been shown to lead to the production of reactive oxygen species (ROS), especially through the NADPH pathway

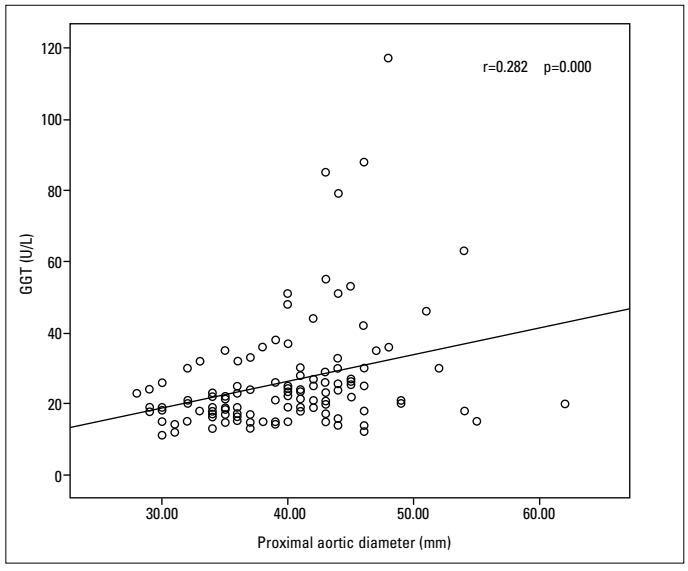


**Figure 2. The correlation between the diameter of the proximal ascending aorta and serum GGT level. There was a significant positive correlation between the diameter of the proximal ascending aorta and the serum GGT level (β=0.131, odds ratio: 1.140, 95% CI: 1.060-1.225, p<0.001).**

GGT - gamma-glutamyltransferase

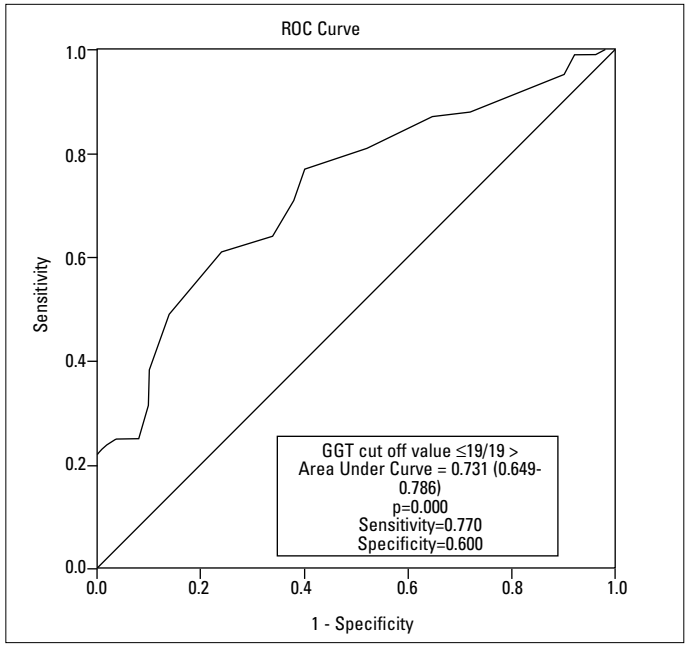


**Figure 3. Receiver operating characteristics (ROC) curve. ROC curve analysis revealed a correlation between GGT cut-off values over 19 U/L and ascending aorta dilation (77% specificity, 60% sensitivity, positive predictive value: 79.4%, negative predictive value: 56.6%) (area under the curve: 0.731, 95% CI: 0.649-0.786, p<0.001).**

GGT - gamma-glutamyltransferase

(28). Therefore, increased oxidative stress due to the production of ROS causes an increase in metalloproteinase activity and apoptosis in smooth muscle cells (29). Thus, the equilibrium between aortic wall destruction and renewal is shifted in favor of destruction, and oxidative stress contributes to the development of aortic dilation (30).

Serum GGT levels are frequently used to evaluate liver functions and alcohol consumption in daily clinical practice. However, in recent years GGT is considered an indirect indicator of oxidative stress (12). Namely, cellular GGT activity is of utmost importance to maintain the intracellular existence of glutathione (GSH), which is an important antioxidant for mammalian cells. Since GSH cannot be transported through the cell membrane, GGT -a membrane-anchored enzyme- degrades extracellular GSH into thiol metabolites, such as cysteinylglycine and glutamate. Thus, the degradation products can be transported to the cytoplasm through the membrane, and there they can carry out GSH synthesis (31). Thus, when oxidative stress increases, GGT activity increases as the cellular need for GSH also increases. At the same time, another important mechanism to explain GGT-oxidative stress coupling is the formation of superoxide anion radicals due to the interaction of thiol metabolites, which are produced as a result of extracellular glutathione degradation by GGT, and free iron (32). Mason et al. (33) evaluated the GGT enzyme, which has been shown to increase in various cardiovascular and metabolic diseases as an indirect marker for oxidative stress, as a novel cardiovascular risk marker.

