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The Relationship of Gamma-Glutamyltransferase to Aortic Elastic Properties in Young Patients with Prehypertension

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Abstract

Some cross-sectional studies have demonstrated a positive association between serum gamma-glutamyltransferase (GGT) levels and blood pressure. Accordingly, we aimed to analyze serum GGT levels in patients with prehypertension and examine the relationship with aortic elasticity parameters. The study population consisted of 25 newly diagnosed prehypertensive individuals and 25 healthy control subjects. Aortic strain, distensibility index, and stiffness index beta were calculated from aortic diameters measured by echocardiography and blood pressures simultaneously measured by sphygmomanometry. Prehypertensive patients were detected to have significantly lower aortic distensibility and strain indexes compared to control subjects aortic distensibility. However, aortic stiffness index beta of the prehypertensive group was significantly higher compared to that of the control group (3.73 ± 1.41 vs. 2.97 ± 0.82, $p = 0.02$). The mean GGT levels were found to be higher in patients with prehypertension compared to those of controls (47.9 ± 15.9 U/L vs. 36.1 ± 9.4 U/L, $p = 0.003$). When multiple linear regression analysis was done to clarify the contributions of GGT to aortic elasticity adjusting for age, body mass index, uric acid, serum glucose, heart rate, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride, we observed that only serum GGT levels were significantly associated with aortic elasticity parameters (for aortic strain beta = –0.247, $p < 0.001$; for aortic distensibility beta = –0.108, $p < 0.001$; for stiffness index beta = 0.063, $p < 0.001$). Whatever the mechanism is, young patients with prehypertension have higher serum GGT levels compared to healthy control subjects. More importantly, increased GGT levels are independently associated with impaired aortic elasticity in patients with prehypertension.

Keywords: prehypertension, aortic elastic properties, young age, gamma-glutamyltransferase (GGT)

INTRODUCTION

In the Joint National Committee's (JNCs) seventh report, the prehypertension category has been used for the patients whose systolic and diastolic blood pressure values are 120–139 mmHg and 80–89 mmHg, respectively (1). Patients with prehypertension have been shown to be at increased risk for progression to hypertension; those patients with prehypertension are at twice the risk to develop hypertension as those with lower values (2).

It is well appreciated that the aorta has a fundamental role in the function of the cardiovascular system. One of the most important physiological roles of the aorta is buffering Windkessel function, which is its capability to store part of the stroke volume during systole by aortic distention and to transfer this storage into the peripheral circulation during diastole (3). It has been demonstrated that arterial stiffness, especially large artery stiffness, is an independent determinant of future cardiovascular disease (4, 5). In addition to its potential etiological role in cardiovascular disease, elevated arterial stiffness may serve as an early marker for the detection of asymptomatic atherosclerotic lesions and/or structural changes resulting from hypertension (6, 7). In particular, it has been proven that large artery stiffness is among the best predictors of cardiovascular mortality and morbidity (8). It has been shown that hypertension is one of the most important predictors of reduced arterial elasticity, independent of age (8–10). More importantly, our group has recently demonstrated that aortic elasticity is impaired in young patients with prehypertension compared to healthy controls (11).

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Gamma-glutamyltransferase (GGT) activity, normally found in serum as well as in the plasma membrane of virtually all cells except erythrocytes, catalyzes the first step in the degradation of extracellular glutathione (GSH), allowing for precursor amino acids to be assimilated and reutilized for intracellular GSH synthesis, which is the main thiol antioxidant in mammalian cells (12). Serum GGT determination is widely used as a diagnostic test for hepatobiliary diseases and alcohol abuse (13). However, several clinical studies have shown that slightly elevated serum GGT which is almost within the reference range is significantly associated with all-cause mortality, as well as increased risks of myocardial infarction (MI), and stroke (14–18). Also, serum GGT within a range regarded as phsiologically normal is shown to be associated with incident hypertension and diabetes mellitus (19, 20). On the other hand, some cross-sectional studies have demonstrated a positive association between serum GGT levels and blood pressure in spite of the fact that this association had not been specifically examined in young prehypertensive patients (21–23). Accordingly, the current study was designated to evaluate whether GGT could be an additional marker of arterial stiffness by using the echocardiographically derived M-mode indices in young patients with prehypertension.

