Journal of Clinical Laboratory Analysis 29: 390–396 (2015)

Gamma Glutamyl Transferase Activity is Associated With Both Paraoxonase Activity and Aortic Stiffness in Hypertensive Patients

Mehmet Yavuz Gözükara,[1] Abdurrezzak Börekçi,[2] Mustafa Gür,[3]* Nurten Aksoy,[4] Taner Şeker,[5] Onur Kaypaklı,[6] Hakan Uçar,[7] Caner Türkoğlu,[8] Mevlüt Koç,[9] İlyas Makca,[10] Selahattin Akyol,[11] Şahbettin Selek,[12] and Murat Çaylı[13]

[1]*Department of Internal Medicine, Mersin State Hospital, Mersin, Turkey*
[2]*Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, Turkey*
[3]*Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, Turkey*
[4]*Department of Clinical Biochemistry, Faculty of Medicine, Harran University, Şanlıurfa, Turkey*
[5]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[6]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[7]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[8]*Department of Cardiology, Ankara Yenimahalle State Hospital, Ankara, Turkey*
[9]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[10]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[11]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*
[12]*Department of Clinical Biochemistry, Bezmialem Vakıf University, İstanbul, Turkey*
[13]*Department of Cardiology, Adana Numune Training and Research Hospital, Adana, Turkey*

Background: We aimed to investigate relationship between gamma glutamyl transferase (GGT) activity with paraoxonase 1 (PON1) activity and aortic stiffness (AS) parameters such as pulse wave velocity (PWV) and augmentation index (AIx). *Methods:* Measurements were obtained from 324 patients with newly diagnosed essential hypertension (mean age: 55.0 ± 8.2 years). The patients were divided into two groups according to their median GGT values. PWV and AIx were calculated using the single-point method via the Mobil-O-Graph® ARC-solver algorithm. *Results:* PWV, Aix, and high-sensitive C-reactive protein (hs-CRP) values were higher and PON1 activity values were lower in GGT_{high} group compared with GGT_{low} group ($P < 0.05$, for all). Multiple linear regression analysis showed that GGT activity was independently associated with PWV ($\beta = 0.496$, $P < 0.001$) and PON1 activity ($\beta = -0.343$, $P < 0.001$) as well as hs-CRP ($\beta = 0.334$, $P < 0.001$). *Conclusion:* These results may support that increased GGT activity would be associated with both impaired antioxidant system and increased AS in hypertensive patients. J. Clin. Lab. Anal. 29:390–396, 2015. © 2014 Wiley Periodicals, Inc.

Key words: GGT; aortic stiffness; PWV; paraoxonase; hypertension; CRP

INTRODUCTION

Gamma glutamyl transferase (GGT) activity is a well-known enzyme marker for increased oxidative stress (1,2). GGT activity is found on the surface of various cells including vascular system and plays a role in the catabolism of glutathione, which is one of the major antioxidants (1, 2). Previous studies have indicated that GGT is involved in the pathophysiologic process of atherosclerosis (3). Also, serum GGT concentrations within the physiologic range have been independently related with most cardiovascular disease risk factors including metabolic

*Correspondence to: Mustafa Gür, Department of Cardiology, Adana Numune Training and Research Hospital, 01170 Çukurova, Adana Turkey. E-mail: drmugur@yahoo.com

Received 26 February 2014; Accepted 21 May 2014
DOI 10.1002/jcla.21785
Published online in Wiley Online Library (wileyonlinelibrary.com).

syndrome and hypertension (4–6). In particular, increased GGT activity has been shown to be associated with hypertension development in previous studies (5, 6).

Increased aortic stiffness (AS) reflects vascular damage and is a measure of the severity of atherosclerosis (7). Also, noninvasive AS is postulated to be a surrogate marker of early atherosclerosis (8). Moreover, AS is independently associated with hypertension (9). Pulse wave velocity (PWV) and augmentation index (AIx), valid, clinically feasible, and reproducible measures of AS, generally allows the comprehensive assessment of patients with cardiovascular diseases (10).

