Can γ-Glutamyltransferase be an Additional Marker of Arterial Stiffness?

Sang Heon Song, MD*,††; Ihm Soo Kwak, MD*,††; Yun Jin Kim, MD**,††;
Seong-Jang Kim, MD†,††; Soo Bong Lee, MD*,††;
Dong Won Lee, MD*,††; Bong Eun Lee, MD*,††

Background It has been recently suggested that γ-glutamyltransferase (GGT) is independently associated with cardiovascular mortality and atherosclerosis, so the present study evaluated whether GGT is an additional marker of arterial stiffness, independent of other risk factors, in screening cohorts.

Methods and Results The 1,387 individuals (741 men, 646 women) who underwent brachial – ankle pulse wave velocity (baPWV) measurement had their serum levels of GGT, creatinine, uric acid, C-reactive protein, lipids, fasting glucose and insulin, and their hepatitis profiles checked. There were statistically significant increments of baPWV according to quartile of GGT, which was statistically significant in women, but not in men. In logistic regression analysis, age, diabetes mellitus, GGT, heart rate, history of hypertension, triglyceride, and systolic blood pressure were significant variables that influenced increased pulse wave velocity (PWV). After age- and blood pressure-adjustment, GGT, homeostatic model assessment-insulin resistance, heart rate, history of hypertension, and metabolic syndrome were significant variables in men, and in women metabolic syndrome and history of hypertension were significant contributors to increased PWV.

Conclusion The present study results suggest that serum GGT may be an additional marker of arterial stiffness, especially in men, though the relationship with arterial stiffness was very weak. Further studies are needed to elucidate the mechanism of GGT's contribution to arteriosclerosis and to confirm the current results. (*Circ J* 2007; **71:** 1715 – 1720)

Key Words: Arteriosclerosis; γ-glutamyltransferase; Risk factors

Gamma-glutamyltransferase (GGT) is a commonly used diagnostic test of alcoholic liver disease and has been regarded as a marker of alcohol consumption[1] but recently, it has been suggested than GGT is independently associated with cardiovascular mortality and atherosclerosis[2–4] One report stated that GGT activity had been detected in atheromatous plaques of carotid and coronary arteries[5] However, the mechanism by which GGT is associated with cardiovascular disease and atherosclerosis has been not fully elucidated.

Increasing arterial stiffness is one of the pathological states of vascular damage, and is closely associated with atherosclerotic cardiovascular disease[6] Recent studies have shown that the brachial – ankle pulse wave velocity (baPWV), which can be measured fairly reproducibly by an automated device[7] correlates well with arterial stiffness determined by an invasive method[8] Although age and blood pressure (BP) are the major determinants of baPWV, the presence of other risk factors, including diabetes mellitus (DM), dyslipidemia, smoking, high C-reactive protein (CRP), and low creatinine clearance, is also associated with increased pulse wave velocity (PWV)[9,10]

(Received February 14, 2007; revised manuscript received June 17, 2007; accepted July 10, 2007)
*Departments of *Internal Medicine, **Family Medicine, †Nuclear Medicine and ††Medical Research Institute, Pusan National University Hospital, Ami-dong, Seo-gu, Busan, Republic of Korea*
Mailing address: Ihm Soo Kwak, MD, Department of Internal Medicine and Medical Research Institute, Pusan National University Hospital 1-10, Ami-dong, Seo-gu, Busan 602-739, Republic of Korea. E-mail: iskwak@pusan.ac.kr, shsong@pusan.ac.kr

The purpose of the present study was to evaluate whether GGT could be an additional marker of arterial stiffness, independent of other risk factors in screening cohorts. We used baPWV as the surrogate of arterial stiffness.

Methods

Subjects

A total of 10,498 individuals aged more than 18 years old participated in a 1-day health-screening program. Of these, 1,451 individuals (785 men, 666 women) underwent voluntary baPWV measurement. The hospital has a registered check-up of baPWV as an optional part of arteriosclerosis screening. No patients had a past history of peripheral arterial disease, aortic disease, or severe renal dysfunction. Subjects whose ankle-brachial index was more than 1.3 and less than 0.95 were excluded to ensure the accuracy of baPWV measurement. In the final analyses, 1,387 individuals (741 men, 646 women) were enrolled. All medical and social histories and symptoms of each individual were confirmed by the consulting doctor. The study was approved by the Ethical Committee of Pusan National University Hospital.