MATERIAL AND METHODS

Patients

The study population consisted of 25 newly diagnosed prehypertensive individuals (18 men, mean age = 34 ± 6 years) and 25 healthy control subjects (16 men, mean age = 33 ± 6 years) eligible for the current retrospectively designed study. The diagnosis of prehypertension was established according to the JNC's seventh report (1). Patients with acute or chronic renal dysfunction, diabetes mellitus, metabolic syndrome, impaired glucose tolerance, heart failure, valvular heart disease, history of coronary artery disease or proven coronary artery disease at coronary angiography or noninvasive tests, familial hyperlipidemia, obesity (body mass index [BMI] > 30 kg/m^2), asthma or chronic obstructive lung disease, pregnancy or taking oral contraceptives, concurrent therapy with medications that might affect blood pressure, history of smoking, history of alcohol consumption, history of coffee intake, aortic disease (Marfan's syndrome, coarctation of aorta, aortic aneursym, or aortic surgery etc.), and connective tissue disorders were excluded from the study. Moreover, the patients with a hostile echocardiographic environment were not included in the current study.

Blood Pressure Measurements

Blood pressure was measured three times for each patient with a standard mercury sphygmanometer on the right arm in the sitting position following 10 min resting. Phase I and V Korotkoff sounds were used to determine systolic and diastolic blood pressure measurements. In each patient, measurements were performed by the same investigator, in the same room, and at the same time of day. The average of three measurements was used for the analyses.

Echocardiographic Examination

Transthoracic echocardiography was performed by using a EASOTE 2,5 Mhz probe (ESAOTE, Genova, Italy) at the left lateral decubitis position in a standard manner. Echocardiographic measurements were made on the screeen by two cardiologists not aware of the patients' clinical data. M mode tracing of the left ventricle were obtained in the parasternal long axis views at a speed of 50 mm/s. Five consecutive cardiac cycles were averaged for every echocardiographic measurement. Left ventricular systolic and diastolic diameters [LVIDs, LVIDd], left ventricular mass index [LVMI], and left atrial systolic diameter [LAd] were calculated from the parasternal long axis view according to standard criteria. The left ventricular ejection fraction [LVEF] was measured by the software using the Teichholz formula. The left ventricular mass was calculated according to the Penn convention (24) and the LVMI was obtained by the left ventricular mass divided by body surface area. Afterwards, the ascending aorta was visualized in the same views. With the M mode, aortic tracing was recorded at the level of approximately 3 cm above the aortic valve. From the M mode recordings, aortic systolic and diastolic diameters [Aos and Aod] were measured. Aos was determined at the time of the full opening of the aortic valve and Aod was determined at the peak of QRS (25). All parameters were measured in five consecutive cardiac cycles and averaged. Simultaneously, cuff brachial artery systolic blood pressures [SBPs] and diastolic blood pressures [DBPs] were measured with an aneroid sphygmomanometer.

The peak early transmitral filling during early diastole (E), peak transmitral atrial filling velocity during late diastole (A), deceleration time (DT) (time elapsed between peak E velocity and the point where the extrapolated deceleration slope of the E velocity crosses the zero baseline), and isovolumetric deceleration time (IVRT) (time period between the end of mitral diastolic flow Doppler tracing and the starting point of aortic flow Doppler tracing) were used to assess left ventricular diastolic functions. The transmitral diastolic flow Doppler tracing was obtained from the apical four-chamber view by using pulsed Doppler echocardiography with the sample volume size of 1 to 2 mm between the tips of the mitral valve during diastole. To measure isovolumetric relaxation time, a 3-to 4-mm size sample volume was placed in the area of the mitral leaflet tips. Next, the transducer beam was angulated toward the left ventricular outflow tract until the aortic valve closure appeared above and below the baseline.

The Measurements of Aortic Elasticity Parameters

Aortic elasticity was assessed using the following indexes (26):

Aortic strain (%) = 100 × (Aos-Aod)/Aod;
Aortic distensibility index (cm^{-2} dyn^{-1} 10^{-6}) = 2 × Aortic Strain × (SBP-DBP);
Aortic stiffness index beta = ln (SBP/DBP)/Aortic Strain.

Blood Chemistry

Venous blood samples were withdrawn into both the tubes containing K_3 EDTA and the tubes containing no anti-coagulant agent. After all tubes were spun at 5000 rpm for 15 min, plasma and serum samples were stored at −80°C until analyses were made. Total plasma cholesterol, triglyceride, and HDL cholesterol were measured by an enzymatic calorimetric method with the Olympus AU 600 autoanalyzer using reagent from Olympus Diagnostics GmbH (Hamburg, Germany). Low-density lipoprotein cholesterol levels were calculated by Friedwald formula. Serum glucose was measured by the glucose oxidase method. The serum insulin levels were determined with the immunoenzymatic method (Beckman Coulter Inc., Immunotech, IRMA Kit, Prague, Czech Republic). Gamma-glutamyl transferase levels were measured with a spectrophotometric technique by an Olympus AU-2700 autoanalyzer and using commercial kits (Olympus, Hamburg, Germany).