High-density lipoprotein (HDL) cholesterol exerts cardioprotective properties through its antioxidant activity and anti-inflammatory effects, which is largely maintained by paraoxonase 1 (PON1) (11, 12). PON1 protects lipoproteins against oxidative modification and to hydrolyze hydrogen peroxide, a major reactive oxygen species (ROS) produced under conditions of inflammation and atherosclerosis (12).

Our hypothesis is that GGT activity, which reflects increased oxidative stress, is associated with PON1 activity (antioxidant enzyme) and AS, which is related with essential hypertension. Therefore, we aimed to investigate relationship between GGT activity with PON1 activity and AS parameters such as PWV and AIx in patients with newly diagnosed hypertensive patients.

METHODS

Study Populations

Of 359 patients having office blood pressure (BP) measurement ≥140/90mmHg, 35 patients were excluded because of their BP was normal according to ambulatory BP monitoring (ABPM). Measurements were obtained from 324 patients with newly diagnosed essential hypertension (mean age: 55.0 ± 8.2 years, male/female: 125/199). The study population was divided into two subgroups as GGT_{low} versus GGT_{high} groups with regard to their median GGT levels. Exclusion criteria were secondary hypertension, heart failure, positive history or clinical signs of ischemic heart disease, positive effort test, positive myocardial perfusion scintigraphy, cerebrovascular disease, severe valve disease, atrial fibrillation, usage of any drugs, renal insufficiency (serum creatinine: ≥1.5 mg/dl in men and ≥1.4 mg/dl in women), major noncardiovascular diseases, and known diabetes or fasting glucose ≥126 mg/dl. In addition, patients taking antioxidant vitamin and alcohol were also excluded. The Local Ethics Committee assessed and approved the study and written informed consent for participation in the study was obtained from all individuals.

BP Measurement and ABPM

BP was measured by using a mercury sphygmomanometer in office setting. Systolic (SBP) and diastolic BPs (DBP) were taken. Noninvasive 24-h ABPM was performed with a portable compact digital recorder (Tracker NIBP2, Delmar Reynolds Ltd., Hertford, UK), and analyzed using a customized analytical software (Delmar Reynolds Medical Inc., Model 2169, Hertford, UK). All subjects wore an ABPM device for a single 24-h period. The device was programmed to inflate and record BP at prespecified intervals (every 15 min during daytime hours and every 30 min during nighttime hours), which provided approximately 80 BP recordings during the 24-h period.

Diagnosis of Hypertension

In each subject, BP was measured in at least three separate days after 15 min of comfortably sitting and averaged. Then each subject undertook 24-h ABPM. Individuals who had SBP ≥ 140 mmHg and/or a DBP ≥ 90 mmHg in office setting, and in ABPM, an average 24-h SBP > 130 mmHg and/or DBP > 80 mmHg, an average daytime SBP > 135 mmHg and/or DBP > 85 mmHg or an average nighttime SBP > 125 mmHg and/or DBP > 75 mmHg were diagnosed as hypertensive (13).

Blood Samples and Echocardiography

Fasting blood samples were collected after the examination for the evaluation of low-density lipoprotein (LDL) cholesterol, HDL cholesterol, triglyceride, GGT activity, and high-sensitivity C-reactive protein (hs-CRP) levels. Plasma triglyceride, total cholesterol, LDL, HDL concentrations, and fasting glucose were measured using an automated chemistry analyzer (Aeroset; Abbott, Holliston, MN) with commercial kits (Abbott). Hs-CRP was measured using an autoanalyzer (Aeroset; Abbott) with a spectrophotometric commercial kit (Scil Diagnostics GmbH, Viernheim, Germany). Serum GGT activities were measured by the enzymatic calorimetric test (Roche/Hitachi analyzer, Mannheim, Germany) and the normal range of GGT activity was identified as 7–49 U/l. The coefficient of variation (CV) for measurement of serum GGT activity was 2%.