Laboratory Data and Measurement of baPWV

Serum levels of GGT, creatinine, uric acid, CRP, lipid profile (total cholesterol, low- and high-density lipoprotein (LDL and HDL)-cholesterols, triglycerides), fasting glucose and insulin, and the hepatitis profile (HBs Ag, anti-HCV) were checked. The GGT level in males [32 (20–53) IU/L] was found to be higher than in females [15 (11–21) IU/L]. Thus, sex-specific quartiles of serum GGT were used

Table 1 Baseline Characteristics of the Male Subjects According to GGT (IU/L)

	Q1	Q2	Q3	Q4	p value
n	192	191	175	183	
Age (years)	52 (45–60)‡	52 (46–57)II	51 (45–59)¶	48 (43–54)	<0.05
Diabetes mellitus	14 (7.3%)	8 (4.2%)§	24 (13.7%)¶	12 (6.6%)	<0.05
Hypertension	31 (16.1%)	35 (18.3%)	40 (22.9%)	26 (14.2%)	NS
Smoking					
Non-smoking	75 (39.1%)†,‡	80 (41.9%)§,II	46 (26.3%)	50 (27.3%)	<0.05
Smoking	72 (37.5%)*,‡	50 (26.2)	50 (28.6%)	40 (21.9%)	<0.05
Ex-smoking	45 (23.4%)†,‡	61 (31.9)§	79 (45.1%)	93 (50.8%)	<0.05
Alcohol					
≥40 g/day	37 (19.3%)†,‡	42 (22%)§,II	83 (47.4%)	95 (51.9%)	<0.05
0.1–39.9 g/day	74 (38.5%)	84 (44%)§	53 (30.3%)	70 (38.3%)	<0.05
0 g/day	81 (42.2%)†,‡	65 (34%)§,II	39 (22.3%)¶	18 (9.8%)	<0.05
Hepatitis B	13 (6.8%)	11 (2.6%)II	8 (4.6%)	17 (9.3%)	<0.05
Hepatitis C	5 (2.6%)	5 (2.6%)	3 (1.7%)	6 (3.3%)	NS

GGT, γ-glutamyltransferase; Q1, 1st quartile ; Q2, 2nd quartile ; Q3, 3rd quartile ; Q4, 4th quartile.
*There were statistically significant results between following groups: *Q1 vs Q2; †Q1 vs Q3; ‡Q1 vs Q4; §Q2 vs Q3; IIQ2 vs Q4; ¶Q3 vs Q4.*

Table 2 Laboratory Data for the Male Subjects According to GGT (IU/L)