Assesment of Insulin-Resistance

Insulin-resistance score the homeostatic model assessment [HOMA-IR] was computed with the formula: [HOMA-IR] = [fasting plasma glucose (mg/dl) × immunoreactive insulin (IRI) (IU/ml)]/405 (27). Low HOMA-IR values represent high-insulin sensitivity, whereas high HOMA-IR values represent low-insulin sensitivity (insulin-resistance) compared to those of the controls.

Statistical Analysis

Statistical analysis was performed by using the SPSS 11.5 Statistical Package Program for Windows (SPSS Inc., Chicago, IL). Results are expressed as the mean ± SD, median and percentages. The means of groups were compared with each other. The differences between groups were tested by chi-square, an independent samples *t*-test, and a Mann-Whitney *U* test. Intra- and inter-observer variability were calculated as a relative error. A linear regression analysis was performed to evaluate the association between GGT and aortic elasticity parameters. Next, a lineer regression analysis was done to evaluate the association between aortic elasticity parameters and other variables. Then, multiple linear regression analysis was done to clarify the contributions of GGT to aortic elasticity adjusting for age, BMI, uric acid, serum glucose, heart rate, LDL-cholesterol, HDL-cholesterol, and triglycerides (TGs). Differences were considered significant at $p < 0.05$.

RESULTS

When baseline charecteristics of patients with prehypertension were compared to those of control subjects, no statistically significant difference was observed between the two groups except for significantly higher GGT and blood pressure levels in patients with prehypertension compared to those in controls as shown in Table 1 (for GGT; 47.9 ± 15.9 U/L vs. 36.1 ± 9.4 U/L, $p = 0.003$).

Table 1. Baseline clinical and biochemical parameters of the study groups

	Prehypertension (n = 25)	Control (n = 25)	p
Age (years)	34 ± 6	33 ± 6	0.35
Gender (M), n (%)	18 (53)	16 (47)	0.54
BMI (kg/m^2)	25.64 ± 2.04	25.81 ± 1.74	0.74
BSA (m^2)	1.85 ± 0.13	1.82 ± 0.09	0.36
GGT (U/L)	47.92 ± 15.95	36.12 ± 9.47	0.003
AST (U/L)	38.71 ± 9.50	35.33 ± 7.71	0.18
ALT (U/L)	38.28 ± 9.07	34.44 ± 8.60	0.13
Total cholesterol (mg/dl)	196 ± 41	197 ± 42	0.95
TG (mg/dl) (median)	137 ± 89 (115)	117 ± 50 (96)	0.76
HDL cholesterol (mg/dl)	48 ± 13	45 ± 11	0.39
LDL cholesterol (mg/dl)	121 ± 38	129 ± 40	0.49
Serum glucose (mg/dl)	98 ± 8	94 ± 7	0.07
Serum insulin (μU/mL)	11 ± 4	10 ± 5	0.47
HOMA-IR	2.66 ± 1.06	2.33 ± 1.29	0.33
Heart rate (bpm)	74 ± 9	72 ± 9	0.37

Abbreviations: BMI - body mass index; BSA - body surface area; GGT - gamma-glutamyltransferase; AST - alanine aminotransferase; ALT - aspartate aminotransferase; TG - triglyceride; HDL - high-density lipoprotein; LDL - low-density lipoprotein; HOMA-IR - the homeostatic model assessment of insulin-resistance.

Echocardiographic Measurements

We noticed no statistically significant difference between two groups regarding LVIDs and LVIDd, LVEF, Lad, and LVMI (Table 2). Although diastolic functions of the left ventricle of the patients with prehypertension were not impaired, the E/A ratio and E velocity values were detected to be lower and deceleration and isovolumetric relaxation times were to be higher in prehypertensives than those in controls (Table 2).