Measurement of serum PON1 activity was performed in the absence of NaCl (basal activity). The rate of paraoxon hydrolysis (diethyl-*p*-nitrophenylphosphate) was measured by monitoring the increase of absorbency at 412 nm at 37°C. The amount of generated *p*-nitrophenol was calculated from the molar absorptivity coefficient at pH 8, which was 17,000 M^{-1} cm^{-1} (14). PON1 activity was expressed as U/l serum. The CV for measurement of serum PON activity was 2.3%.

Standard two-dimensional echocardiography was performed using a commercially available echocardiographic machine (Vivid 7R GE Medical System, Horten, Norway) with a 2.0–3.5 MHz transducer. Left Ventricle ejection fraction was determined by the biplane Simpson's method (15).

The ARC Solver Method

The ARC Solver method is commercially available in the oscillometric Mobil-O-Graph NGW 24-h PWA monitor (IEM; Stolberg, Germany) and aims to be a novel method for the determination of the aortic SBP, aortic BP curves, and AIx based on oscillometric BP measurement. The method (16) has been developed by the Austrian Institute of Technology, Vienna, Austria. The method uses the pulse waves assessed at arteria brachialis. The algorithm for the generation of, using the oscillometric method, have been reported previously (16,17) but are briefly explained. After the conventional oscillometric BP assessment, peripheral pressure waves are recorded, using the appropriately sized brachial cuff and a high fidelity pressure sensor (MPX5050, Freescale Inc., Tempe, AZ), at DBP level for 10 sec. The sensor is connected to a 12 bit A/D converter by means of an active analogue band bass filter (0.425 Hz). Following digitalization, the signal processing is performed using a three-step algorithm. In a first step, the single pressure waves are verified for their plausibility by testing the position of minima and the corresponding wavelengths. Minima are detected by means of an iterative procedure evaluating higher order time derivatives of the pressure signal. The second stage involves comparison of all single pressure waves with one another to recognize artifacts. Aortic pulse waves are then generated via a general transfer function. Modulus and phase characteristics of the ARC Solver transfer function are available. Finally, the coherence of the measured parameters is verified and displayed within the Mobil-O-Graph NG software package, which also allows visual inspection to unveil consistently recorded intrinsic waveform distortion manually.

Measurements of the Aortic PWV and AIx

All recordings were performed with the ARC Solver method and standard oscillometric BP measurement procedures. After 10 min of rest, an appropriately sized BP cuff was attached to the patient's right arm. Applanation tonometry of the radial artery and oscillometric pulse wave recordings at the brachial artery were performed in the supine position. This was followed by a 10-sec pulsed wave analysis recording with the cuff inflated at the DBP level.

Using the Mobil-O-Graph NG, the aortic BP curves, aortic SBP, and aortic pulse pressure (aPP: aortic SBP − aortic DBP) were obtained. A characteristic point of the aortic BP curve, the inflection point, is identified within the time domain, indicating the arrival of the reflected wave in the ascending aorta. The BP at this point of time is called "inflection pressure." The difference between aortic SBP and inflection pressure is called "augmentation pressure" (AP). The AIx is then calculated by AP/aPP × 100. The Mobil-O-Graph NG software package allows us to automatically calculate aortic PWV and AIx (17).

Statistical Analysis

Statistical analysis was carried out using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). Data are expressed as mean value ± SD. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. An independent simple *t*-test was used in the analysis of continuous variables. Categorical variables were compared using the chi-square test. The correlations between GGT and laboratory, AS parameters, hemodynamic, and echocardiographic parameters were assessed by the Pearson correlation test. A multivariate stepwise linear regression analysis was performed to identify the independent associations of GGT activity. All significant ($P < 0.05$) parameters in the bivariate analysis (Average 24-h SBP, Office SBP, AIx, PWV, hs-CRP, PON1 activity) were selected in the multivariate model. A two-tailed $P < 0.05$ was considered as statistically significant.

RESULTS

The patients were divided into two subgroups as GGT_{low} (mean age: 54.7 ± 6.4; 162 patients) versus GGT_{high} (mean age: 55.3 ± 9.8; 162 patients) groups with regard to their median GGT levels ($GGT_{low} < 27.3$ U/l and $GGT_{high} \geq 27.3$ groups).