	Q1	Q2	Q3	Q4	p value
Systolic BP (mmHg)	120 (109–132)†,‡	124 (114–135)II	126 (116–138)	131 (118–143)	<0.01
Diastolic BP (mmHg)	75 (68–83)†,‡	77 (71–85)II	79 (73–85)	82 (75–89)	<0.01
Pulse pressure (mmHg)	45 (39.3–51)†,‡	46 (42–53)	48 (43–54)	49 (42–53)	<0.01
MAP (mmHg)	89.7 (82.3–99.6)†,‡	93.7 (85.7–100.7)II	95.0 (87.0–102.3)	98.7 (90.7–106.7)	<0.01
Heart rate (beats/min)	68 (61–73)	67 (60–72)	69 (63–76)	69 (64–75)	NS
Proteinuria (%)	10 (5.2%)	7 (3.7%)	11 (6.3%)	17 (9.3%)	NS
Hemoglobin (g/dl)	14.8 (14.1–15.4)†,‡	15.0 (14.3–15.6)II	15.3 (14.6–16.1)	15.5 (14.7–16.2)	<0.05
GGT (IU/L)	16 (13–18)*,†,‡	25 (23–28)§,II	41 (37–45)¶	81 (64–116)	<0.001
Uric acid (mg/dl)	5.8 (5.1–6.7)†,‡	6.2 (5.4–6.9)	6.2 (5.6–7.0)	6.4 (5.6–7.3)	<0.05
Creatinine (mg/dl)	0.9 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.9 (0.9–1.0)	NS
GFR ($ml \cdot min^{-1} \cdot 1.73^{-2}$)	91.5 (82.4–101.4)	90.0 (81.6–97.0)	88.4 (82.5–97.9)	92.4 (84.4–98.4)	NS
Lipid profile					
Total cholesterol (mg/dl)	192 (172–212)†,‡	199 (180–219)	203 (181–229)	208 (182–236)	<0.01
LDL-C (mg/dl)	121 (99–138)	127 (106–145)	126 (100–143)	120 (99–145)	NS
HDL-C (mg/dl)	52 (43–60)†	49 (43–57)	47 (42–54)	50 (43–58)	<0.05
Triglyceride (mg/dl)	94.0 (69.3–131.0)†,‡	106 (79–143)§,II	137 (99–191)¶	148 (105–215)	<0.001
Non-HDL-C (mg/dl)	141 (119–159)†,‡	147 (129–169)	154 (133–180)	156 (129–184)	<0.001
Glucose metabolism					
Glucose (mg/dl)	88 (82–94)†,‡	89 (84–97)II	90 (84–100)	95 (86–106)	<0.05
Insulin (μIU/ml)	3.70 (2.18–6.04)*,†,‡	4.90 (3.09–7.04)II	5.53 (3.45–8.00)	6.58 (3.93–9.07)	<0.05
HOMAIR	0.84 (0.49–1.36)*,†,‡	1.11 (0.65–1.56)II	1.32 (0.78–1.86)	1.58 (0.95–2.09)	<0.05
Metabolic syndrome	16 (8.3%)†,‡	18 (9.4%)§,II	29 (16.6%)¶	52 (28.4%)	<0.05
Waist (cm)	83 (78–88)*,†,‡	87 (83–90)II	88 (84–92.8)	90 (84–94.7)	<0.05
Body mass index	23.1 (21.4–25.0)*,†,‡	24.5 (22.8–26.1)	24.8 (23.4–26.4)	25.1 (23.5–27.1)	<0.001
C-reactive protein (mg/L)	0.5 (0.3–1.1)*,†,‡	0.7 (0.4–1.6)	1.0 (0.6–1.7)	0.9 (0.5–1.5)	<0.01

BP, blood pressure; MAP, mean arterial pressure; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; HOMAIR, homeostatic model assessment-insulin resistance. Other abbreviations see in Table1.
*There were statistically significant results between following groups: *Q1 vs Q2; †Q1 vs Q3; ‡Q1 vs Q4; §Q2 vs Q3; IIQ2 vs Q4; ¶Q3 vs Q4.*

for the analyses. Homeostatic model assessment-insulin resistance (HOMAIR) was calculated using serum levels of fasting glucose and insulin.[11] Glomerular filtration rate was calculated by the Abbreviated Modification of Diet in Renal Disease equation.[12] Diagnosis of metabolic syndrome (MS) was made according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III and Asia-Pacific criteria with abdominal waist circumference (≥90 cm in males, ≥80 cm in females).[13,14] Proteinuria was defined as more than 1+ in spot urine sample.

The baPWV was measured using an automatic waveform analyzer (VP-2000, Colin Co, Komaki, Japan). All individuals were examined after resting in the supine position for at least 5 min. We used the mean baPWV as a marker of arterial stiffness. All baPWV values were adjusted by age and systolic BP, because age and systolic BP are regarded as the most important determinants of PWV. Finally, the unadjusted baPWV and adjusted baPWV were used together and we performed sex-specific analysis to determine the factors for increasing baPWV using the adjusted baPWV. High PWV was designated as the cut-off value, which was between the 3rd quartile and 4th quartiles of the unadjusted and adjusted baPWV individually because an absolute cut-off value of normal baPWV is not available.