Aortic Elastic Parameters

Aortic elastic properties of both groups are summarized in Table 3. The mean systolic, diastolic, and pulse pressure measurements were significantly higher in prehypertensive patients than in control subjects. The mean aortic systolic and diastolic diameters of prehypertensive patients were detected to be significantly higher than those of control subjects (aortic systolic diameter: 31.76 ± 1.66 mm vs. 29.84 ± 2.28 mm, respectively, $p = 0.001$; aortic diastolic diameter: 27.96 ± 2.03 mm vs. 25.44 ± 2.21 mm, respectively, $p < 0.001$, Table 3). However, the mean aortic diameter change of prehypertensive patients was detected to be significantly lower than those of control subjects (3.80 ± 1.04 mm vs. 4.40 ± 0.95 mm, respectively, $p = 0.03$). The coefficients of variation for aortic systolic diameter, diastolic diameter, SBPs, and DBPs, all of which are the main determinants of the formulas to calculate aortic elasticity, were 5%, 7%, 3%, and 8%, respectively. Intra- and inter-observer variabilities were found to be 2.7% and 4.3% for aortic systolic diameter; 2.8% and 4.9% for aortic diastolic diameter; 2.1% and 3.3% for SBP; 2.4% and 2.9% for DBP, consecutively.

When the mean aortic distensibility and strain indexes were analyzed, aortic distensibility and strain indexes of the patients with prehypertension were found to be significantly lower than those of control subjects (aortic distensibility: 5.77 ± 1.91 cm^{-2} dyn^{-1} 10^{-6} vs. 8.63 ± 2.67 cm^{-2} dyn^{-1} 10^{-6}, respectively, $p < 0.001$; aortic strain: 13.81 ± 4.50% vs. 17.47 ± 4.25%, respectively, $p = 0.005$, Table 3). In contrast, the mean aortic stiffness index beta [SI] of the prehypertensive

Table 2. Echocardiographic findings of both groups

	Prehypertension (n = 25)	Control (n = 25)	p
LVIDd (mm)	45.44 ± 2.00	45.20 ± 1.89	0.66
LVIDs (mm) (median)	26.20 ± 1.63 (26)	26.40 ± 1.68 (26)	0.67
IVSd (mm)	9.56 ± 1.50	9.44 ± 1.08	0.74
IVSs (mm)	13.56 ± 1.50	13.44 ± 1.08	0.73
LVPWd (mm) (median)	8.52 ± 1.68 (8)	8.04 ± 1.27 (8)	0.24
LVPWs (mm) (median)	12.88 ± 1.85 (13)	12.24 ± 1.33 (12)	0.15
LVEF (%)	66.70 ± 2.84	65.83 ± 2.97	0.29
LVMI (gr/m^2)	124.53 ± 17.26	117.45 ± 17.85	0.16
Left atrial diameter (mm)	34.00 ± 3.14	32.72 ± 3.08	0.14
E velocity(cm/s) (median)	78.80 ± 8.91 (80)	83.72 ± 4.60 (84)	0.07
A velocity(cm/s) (median)	67.00 ± 15.80 (63)	56.44 ± 9.25 (58)	0.02
E/A	1.23 ± 0.30	1.52 ± 0.26	0.001
Deceleration time (ms) (median)	184.32 ± 21.42 (188)	168.88 ± 10.17 (165)	0.004
IVRT (ms) (median)	78.04 ± 10.61 (75)	72.08 ± 4.99 (72)	0.04

Abbreviations: LVIDd - left ventricular internal diameter (diastolic); LVIDs - left ventricular internal diameter (systolic); IVSd - interventricular septum diameter (diastolic); IVSs - interventricular septum diameter (systolic); LVPWd - left ventricular posterior wall diameter (diastolic); LVPWs - left ventricular posterior wall diameter (systolic); LVEF - left ventricular ejection fraction; LVMI - left ventricular mass index; E - early rapid filling wave; A - filling due to atrial contraction; IVRT - isolometric relaxation time.

Table 3. Aortic elastic properties of the study groups

	Prehypertension (n = 25)	Control (n = 25)	p
SBP (mmHg) (median)	131 ± 5 (130)	107 ± 9 (110)	<0.001
DBP (mmHg)	82 ± 6	65 ± 6	<0.001
PP (mmHg) (median)	49 ± 7 (45)	42 ± 10 (40)	0.01
ASD (mm)	31.76 ± 1.66	29.84 ± 2.28	0.001
ADD (mm)	27.96 ± 2.03	25.44 ± 2.21	<0.001
Diameter change (mm)	3.80 ± 1.04	4.40 ± 0.95	0.03
Distensibility ($cm^{-2}dyn^{-1}10^{-6}$)	5.77 ± 1.91	8.63 ± 2.67	<0.001
Aortic strain (%)	13.81 ± 4.50	17.47 ± 4.25	0.005
Stiffness index	3.73 ± 1.41	2.97 ± 0.82	0.02

Abbreviations: SBP - systolic blood pressure; DBP - diastolic blood pressure; PP - pulse pressure; ASD - aortic systolic diameter; ADD - aortic diastolic diameter.

group was significantly higher compared to that of the control group (3.73 ± 1.41 vs. 2.97 ± 0.82, respectively, p = 0.02, Table 3).