Comparison of baseline and laboratory characteristics was demonstrated in Table 1. Both average 24-h SBP and office SBP values were higher in GGT_{high} group compared with GGT_{low} group ($P < 0.05$, for all). Other baseline characteristics were not different between the groups ($P > 0.05$, for all). PON1 activity levels of GGT_{high} group were higher than GGT_{low} group ($P < 0.05$). Similarly, hs-CRP levels were higher in GGT_{high} group compared with GGT_{low} group ($P < 0.05$).

PWV and AIx values were higher in GGT_{high} group compared with GGT_{low} group ($P < 0.05$, for all) (Table 1).

GGT activity was significantly associated with office SBP ($r = 0.112$, $P = 0.043$), average 24-h SBP ($r = 0.176$, $P = 0.002$), AIx ($r = 0.188$, $P = 0.001$), PWV ($r = 0.624$, $P < 0.001$), hs-CRP ($r = 0.509$, $P < 0.001$), PON1 activity ($r = -0.558$, $P < 0.001$) in bivariate analysis (Table 2). Relationships between GGT activity with PON1 and PWV were shown in Figures 1 and 2.

TABLE 1. Baseline, Laboratory, Echocardiographic, and Aortic Stiffness Characteristics of Groups

Variables	GGT_{low} group ($n = 162$)	GGT_{high} group ($n = 162$)	*P* value
Baseline characteristics			
Age (years)	54.7 ± 6.4	55.3 ± 9.8	0.541
Gender (male)[a]	56 (34.6%)	69 (42.6%)	0.085
BMI (kg/m^2)	28.4 ± 5.7	29.1 ± 5.3	0.270
Office SBP (mmHg)	152.3 ± 17.4	157.9 ± 18.4	0.005
Office DBP (mmHg)	92.6 ± 9.5	94.2 ± 10.3	0.148
Average 24-h SBP (mmHg)	132.5 ± 8.8	135.3 ± 11.2	0.013
Average 24-h DBP (mmHg)	83.9 ± 9.6	83.1 ± 9.8	0.439
Heart rate (beat/min)	73.5 ± 8.7	73.9 ± 7.9	0.449
Smoking[a]	46 (28.4%)	41 (25.3%)	0.308
Laboratory findings			
Glucose (mg/dl)	96.7 ± 9.4	95.9 ± 12.5	0.501
Total cholesterol (mg/dl)	207.3 ± 37.2	208.8 ± 41.9	0.748
Triglyceride (mg/dl)	178.2 ± 90.5	175.0 ± 116.8	0.785
HDL-C (mg/dl)	47.4 ± 11.0	47.2 ± 11.5	0.911
LDL-C (mg/dl)	135.7 ± 34.4	137.6 ± 34.8	0.622
Creatinin (mg/dl)	0.77 ± 0.20	0.80 ± 0.23	0.095
hs-CRP (mg/dl)	0.56 ± 0.14	0.76 ± 0.22	<0.001
Uric acid (mg/dl)	5.0 ± 1.14	5.1 ± 1.3	0.404
PON1 activity (Ul^{-1})	109.3 ± 44.7	64.5 ± 33.0	<0.001
Echocardiography			
Ejection fraction (%)	61.3 ± 4.6	61.3 ± 5.3	0.954
Aortic stiffness parameters			
PWV (m/sec)	7.4 ± 1.5	9.8 ± 2.5	<0.001
AIx (%)	24.9 ± 11.0	28.0 ± 11.6	0.015

GGT, gamma glutamyl transferase; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; hs-CRP, high-density lipoprotein cholesterol; PON1, paraoxonase1; PWV, pulse wave velocity; AIx, augmentation index.
[a]Chi square.