Statistical Analysis

All continuous variables are expressed as median (interquartile range) and proportions are expressed as number (%).

Table 3 Baseline Characteristics of the Female Subjects According to GGT (IU/L)

	Q1	Q2	Q3	Q4	p value
n	170	161	158	157	
Age (years)	48 (43–55)†,‡	51 (45–57)ǁ	53 (46–59)	54 (49–59)	<0.01
Diabetes mellitus	6 (3.5%)	9 (5.6%)	7 (4.4%)	15 (9.6%)	NS
Hypertension	21 (12.4%)	24 (14.9%)§,ǁ	36 (22.8%)	35 (22.3%)	<0.01
Smoking					
Non-smoking	161 (94.7%)	155 (96.3%)	149 (94.3%)	148 (94.3%)	NS
Smoking	2 (1.2%)	1 (0.6%)	3 (1.9%)	5 (3.2%)	NS
Ex-smoking	7 (4.1%)	5 (3.1%)	6 (3.8%)	4 (2.5%)	NS
Alcohol					
≥40 g/day	6 (3.5%)	4 (2.5%)	3 (1.9%)	9 (5.7%)	NS
0.1–39.9 g/day	23 (14.1%)	16 (9.9%)	27 (17.1%)	26 (16.6%)	NS
0 g/day	140 (82.4%)	141 (87.6%)	126 (79.7%)	122 (77.7%)	NS
Hepatitis B	5 (2.9%)	7 (4.3%)	10 (6.3)	5 (3.2%)	NS
Hepatitis C	5 (2.9%)‡	5 (3.1%)	5 (3.2%)	8 (5.1%)	NS

Abbreviations see in Tables 1,2.
There were statistically significant results between following groups: †Q1 vs Q3; ‡Q1 vs Q4; §Q2 vs Q3; ǁQ2 vs Q4.

Table 4 Laboratory Data for the Female Subjects According to GGT (IU/L)

	Q1	Q2	Q3	Q4	p value
Systolic BP (mmHg)	114 (104–128)†,‡	120 (106–129)	125 (109–141)	122 (111–139)	<0.01
Diastolic BP (mmHg)	72 (64–79)†,‡	73 (66–80)§	77 (68–85)	75 (68–84)	<0.05
Pulse pressure (mmHg)	43 (39–50)†,‡	46 (40–52)	48 (41–56)	47 (42–55)	<0.05
MAP (mmHg)	85.7 (76.9–96.0)†,‡	87.3 (79.3–96.2)	92.5 (82.2–102.5)	91.7 (82.5–101.0)	<0.01
Heart rate (beats/min)	68 (62–75)	68 (63–76)	69 (64–74)	71 (64–78)	NS
Proteinuria (%)	3 (1.8%)	2 (1.2%)	2 (1.3%)	6 (3.8%)	NS
Hemoglobin (g/dl)	12.7 (12.0–13.2)†,‡	12.9 (12.2–13.4)ǁ	13.1 (12.4–13.7)	13.2 (12.7–13.8)	<0.001
GGT (IU/L)	9 (8–10)*†,‡	13 (12–14)§,ǁ	18 (17–20)¶	31 (25–47)	<0.001
Uric acid (mg/dl)	4.2 (3.7–4.7)*,†,‡	4.5 (4.0–5.0)ǁ	4.5 (3.9–5.5)	4.7 (4.2–5.3)	<0.05
Creatinine (mg/dl)	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)	0.7 (0.7–0.8)	NS
GFR ($ml \cdot min^{-1} \cdot 1.73^{-2}$)	91.7 (81.0–97.5)	90.1 (80.6–96.0)	91.0 (80.6–95.3)	90.4 (79.1–94.1)	NS
Lipid profile					
Total cholesterol (mg/dl)	189 (167–210)*,†,‡	201 (178–222)ǁ	205 (182–229)	212 (186–238)	<0.05
LDL-C (mg/dl)	114 (91–131)*,†,‡	120 (104–138)	123 (103–144)	131 (103–154)	<0.05
HDL-C (mg/dl)	58 (50–68)	57 (51–70)	55 (48–66)	55 (47–65)	NS
Triglyceride (mg/dl)	77 (55–101)*,†,‡	86 (68–116)ǁ	99 (74–144)	113 (83–157)	<0.05
Non-HDL-C (mg/dl)	131 (105–151)*,†,‡	140 (121–158)ǁ	146 (125–170)	155 (130–185)	<0.05
Glucose metabolism					
Glucose (mg/dl)	85 (79–90)†,‡	86 (81–92)ǁ	86 (81–93)¶	91 (84–100)	<0.05
Insulin (μIU/ml)	3.52 (2.09–5.26)†,‡	3.80 (2.48–6.28)§,ǁ	5.06 (3.28–7.40)	5.32 (3.63–8.15)	<0.01
HOMA$_{IR}$	0.74 (0.43–1.18)†,‡	0.82 (0.52–1.37)§,ǁ	1.14 (0.69–1.64)	1.20 (0.77–2.02)	<0.01
Metabolic syndrome	14 (8.2%)†,‡	13 (8.1%)§,ǁ	29 (18.4%)	42 (26.8%)	<0.05
Waist (cm)	76 (72–82)†,‡	78 (74–84)ǁ	80 (75–86)	81 (76–87)	<0.01
Body mass index	22.8 (21.2–24.7)†,‡	23.3 (21.5–25.2)ǁ	23.9 (22.7–25.8)	24.5 (23.3–26.4)	<0.001
C-reactive protein (mg/L)	0.5 (0.2–0.8)†,‡	0.5 (0.3–0.9)ǁ	0.6 (0.3–1.1)	0.7 (0.4–1.6)	<0.01