When the multiple linear regression analysis was done to clarify the contributions of GGT to aortic elasticity adjusting for age, BMI, uric acid, serum glucose, heart rate, LDL cholesterol, HDL cholesterol, and TG, we observed that only serum GGT levels was significantly associated with aortic elasticity parameters as shown in Tables 4–6.

Table 4. Multiple lineer regression analysis with aortic strain as the dependent variable in patients with prehypertension

	Beta	95% CI	p
GGT (U/L)	–0.247	(–0.309)–(–0.185)	<0.001
Uric acid (mg/dl)	–0.956	(–2.023)–(0.111)	0.078
Glucose (mg/dl)	–0.120	(–0.293)–(0.054)	0.17
LDL (mg/dl)	–0.011	(–0.035)–(0.013)	0.38
TG (mg/dl)	–0.004	(–0.017)–(0.009)	0.51
HDL (mg/dl)	–0.027	(–0.107)–(0.053)	0.50
Age (years)	–0.076	(–0.230)–(0.077)	0.32
BMI (kg/m^2)	0.012	(–0.516)–(0.539)	0.97
Heart rate (bpm)	0.015	(–0.097)–(0.127)	0.79

Abbreviations: GGT - gamma-glutamyltransferase; LDL - low-density lipoprotein; TG - triglyceride; HDL - high-density lipoprotein; BMI - body mass index.

Table 5. Multiple lineer regression analysis with aortic distensibility as the dependent variable in patients with prehypertension

	Beta	95% CI	p
GGT (U/L)	–0.108	(–0.150)–(–0.066)	<0.001
Uric acid (mg/dl)	–0.361	(–1.087)–(0.365)	0.32
Glucose (mg/dl)	–0.151	(–0.267)–(0.035)	0.05
BMI (kg/m^2)	–0.214	(–0.537)–(0.110)	0.19
TG (mg/dl)	0.003	(–0.005)–(0.012)	0.42
HDL (mg/dl)	–0.014	(–0.072)–(0.043)	0.62
LDL (mg/dl)	0.004	(–0.013)–(0.021)	0.67
Age (years)	–0.019	(–0.128)–(0.090)	0.73
Heart rate (bpm)	–0.016	(–0.086)–(0.055)	0.67

Abbreviations: GGT - gamma-glutamyltransferase; BMI - body mass index; TG - triglyceride; HDL - high density lipoprotein.

Table 6. Multiple lineer regression analysis with stiffness index beta as the dependent variable in patients with prehypertension

	Beta	95% CI	p
GGT (U/L)	0.063	(0.046)–(0.079)	<0.001
Age (years)	0.028	(–0.013)–(0.069)	0.18
Uric acid (mg/dl)	–0.025	(–0.336)–(0.285)	0.87
Glucose (mg/dl)	0.019	(–0.028)–(0.065)	0.42
LDL (mg/dl)	0.000	(–0.007)–(0.007)	0.94
TG (mg/dl)	–0.001	(–0.005)–(0.002)	0.46
HDL (mg/dl)	–0.002	(–0.022)–(0.025)	0.90
BMI (kg/m^2)	0.025	(–0.111)–(0.162)	0.71
Heart rate (bpm)	0.011	(–0.016)–(0.038)	0.42

Abbreviations: GGT - gamma-glutamyltransferase; LDL - low-density lipoprotein; TG - triglyceride; HDL - high-density lipoprotein; BMI - body mass index.

DISCUSSION

The current study revealed that not only were serum GGT levels significantly increased in young patients with prehypertension compared to those of controls, but elevated GGT levels were also independently associated with decreased aortic elasticity in young prehypertensive patients.

Hypertension is one of the most common chronic diseases in the world and affects approximately 1 billion people in the world (1). The relationship between blood pressure and risk of cardiovascular events is continous, consistent, and independent of other known risk factors (1). The classification of prehypertension introduced in the JNC seventh report has delineated these relationships and urged the need for increased education of healthcare professionals to decrease blood pressure levels and prevent the development of hypertension in the general population (28). In addition, patients with prehypertension have also been shown to have an increased risk to develop hypertension (2).