TABLE 2. Bivariate and Multivariate Relationships of GGT

Variables	Pearson correlation coefficient	*P* value	Standardized β-regression coefficients	*P* value
Average office SBP (mmHg)	0.112	0.043	−0.017	0.703
Average 24-h SBP (mmHg)	0.176	0.002	−0.074	0.110
AIx (%)	0.188	0.001	−0.038	0.366
PWV (m/sec)	0.624	<0.001	0.496	<0.001
hs-CRP (mg/dl)	0.509	<0.001	0.334	<0.001
PON1 activity (UL^{-1})	−0.558	<0.001	−0.343	<0.001

Abbreviations as in Table 1.

Multivariate regression analysis showed that GGT activity was independently associated with PWV (β = 0.496, $P < 0.001$), hs-CRP (β = 0.334, $P < 0.001$), and PON1 activity (β = −0.343, $P < 0.001$) (Table 2).

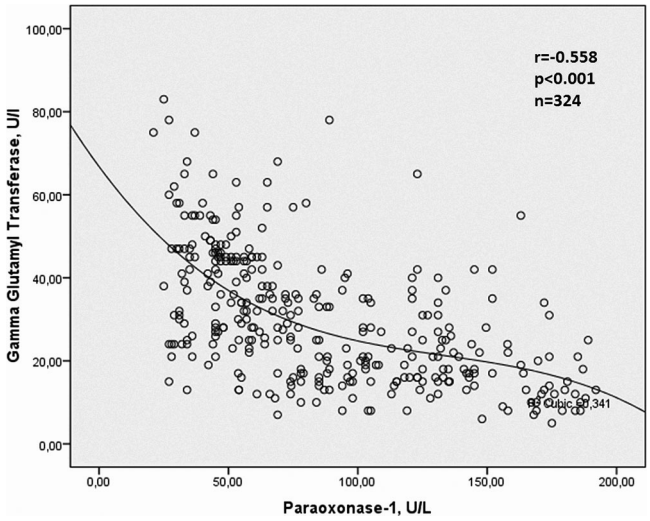

Fig. 1. Relationship between GGT activity and PON1.

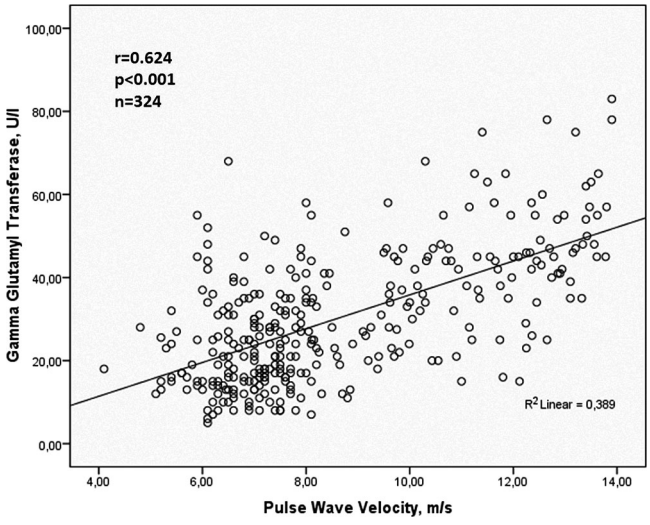

Fig. 2. Relationship between GGT activity and PWV.

DISCUSSION

This is the first study that investigated the relationship between GGT activity with PON1 activity and AS in newly diagnosed hypertensive patients. The main finding of the present study was that GGT activity was independently associated with PON1 activity and PWV as well as hs-CRP in newly diagnosed hypertensive patients.

It is well known that there is an independent association between GGT activity and hypertension (5, 6). Moreover, GGT activity is positively associated with the development of hypertension (5, 6).