Abbreviations see in Tables 1,2.
There were statistically significant results between following groups: *Q1 vs Q2; †Q1 vs Q3; ‡Q1 vs Q4; §Q2 vs Q3; ǁQ2 vs Q4; ¶Q3 vs Q4.

Comparison of GGT quartiles was performed using the Kruskal-Wallis test with post test (Dunn's comparison of all pairs of quartiles) and chi-square test as appropriate. Stepwise logistic regression analysis was used for analysis of variables that had an influence on serum GGT. The comparison between high and low baPWV was performed using the Mann-Whitney U test. Adjustments by age and systolic BP were performed using constant values of the results of simple linear regression analysis. Stepwise logistic regression analyses were performed to show independent contributions to baPWV using computer software, MedCalc® (version 8,1,0,0). A value of $p<0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

Median serum GGT level was 21 (14–38) IU/L. Because there was statistically different between males and females, sex-specific analyses were done. Tables 1 and 3 show the baseline characteristics in 741 men. and 646 women, respectively. In men, smoking and amount of alcohol consumption, age, and proportion of cases of DM were different in each quartile group. In women, age and proportion of those with hypertension were different in each quartile group.

Laboratory Results for the Quartiles of GGT and the Association Between GGT and baPWV

Tables 2 and 4 show the laboratory results for both sexes. From the view point of baPWV, there was no statistical difference according to the quartiles of GGT, though an increasing trend of baPWV was noted in men. However, in women, the baPWV of the 3rd quartile of GGT was higher than that of the 1st quartile, and the baPWV of the 4th quartile of GGT was higher than that of the 1st quartile (Table 5).

Table 5 Association Between GGT and baPWV

	Quartiles of GGT				p value
	Q1	Q2	Q3	Q4	
Men	1,361.8 (1,255.3–1,498.8)	1,364.5 (1,282.0–1,508.0)	1,402.5 (1,275.5–1,544.0)	1,410.5 (1,300.5–1,545.0)	NS
Women	1,268.8 (1,164.4–1,387.5)*,†	1,313.0 (1,199.0–1,446.3)	1,360.0 (1,233.8–1,538.3)	1,370.0 (1,244.8–1,580.8)	<0.001

baPWV, brachial-ankle pulse wave velocity. Other abbreviation see in Table 1.
*There were statistically significant results between the following groups: *Q1 vs Q3; †Q1 vs Q4.*

Table 6 Logistic Regression Analysis Showing Independent Contributions to Increased GGT