Although serum GGT activity has long been accepted as a marker for hepatobiliary disease and alcohol consumption, there has been some epidemiologic evidence suggesting that GGT might evolve as a potential biochemichal risk indicator of cardiovascular mortality and morbidity (29). Serum GGT levels appeared to be an independent risk factor for the development of cardiovascular disease, arterial hypertension, stroke, and type 2 diabetes mellitus, and their complications in several prospective cohort clinical studies after adjusting for alcohol consumption (18, 19, 30, 31). Lee et al. found that even in the young adult population, after adjusting for alcohol consumption, serum GGT concentration was associated with many cardiovascular disease risk factors, including black race, male gender, older age, cigarette smoking, BMI, higher blood pressure, higher fasting blood sugar, higher fasting blood triglycerides, higher blood LDL-cholesterol, and lower blood HDL-cholesterol. In addition, other variables, such as white blood cell count, red blood cell count, hematocrit, and hemoglobin, were positively associated with GGT (19).

Gamma-glutamyltransferase is also a modest risk factor for hypertension (32). There-fore the mechanism underlying these observations is not fully elucidated. Some cross-sectional studies have demonstrated a positive association between serum GGT levels and blood pressure (21–23). Although the positive association between GGT level and blood pressure may simply reflect the well-known relationship between alcohol consumption and hypertension, several investigators reported that the association was independent of the amount of alcohol consumed (22). There have been a few longitudinal studies (33–36), with results that are not entirely consistent. Studies from Japan (33, 35, 36) reported positive associations of serum GGT with blood pressure, but a study from Norway (34) found a

weak positive association, restricted to SBP among women, with no association among men. One Japanese study (33) reported a positive association between baseline GGT and incidence of hypertension only in drinkers, but not in nondrinkers, which could be interpreted as different alcohol-blood pressure relationships in subjects with different serum GGT levels.

Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension. The Coronary Artery Risk Development in Young Adults (CARDIA) study is a large-scale prospective study aiming to examine whether serum GGT predicts diabetes mellitus and hypertension (19). In this landmark study, serum GGT concentrations measured at ages 18–30 years predicted a 15-year incidence of diabetes and/or hypertension and the future concentrations of oxidative stress and inflammation markers such as fibrinogen, uric acid, C-reactive protein (CRP), and F2-isoprostanes, which were measured at various times during the 15 years of follow-up. In that study, the authors concluded that GGT might be an early marker of oxidative or other cellular stress and that it is possibly directly related to the pathogenesis of diabetes and hypertension, perhaps as an oxidative stressor itself. This study suggests that serum GGT is a strong predictor of diabetes and hypertension. Neither alcohol consumption nor liver damage likely explains this association. The authors speculate that it might be involved in the pathogenesis of diabetes and hypertension through a mechanism related to oxidative stress. On the other hand, Lee et al. showed that elevated GGT could be a predictor for hypertension in alcohol drinkers and the relationship between alcohol consumption and hypertension was demonstrated only among those with GGT $\geq$ 30 U/L at baseline (32). The authors concluded that increased serum GGT levels may reflect individual susceptibility to the blood pressure-raising effect of alcohol. However, in the present study, we found that serum GGT was independently associated with decreased arterial elasticity in young prehypertensives not consuming alcohol in accordance with the data obtained from the CARDIA study.

Although the mechanism underlying the associations of increased serum GGT levels with cardiovascular diseases remains largely unknown, some possible mechanisms exist. Previous experimental studies (37–39) have reported that GGT plays an important role in antioxidant systems with the primary function of maintaining intracellular concentrations of glutathione. Increases in GGT activity can be a response to oxidative stress, marking increased transport of glutathione into cells. In addition, GGT is leaked into the serum, possibly as a result of normal cell turnover and cellular stresses. From that standpoint, increased serum GGT may identify those individuals with low but persistent increases in oxidative and other cellular stresses. On the other hand, recent experimental studies (40–43) indicated that under physiologic conditions, GGT is involved directly in the generation of reactive oxygen species in the presence of iron or other transition metals. Gamma-glutamyltransferase might alternatively be a specific marker of oxidative stress, e.g., as a result of iron overload, because several experimental and epidemiologic studies have suggested a close relationship between iron overload and cellular or serum GGT activity (44, 45). We speculate that GGT might be an early marker of oxidative or other cellular stress and that it is possibly directly related to the pathogenesis of prehypertension, perhaps as an oxidative stressor itself.

The major limitation of the study is the small sample size. Since coronary angiography was not performed, the probability of subclinical coronary artery disease cannot be fully excluded. But coronary flow is not impaired by insignificant coronary artery stenosis which may result in increased arterial stiffness. On the other hand, our study group consisted of the patients of a younger age in whom the prevalance of coronary artery disease with clinical sequela was relatively low. The current study could not identify a casual role for relationship that was found between serum GGT and aortic elasticity parameters. Self-reported alcohol consumption as a variable was questionable because of its reliability and validity. Lastly, although noninvasive assesment of aortic elasticity is convenient and reproducible, this method itself has some limitation in reflecting arterial stiffness.