This study revealed that serum GGT levels were higher in patients with ascending aortic dilation compared to the control group. Patients with ascending aortic dilation mostly consisted of patients with high blood pressure. High blood pressure is one of the major causes of aortic dilation (34). Endothelial dysfunction, which usually accompanies high blood pressure, and the resulting dysregulation in nitric oxide-mediated vasodilation, and local and systemic effects of endothelial-derived vasoconstrictors, which also play role in the development of high blood pressure, lead to the reshaping of aortic wall (34). Moreover, increased preload, as a result of increased blood pressure, contributes to the development of aneurysms (34). On the other hand, various findings indicate a correlation between serum GGT levels and high blood pressure (35). High serum GGT levels may be an indicator of increased oxidative stress in the patients. In addition, GGT is also correlated with inflammation markers, which plays a major role in high blood pressure development and endothelial dysfunction (36). Moreover, GGT has been shown to be correlated with decreased renal function in male patients who do not have high blood pressure or DM (37). Decreased renal functions can contribute to the aortic dilation by leading to the activation of the renin-angiotensin system (RAS), and increasing the reshaping of the aortic wall through RAS. The evidence of RAS's role on the development of aorta aneurysms supports this hypothesis (38).

Atherosclerosis is the most frequent cause of aortic aneurysms (21). Even though the relation between atherosclerosis and abdominal aortic aneurysms is more prominent, atherosclerosis has also been shown to play a role in ascending aortic dilations (21). GGT has been also shown to be located on the plaques that are responsible for atherosclerosis (39). Cysteinylglycine, which is produced by the hydrolysis of GSH by

GGT, is a strong reductor of $Fe^{3+}$ (39). These findings have shown that in the presence of $Fe^{3+}$ and $Cu^{2+}$, GGT plays a role in the production of ROS, which creates oxidative stress for the cells (40). Thus, free radicals including superoxide and hydrogen peroxide, which are formed on the arterial wall plaque through GGT, are believed to cause LDL oxidation (41). At the same time, the free radicals that are formed through GGT not only lead to LDL oxidation, but also metalloproteinase activation, cell proliferation, and programmed cell death (apoptosis) (39). Therefore, GGT, owing to its local effect on plaque, can lead to the activation of metalloproteinases, and may contribute to the reshaping of the aortic wall and aneurysm development. The finding of the current study that serum GGT levels were higher in patients with ascending aortic dilation may be an indicator of GGT's role in the development of aortic dilation. In other words, GGT may play a role in reshaping of the aortic wall through its systemic (over oxidative stress) and local effects (due to its presence on the arterial wall). In addition, the maximum serum GGT levels in patients with ascending aortic dilation implies that these patients have more oxidative stress load compared to the patients with normal aortic diameter (control group). On the other hand, since the ascending aortic dilation group includes more patients with high blood pressure, this could contribute to higher serum GGT levels and increased oxidative stress (35).

Despite excluding various cardiovascular and metabolic diseases including DM, metabolic syndrome and documented coronary artery disease, in which serum GGT levels are high, serum GGT levels were higher in patients with ascending aortic dilation. Similarly, serum uric acid concentration was slightly higher in patients with aortic dilation compared to the control group. Molecular studies have shown that xanthine oxidoreductases are a source for free oxygen radical in the cardiovascular system (42). Similar to GGT, two studies have shown that uric acid is a marker of oxidative stress (43-45). Esen et al. (10) found that serum uric acid levels were higher in patients with aortic dilation compared to the control group, and considered this a marker of increased oxidative stress. In addition, Patetsios et al. (46) showed significantly increased urate levels in the aortic wall in patients with aortic dilation. Increased xanthine oxidase activity within the artery may cause urate accumulation to trigger arterial wall damage, and may contribute to the development of an aneurysm (46). Overall, like GGT, uric acid may play a role in the reshaping of the aortic wall, and aneurysm development, due to increased oxidative stress, as well as its local effect.

### Study limitations

The main limitation of this study is the low number of patients. The researchers were unable to evaluate the oxidative stress markers serum TOS, TAS, glutathion peroxidase, superoxide dismutase, ferric reducing antioxidant power, and advanced protein oxidation product levels together with GGT, which could be considered one of the major limitations of this study. The researchers were also unable to evaluate asymptomatic hepatic lipidosis by using abdominal ultrasonography, which can be considered another limitation. Moreover, a lack of analysis of plasma matrix metalloproteinase levels can be considered another limitation. The diagnosis of ascending aortic dilation was made by using TTE, and more sensitive and specific imaging methods (such as CT angiography and MR angiography) were not used, which can be considered a limitation. In addition, atherosclerosis may be present within the patient group in the study. To identify atherosclerosis, various stress tests or screening tests (such as carotid intima-media thickness) can be performed, and the lack of such tests can be considered a limitation of this study.

Moreover, 77% sensitivity and 60% specificity rates for GGT cut-off values over 19 U/L are relatively low. These findings may result from the heterogeneity of the patient group, and the fact that GGT enzyme level is affected by various factors. On the other hand, the measurement of a single basal GGT level may not reflect the patients' actual conditions in the long term.

## Conclusion

Various studies have demonstrated the correlation between the GGT enzyme and cardiovascular diseases. This is the first study to investigate the correlation between GGT and patients with aortic dilation. More comprehensive studies are needed to fully elucidate the role of GGT in disease progression in patients with aortic dilation.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Idea - B.D., C.Ö., S.Ç.; Design - B.D., İ.M.Ç., H.O.T.; Denetleme - B.D., O.K.; References - O.K., H.O.T., İ.Ü.; Data collection and/or processing - B.D., İ.M.Ç., E.D., C.Ö., S.Ç.; Analysis and/or interpretation - B.D.; Literature search - B.D., İ.Ü.; Writing - B.D., S.Ö.; Critical reading - O.K., S.Ö.

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