Independent variables	OR (95%CI)
Men	
Age	0.975 (0.995–0.994)
Alcohol	1.956 (1.512–2.530)
Diastolic BP	1.023 (1.005–1.041)
Uric acid	1.183 (1.016–1.379)
HDL-C	1.033 (1.015–1.051)
Triglyceride	1.004 (1.002–1.006)
HOMAIR	1.411 (1.176–1.693)
Waist circumference	1.031 (1.002–1.062)
Women	
Age	1.034 (1.010–1.058)
Total cholesterol	1.006 (1.000–1.011)
Triglyceride	1.004 (1.001–1.007)
Glucose	1.024 (1.012–1.037)
Waist circumference	0.953 (0.914–0.994)
Body mass index	1.260 (1.125–1.411)

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 1,2. GGT was designated as more than 53 IU/L, which was the cut-off value between the 3rd and 4th quartiles of GGT in men. In women, the cut-off point was 21 IU/L.

The median baPWV in men was 1,389.5 (1,280.0–1,530.0) cm/s, which was higher than in women [1,315.3 (1,208.4–1,484.6) cm/s]. High baPWV was designated as more than 1,510.5 cm/s, which was the cut-off value between the 3rd and 4th quartiles of baPWV (Tables 7,8). In order to identify the variables that contribute to arterial stiffness, we performed multivariate logistic regression analysis including age, DM, hypertension, consumption of alcohol, BP, heart rate, MS, proteinuria, hemoglobin, GGT, uric acid, HDL-cholesterol, triglycerides, non-HDL-cholesterol, glucose, insulin, HOMAIR, waist circumference, body mass index, and CRP, which were significant variables between the low and high PWV groups. Among these, age, DM, GGT, heart rate, history of hypertension, triglycerides and systolic BP were significant variables (Table 9).

Factors That Influenced Serum GGT Level

In this analysis, increased serum GGT was designated as more than 53 IU/L, which was the cut-off value between the 3rd and 4th quartiles of GGT in men. In women, the cut-off point was 21 IU/L. In both genders, serum triglycerides had an influence on serum GGT level. Otherwise, alcohol consumption, diastolic BP, uric acid, HOMAIR, and waist circumference were positively related to serum GGT in men. In women, glucose, body mass index, and total cholesterol were the significant variables (Table 6).

Association Between GGT and baPWV After Age- and BP-Adjustment in the Gender-Specific Analysis

Age and BP were significant determinants of an increased PWV, as many studies have previously reported. Thus, we performed an adjustment by age and systolic BP. The median baPWV was 1,526.3 (1,359.6–1,704.1) cm/s. The gender-specific interquartile cut-off points for adjusted baPWV were 1,418.6, 1,574.3, and 1,746.4 cm/s in men and 1,318.7, 1,471.0, and 1,660.1 cm/s in women. In this situation, high baPWV was designated as more than 1,746.4 cm/s in men and 1,660.1 cm/s in women. In men, GGT (odds ratio (OR) 1.004 confidence interval (CI) [1.001–1.008]) HOMAIR (OR 1.181 CI [1.002–1.069]), heart rate (OR 1.052 CI [1.034–1.069]), history of hypertension (OR 1.573 CI [1.017–2.433]), and MS (OR 3.772 CI [2.336–6.092]) were

Table 7 Baseline Characteristics According to PWV

	Low PWV	High PWV	p value
n	1,040	347	
Age (years)	49 (43–55)	58 (53–64)	<0.001
Sex (male, %)	535 (51.4%)	206 (59.4%)	0.01
Diabetes mellitus	43 (4.1%)	52 (15.0%)	<0.001
Hypertension	128 (12.3%)	120 (34.6%)	<0.001
Smoking			
Non-smoking	652 (62.7%)	212 (61.1%)	NS
Smoking	160 (15.4%)	63 (18.2%)	NS
Ex-smoking	228 (21.9%)	72 (20.7%)	NS
Alcohol			
≥40 g/day	196 (18.8%)	85 (24.5%)	0.03
0.1–39.9 g/day	291 (28%)	83 (23.9%)	NS
0 g/day	553 (53.2%)	179 (51.6%)	NS
Hepatitis B	56 (5.4%)	20 (5.8%)	NS
Hepatitis C	26 (2.5%)	16 (4.6%)	NS

PWV, pulse wave velocity.
High PWV was designated as more than 1,510.5 cm/s, which was the cut-off value between the 3rd and 4th PWV quartiles.