In conclusion, increased serum GGT may be an additional marker of decreased aortic elasticity in young patients with prehypertension. Emerging evidence has shown that serum GGT might be an important enzyme in the pathogenesis of cardiovascular diseases, including arterial hypertension. Although arterial stiffness is generally regarded as developing as a consequence of long-standing hypertension, our findings have suggested that it may develop prior to development of overt hypertension, even at the prehypertensive stage, and serum GGT levels may be a marker underlying increased oxidative stres in those patients. Considering that GGT is easily measured and is extensively used, further large-scale prospective studies are needed to clarify the mechansims responsible for the relationship existing between GGT and aortic elasticity, as well as the clinical implication of that association.

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REFERENCES

[1] Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education

Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA* 2003 ;289:2560–2572.

[2] Vasan RS, Larson MG, Leip EP, Kannel WB, Levy D. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. *Lancet* 2001;358:1682–1686.

[3] Belz GG. Elastic properties and Windkessel function of the human aorta. *Cardiovasc Drugs Ther* 1995;9:73–83

[4] Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. *Circulation* 2001; 103:1245–1249.

[5] 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.

[6] Blankenhorn DH, Kramsch DM. Reversal of atherosis and sclerosis. The two components of atherosclerosis. *Circulation* 1989;79:1–7.

[7] Frohlich ED. Target organ involvement in hypertension: a realistic promise of prevention and reversal. *Med Clin North Am* 2004;88:209–221.

[8] Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol* 1994;140:669–682.

[9] Hodes RJ, Lakatta EG, McNeil CT. Another modifiable risk factor for cardiovascular disease? Some evidence points to arterial stiffness. *J Am Geriatr Soc* 1995;43:581–582.

[10] Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 1995;91:1432–1443.

[11] Celik T, Iyisoy A, Kursaklioglu H, et al. Impaired aortic elastic properties in young patients with prehypertension. *Blood Press Monit* 2006;11:251–255.

[12] Krefetz RG, McMillin GA. Enzymes. In: *Clinical Chemistry*. Bishop ML, Fody EP, Schoeff LE (eds.). Baltimore: Lippincott Williams & Wilkins, 2005, 255–256.

[13] Rollason JG, Pincherle G, Robinson D. Serum gamma glutamyl transpeptidase in relation to alcohol consumption. *Clin Chim Acta* 1972;39:75–80.

[14] Arndt V, Brenner H, Rothenbacher D, Zschenderlein B, Fraisse E, Fliedner TM. Elevated liver enzyme activity in construction workers: prevalence and impact on early retirement and all-cause mortality. *Int Arch Occup Environ Health* 1998;71:405–412.

[15] Karlson BW, Wiklund O, Hallgren P, Sjolin M, Lindqvist J, Herlitz J. Ten-year mortality amongst patients with a very small or unconfirmed acute myocardial infarction in relation to clinical history, metabolic screening and signs of myocardial ischaemia. *J Intern Med* 2000;247:449–456.

[16] Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyl-transferase: determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol* 1995;142:699–708.

[17] Jousilahti P, Rastenyte D, Tuomilehto J. Serum gamma-glutamyl transferase, self-reported alcohol drinking, and the risk of stroke. *Stroke* 2000;31:1851–1855.

[18] Bots ML, Salonen JT, Elwood PC, et al. Gamma-glutamyl-transferase and risk of stroke: The EUROSTROKE project. *J Epidemiol Community Health* 2002;(suppl. 1):i25–29.

[19] Lee DH, Jacobs DR Jr, Gross M, Kiefe CI, Roseman J, Lewis CE, Steffes M. 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.

[20] Yamada Y, Ikai E, Tsuritani I, Ishizaki M, Honda R, Ishida M. The relationship between serum gamma-glutamyl transpeptidase levels and hypertension: Common in drinkers and non-drinkers. *Hypertens Res* 1995;18:295–301.

[21] Yamada Y, Ishizaki M, Kido T, Honda, et al. Relationship between serum gamma-glutamyltranspeptidase activity, blood pressure and alcohol consumption. *J Human Hyperten* 1989;3:409–417.

[22] Yamada Y, Ishizaki M, Kido T, Honda R, Tsuritani I, Yamaya Y. Relationship between serum gamma-glutamyl-transpeptidase activity and blood pressure in middle-age male and female non-drinkers. *J Human Hyperten* 1990;4:609–614.