Present study showed that GGT activity within the normal range was independently and negatively associated with PON1 activity. Hypertension is associated with

increased vascular production of ROS (18, 19). Vascular oxidant stress, particularly interactions between nitric oxide and oxygen derived radicals, represents a common pathologic mechanism in many risk factors for atherosclerosis including hypertension (19). GGT has been proposed as a marker of oxidative stress (1,2). Previous experimental studies have reported that GGT plays an important role in antioxidant systems with the primary function of maintaining intracellular concentrations of glutathione, a critical antioxidant defense for the cell (20,21). Also, it was shown that GGT activities within the reference range catalyze oxidative reactions in the presence of iron ions that lead to the production of free radicals and ROS and LDL oxidation (22). Oxidative stress, owing to increased lipid and protein oxidation products and decreased antioxidant enzymes and vitamins, affects PON1 expression and activities (23). There is direct evidence for a mechanistic link between activity of PON1 with systemic oxidative stress and prospective cardiovascular risk, indicating a potential mechanism for the atheroprotective function of PON1 (24). Fallah et al. showed PON1 192 genes potentially play a role in the manifestation of coronary atherosclerosis (25). These findings shows that serum PON1 activity is inhibited by increased oxidative stress (23,24). It has been assumed that antioxidants such as PON1, which physiologically protect against excess of ROS, are consumed, thereby further increasing ROS induced damage (26). Therefore, the inverse relationship between GGT activity and PON1 activity (antioxidant enzyme) may be plausible because GGT activity is associated with oxidative stress.

Present study also showed that GGT activity was independently associated with PWV, with reproducible measures of AS. The relationship between GGT activity and AS was investigated in various patient groups (27, 31). However, this relationship was not investigated in newly diagnosed hypertensive patients. Saijo et al. reported that GGT was independently related to an increased level of arterial stiffness in male patients who were examined for routine checkup (27). Song et al. suggested that serum GGT activity may be an additional marker of arterial stiffness, especially in men, though the relationship with arterial stiffness was weak (28). Jung et al. demonstrated that GGT activity in healthy subjects was independently associated with the increased level of arterial stiffness both in men and women, even it was stronger in men (28). Also, the similar relationship between GGT activity and arterial stiffness was shown in patients with established coronary artery disease and in young patients with prehypertension (30, 31). The pathophysiological mechanisms underlying the association between GGT activity with increased AS are unclear. GGT levels were found to be associated with subclinical aortic atherosclerosis (32). Furthermore, higher serum GGT activity has been reported in atherosclerotic plaques and foam cells (33). Moreover, GGT contributes to oxidative stress pathways in several organ systems, localizes to atheromatous plaques containing oxidized LDL, and is proinflammatory, further implicating this protein in atherogenesis (34). On the other hand, the association between increased AS with oxidative stress, inflammation, and subclinical atherosclerosis has been demonstrated in previous studies (35,36). Therefore, increased GGT activity may reflect to increased oxidative stress, inflammation, and subclinical atherosclerosis in hypertensive patients with increased AS. In present study, the independent relationship between GGT activity with hs-CRP and PON1 activity may support this hypothesis.

Present study showed that GGT activity was also independently associated with hs-CRP levels. This result is consistent with previous studies (27,34,37). Previous studies have reported a significant association between serum GGT and CRP levels after adjustment for age, smoking, alcohol consumption, and BMI (1). Moreover, CRP has been found to be deposited in coronary artery plaque, and it has a pro-oxidative effect on cultured coronary artery smooth muscle cells (37). Therefore, it was suggested that the significant relationship between GGT and CRP may possibly be due to their association with oxidative stress (27).

Study Limitations

Coronary atherosclerosis may affect GGT and PON1 activities in this patient group. Coronary angiography was not performed in our patients although patients with coronary artery disease have been excluded according to clinical characteristics and patient history, electrocardiography, and treadmill exercise test. Also, smoking may be effective on PON1 activity and AS. However, smoking frequencies of groups were not different and there was no correlation between GGT activity and smoking frequency in our study. Furthermore, in present study, there was an independent relationship between GGT activity with AS and PON1 activity.

Finally, in present study, PON1 phenotype or genotype was not determined. PON1 has two coding region amino acid polymorphisms, one at position 55 and another at position 192 (38). The Q192R polymorphism has such a significant effect on PON1 activity. It is possible, but not advisable, to use paraoxonase activity within a 192 genotype/phenotype (e.g., Q/Q, Q/R, or R/R). Also, it was reported that serum PON1 activity is a better predictor of the risk for cardiovascular diseases than the PON1 genotype (39).