Table 8 Laboratory Data According to PWV

	Low PWV	High PWV	p value
Systolic BP (mmHg)	119 (108–130.8)	137.0 (123.0–149.0)	<0.001
Diastolic BP (mmHg)	74 (67–81)	83.0 (76.0–92.0)	<0.001
Pulse pressure (mmHg)	45 (40–50)	52 (46–60)	<0.001
MAP (mmHg)	88.7 (81.0–97.6)	100.7 (92.3–110.0)	<0.001
Heart rate (beats/min)	68 (62–74)	70.0 (64.0–78.0)	<0.001
Metabolic syndrome (%)	114/1,040 (11%)	99/347 (28.5%)	<0.001
Proteinuria (%)	34/1,040 (3.3%)	24/347 (6.9%)	0.006
Hemoglobin (g/dl)	13.9 (12.9–15.2)	14.4 (13.3–15.3)	0.002
GGT (IU/L)	20.0 (13.0–36.0)	26.0 (17.0–46.0)	<0.001
Uric acid (mg/dl)	5.2 (4.3–6.2)	5.6 (4.5–6.6)	<0.001
Creatinine (mg/dl)	0.9 (0.7–1.0)	0.9 (0.7–1.0)	NS
GFR ($ml \cdot min^{-1} \cdot 1.73^{-2}$)	91.7 (82.4–97.9)	90 (78.2–95.4)	NS
Lipid profile			
Total cholesterol (mg/dl)	199.0 (178.0–222.0)	203.0 (181.0–230.0)	NS
LDL-C (mg/dl)	122.4 (101.3–141.2)	122.4 (99.2–144.2)	NS
HDL-C (mg/dl)	53.0 (46.0–63.0)	51.0 (44.0–60.0)	0.003
Triglyceride (mg/dl)	99.0 (71.0–140.8)	123.0 (91.0–171.0)	<0.001
Non-HDL-C (mg/dl)	144.0 (123.3–168.0)	150.0 (129.0–177.0)	0.005
Glucose metabolism			
Glucose (mg/dl)	88.0 (82.0–94.0)	92.0 (85.0–106.0)	<0.001
Insulin (μIU/ml)	4.58 (2.76–6.75)	5.44 (3.45–7.95)	<0.001
HOMA$_{IR}$	1.01 (0.58–1.57)	1.26 (0.79–1.99)	<0.001
Waist (cm)	83.0 (76.0–89.0)	85.2 (80.0–90.0)	<0.001
Body mass index	24.1 (22.2–25.8)	24.3 (22.6–26.4)	0.03
C-reactive protein (mg/L)	0.6 (0.3–1.3)	0.8 (0.5–1.5)	<0.001

Abbreviations see in Tables 1,2,7.
High PWV was designated as more than 1,510.5 cm/s, which was the cut-off value between the 3rd and 4th PWV quartiles.

Table 9 Logistic Regression Analysis Showing Independent Contributions to High PWV

Independent variables	OR (95%CI)
High PWV	
Age	1.139 (1.115–1.163)
Diabetes mellitus	2.434 (1.429–4.144)
GGT	1.007 (1.003–1.038)
Heart rate	1.022 (1.007–1.038)
Hypertension history	1.440 (1.012–2.048)
Systolic BP	1.074 (1.060–1.089)
Triglyceride	1.002 (1.001–1.003)

Abbreviations see in Tables 1,2,6,7.
High PWV was designated as more than 1,510.5 cm/s, which was the cut-off value between the 3rd and 4th quartiles of brachial-ankle PWV.