[23] Ikai E, Noborizaka Y, Tsuritani I, Honda R, Ishizaki M, Yamada Y. Serum gamma-glutamly transpeptidase levels and hypertension in non-drinkers: A possible role of fatty liver in the pathogenesis of obesity related hypertension. *Obesity Res* 1993;1:469–473.

[24] Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977;55:613–618.

[25] Pitsavos C, Toutouzas K, Dernellis J, et al. Aortic stiffness in young patients with heterozygous familial hypercholesterolemia. *Am Heart J* 1998;135:604–608.

[26] Lacombe F, Dart A, Dewar E, Jennings G, Cameron J, Laufer E. Arterial elastic properties in man: A comparison of echo-Doppler indices of aortic stiffness. *Eur Heart J* 1992;13:1040–1045.

[27] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–419.

[28] Whelton PK, He J, Appel LJ, et al. National High Blood Pressure Education Program Coordinating Committee. Primary prevention of hypertension: Clinical and public health advisory from the National High Blood Pressure Education Program. *JAMA* 2002;288:1882–1888.

[29] Teschke R, Brand A, Strohmeyer G. Inducion of hepatic microsomal gamma-glutamyltransferase activity following chronic alcohol comsumption. *Biochem Biophys Res Commun* 1977;75:718–724.

[30] Brenner H, Rothenbacher D, Arndt V, Schuberth S, Fraisse E, Fliedner TM. Distribution, determinants and prognostic value of gammaglutamyltransferase for all-cause mortality in a cohort of constuction workers from southern Germany. *Prev Med* 1997;26:305–310.

[31] Lee DH, Ha MH, Kim JH, et al. Gamma-glutamyltransferase and diabetes: A 4-year follow-up study. *Diabetologia* 2003;46:359–364.

[32] Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR. Gamma-Glutamyltransferase, alcohol, and blood pressure: a four year follow-up study. *Ann Epidemiol* 2002;12:90–6.

[33] Yamada Y, Ishizaki M, Kido T, et al. Alcohol, high blood pressure, and serum gamma-glutamly transpeptidase level. *Hypertension* 1991;18:819–826.

[34] Nilssen O, Førde OH. Seven-year longitudinal population study of change in gamma-glutamyltransferase: The Tromsø Study. *Am J Epidemiol* 1994;139:787–792.

[35] Ikai E, Honda R, Yamada Y. Serum gamma-glutamyl-transpeptidase level and blood pressure in nondrinkers: A possible pathogenic role of fatty liver in obesity-related hypertension. *J Hum Hyperten* 1994;8:95–100.

[36] Miura K, Nakagawa H, Nakamura H, Tabata M, Nagase H, Yoshida M, et al. Serum gamma-glutamyltransferase level in predicting hypertension among male drinkers. *J Hum Hyperten* 1994;8:445–449.

[37] 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.

[38] Takahashi Y, Oakes SM, Williams MC, Takahashi S, Miura T, Joyce-Brady M. Nitrogen dioxide exposure activates gamma-glutamyl transferase gene expression in rat lung. *Toxicol Appl Pharmacol* 1997;143:388–396.

[39] 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.

[40] Stark AA. Oxidative metabolism of glutathione by gamma-glutamyl transpeptidase and peroxisome proliferation: the relevance to hepatocarcinogenesis. A hypothesis. *Mutagenesis* 1991;6:241–245.

[41] Stark AA, Russell JJ, Langenbach R, Pagano DA, Zeiger E, Huberman E. Localization of oxidative damage by a glutathione-gamma- glutamyl transpeptidase system in preneoplastic lesions in sections of livers from carcinogen-treated rats. *Carcinogenesis* 1994;15:343–348.

[42] 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.

[43] Drozdz R, Parmentier C, Hachad H, Leroy P, Siest G, Wellman M. Gamma-glutamyltransferase dependent generation of reactive oxygen species from a glutathione/transferrin system. *Free Radic Biol Med* 1998;25:786–792.

[44] Brown KE, Kinter MT, Oberley TD, et al. Enhanced gamma-glutamyl transpeptidase expression and selective loss of CuZn superoxide dismutase in hepatic iron overload. *Free Radic Biol Med* 1998;24:545–555.

[45] Lakka TA, Nyyssonen K, Salonen JT. Higher levels of conditioning leisure time physical activity are associated with reduced levels of stored iron in Finnish men. *Am J Epidemiol* 1994;140:148–160.