CONCLUSIONS

In hypertensive patients, GGT activity was independently associated with PON1 activity and PWV as well as hs-CRP. These results may support that increased GGT activity would be associated with both impaired antioxidant system and increased AS in hypertensive patients.

REFERENCES

1. Yamada J, Tomiyama H, Yambe M, et al. Elevated serum levels of alanine aminotransferase and gamma glutamyltransferase are markers of inflammation and oxidative stress independent of the metabolic syndrome. Atherosclerosis 2006;189:198–205.
2. Jimba S, Nakagami T, Takahashi M, et al. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. Diabet Med 2005;22:1141–1145.
3. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001;38:263–355.
4. Bozbaş H, Yıldırır A, Karaçağlar E, et al. Increased serum gamma-glutamyltransferase activity in patients with metabolic syndrome. Turk Kardiyol Dern Ars 2011;39:122–128.
5. Lee DH, Jacobs DR Jr, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Clin Chem 2003;49:1358–1366.
6. Cheung BM, Ong KL, Tso AW, et al. Gamma-glutamyl transferase level predicts the development of hypertension in Hong Kong Chinese. Clin Chim Acta 2011;412:1326–1331.
7. Cohn JN. Vascular wall function as a risk marker for cardiovascular disease. J Hypertens Suppl 1999;17:s41–s44.
8. Dart AM, Kingwell BA. Pulse pressure—A review of mechanisms and clinical relevance. J Am Coll Cardiol 2001;37:975–984.
9. Laurent S, Boutouyrie P, Asmar R, et al. Aortic stiffness is an independent predictor of all cause and cardiovascular mortality in hypertensive patients. Hypertension 2001;37:1236–1241.
10. Weber T, Auer J, O'Rourke MF, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation 2004;109:184–189.
11. Watson AD, Berliner JA, Hama SY, et al. Protective effect of high density lipoprotein associated paraoxonase. Inhibition of the biological activity of minimally oxidized low density lipoprotein. J Clin Invest 1995;96:2882–2891.
12. Aviram M, Rosenblat M, Bisgaier CL, et al. Paraoxonase inhibits high density lipoprotein oxidation and preserves its functions. A possible peroxidative role for paraoxonase. J Clin Invest 1998;101:1581–1590.
13. Stergiou GS, Salgami EV. World Health Organization-International Society of Hypertension (WHO-ISH); USA Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7); European Society of Hypertension-European Society of Cardiology (ESH-ESC). New European, American and International guidelines for hypertension management: Agreement and disagreement. Expert Rev Cardiovasc Ther 2004;2:359–368.
14. Eckerson HW, Wyte CM, La Du BN. The human serum paraoxonase/arylesterase polymorphism. Am J Hum Genet 1983;35:1126–1138.
15. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Stand-ards, Subcommittee on quantitation of two-dimensional echocardiograms. J Am Soc Echocardiogr 1989;2:358–367.
16. Wassertheurer S, Mayer C, Breitenecker F. Modeling arterial and left ventricular coupling for non-invasive measurements. Simul Model Pract Th 2008;16:988–997.
17. Wassertheurer S, Kropf J, Weber T, et al: A new oscillometric method for pulse wave analysis: Comparison with a common tonometric method. J Hum Hypertens 2010;24:498–504.
18. Lasse`gue B, Griendling K. Reactive oxygen species in hypertension. An update. Am J Hypertens 2004;17:852–860.
19. Rodrigo R, Prat H, Passalacqua W, Araya J, Guichard C, Bächler JP. Relationship between oxidative stress and essential hypertension. Hypertens Res 2007;30:1159–1167.
20. Kugelman A, Choy HA, Liu R, Shi MM, Gozal E, Forman HJ. Gamma-glutamyl transpeptidase is increased by oxidative stress in rat alveolar L2 epithelial cells. Am J Respir Cell Mol Biol 1994;11:586–592.
21. Karp DR, Shimooku K, Lipsky PE. Expression of gamma-glutamyl transpeptidase protects ramos B cells from oxidation-induced cell death. J Biol Chem 2001;276:3798–3804.
22. Paolicchi A, Tongiani R, Tonarelli P, Comporti M, Pompella A. Gamma-glutamyl transpeptidase-dependent lipid peroxidation in isolated hepatocytes and HepG2 hepatoma cells. Free Radic Biol Med 1997;22:853–860.
23. Navab M, Hama-Levy S, Van Lenten BJ, et al. Mildly oxidized LDL induces an increased apolipoprotein J/paraoxonase ratio. J Clin Invest 1997;99:2005–2019.
24. Bhattacharyya T, Nicholls SJ, Topol EJ, et al. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. JAMA 2008;299:1265–1276.
25. Fallah S, Seifi M, Ghasemi A, Firoozrai M, Samadikuchaksaraei A. Matrix metalloproteinase-9 and paraoxonase 1 Q/R192 gene polymorphisms and the risk of coronary artery stenosis in Iranian subjects. J Clin Lab Anal 2010;24:305.
26. Becker LB. New concepts in reactive oxygen species and cardiovascular reperfusion physiology. Cardiovasc Res 2004;61:461–470.
27. Saijo Y, Utsugi M, Yoshioka E, et al. The relationship of gamma-glutamyltransferase to C-reactive protein and arterial stiffness. Nutr Metab Cardiovasc Dis 2008;18:211–219.
28. Song SH, Kwak IS, Kim YJ, et al. Can gamma-glutamyltransferase be an additional marker of arterial stiffness? Circ J 2007;71(11):1715–1720.
29. Jung CH, Yu JH, Bae SJ, et al. Serum gamma-glutamyltransferase is associated with arterial stiffness in healthy individuals. Clin Endocrinol (Oxf) 2011;75:328–334.
30. Zhu C, Xiong Z, Zheng Z, Chen Y, Qian X, Chen X. Association of serum gamma-glutamyltransferase with arterial stiffness in established coronary artery disease. Angiology 2013;64:15–20.
31. Celik T, Yuksel UC, Kilic S, et al. The relationship of gamma-glutamyltransferase to aortic elastic properties in young patients with prehypertension. Clin Exp Hypertens 2010;32:377–384.
32. Caylı M, Gür M, Kalkan GY, et al. Gamma glutamyl transferase activity : Relationship with thoracic aortic intima media thickness and inflammation. Herz 2013. doi: 10.1007/s00059-013-3921-0
33. Paolicchi A, Emdin M, Ghliozeni E, et al. Images in cardiovascular medicine. Human atherosclerotic plaques contain gamma-glutamyl transpeptidase enzyme activity. Circulation 2004;109:1440.
34. Lee DH, Jacobs DR Jr. Association between serum gamma-glutamyltransferase and C-reactive protein. Atherosclerosis 2005;178:327–330.

35. Wang J, Xu J, Zhou C, et al. Improvement of arterial stiffness by reducing oxidative stress damage in elderly hypertensive patients after 6 months of atorvastatin therapy. J Clin Hypertens (Greenwich) 2012;4:245–249.
36. Elbasan Z, Sahin DY, Gür M, et al. Aortic distensibility and aortic intima-media thickness in patients without clinical manifestation of atherosclerotic cardiovascular disease. Echocardiography 2013;30:407–413.
37. Kobayashi S, Inoue N, Ohashi Y, et al. Interaction of oxidative stress and inflammatory response in coronary plaque instability: Important role of C-reactive protein. Arterioscler Thromb Vasc Biol 2003;23:1398–1404.
38. Mackness MI, Mackness B, Durrington PN. Paraoxonase and coronary heart disease. Atheroscler Suppl 2002;3:49–55.
39. Mackness B, Davies GK, Turkie W, et al. Paraoxonase status in coronary heart disease: Are activity and concentration more important than genotype? Arterioscler Thromb Vasc Biol 2001;21:1451–1457.