Table 10 Logistic Regression Analysis Showing Independent Contributions to Age- and BP-Adjusted High PWV

Independent variables	OR (95%CI)
Total	
Alcohol consumption	1.309 (1.090–1.571)
GGT	1.004 (1.001–1.007)
Heart rate	1.040 (1.026–1.052)
Hypertension history	2.394 (1.738–3.296)
Metabolic syndrome	4.615 (3.249–6.557)
Uric acid	1.164 (1.052–1.288)
Men	
GGT	1.004 (1.001–1.008)
HOMA$_{IR}$	1.181 (1.002–1.069)
Heart rate	1.052 (1.034–1.069)
Hypertension history	1.573 (1.017–2.433)
Metabolic syndrome	3.772 (2.336–6.092)
Women	
Hypertension history	3.820 (2.386–6.118)
Metabolic syndrome	5.736 (3.529–9.323)

Abbreviations see in Tables 1,2,6,7.
Adjusted high PWV in the total group was designated as more than 1,704.1 cm/s, which was the cut-off value between the 3rd and 4th quartiles of brachial-ankle PWV after age- and systolic BP (adjusted high PWV in men >1,746.4 cm/s, in women >1,660.1 cm/s).

significant contributors to increased PWV. However, in women, history of hypertension (OR 3.820 CI [2.386–6.118]) and MS (OR 5.736 CI [3.529–9.323]) were significant contributors to increased PWV. Serum GGT contributed to increased PWV only in men. Table 10 depicts the detailed results.

Discussion

Serum GGT activity has long been regarded as a marker for hepatobiliary disease and alcohol consumption[1], but recent epidemiological evidence suggests that serum GGT might evolve as a potential biochemical risk indicator of cardiovascular morbidity and mortality[15] GGT is an enzyme responsible for the extracellular catabolism of antioxidant glutathione and act as a pro-oxidant in the extracellular space. GGT is expressed in the liver, kidney, cerebrovascular endothelium and pericytes. As a potential mechanism it has been proposed that GGT reduces Fe^{3+} to its bivalent form and releases a free thyil radical, which oxidizes LDL in the extracellular space[3,5,16] Although the exact mechanism has not been fully elucidated, GGT levels appeared to be an independent risk factor for the development of cardiovascular disease, hypertension, stroke, and type 2 DM, and their complications, in several prospective cohort studies after adjusting for alcohol consumption[17–20] From the viewpoint of GGT level in our results, serum triglycerides had an influence on serum GGT level in both genders. Additionally, alcohol consumption, diastolic BP, uric acid, HOMA$_{IR}$ and waist circumference were positively related to serum GGT in men. In women, fasting glucose, body mass index, and total cholesterol were the significant variables. In 2007, it was reported that serum GGT was posi-

tively correlated with waist circumference, triglyceride, fasting glucose, fasting insulin, HOMAIR in both genders.[21] In summary, serum GGT level could be influenced by the lipid profile and insulin resistance.

In the present study, although the relationship was very weak, GGT independently contributed to increased PWV in men, but not in women. In arterial stiffness, age and BP are the most important determinants and in 2003 it was reported that baPWV reflecting arterial stiffness was lower in females than in males until age 60, and then became similar in both genders after age 60.[22] This gender effect on increased PWV has been considered to be a hormonal environmental difference, though the exact mechanism is not fully elucidated. In the current study, a gender-specific difference in baPWV was noted (age- and BP-adjusted median baPWV: 1,574.3 cm/s in men vs 1,471.0 cm/s in women). In another study of baPWV as a marker of atherosclerotic vascular damage and cardiovascular risk, a cut-off value of 1,400 cm/s was an independent variable for risk stratification by Framingham score.[23] Thus, our high baPWV value, as determined by the 75 percentile value of each gender, may have clinical significance (1,746.4 cm/s in men, 1,660.1 cm/s in women). In the final stepwise logistic regression analysis after age and BP adjustment, GGT was an independent contributor to increased PWV in men. Interestingly, MS and history of hypertension were the same contributors to increase PWV in both genders. This result is consistent with a report on MS in 2007, in which the authors concluded that MS determined increased arterial stiffness independently of other known cardiovascular risk factors.[24]

Additionally, HOMAIR and heart rate had an influence on increased PWV in men. Because insulin resistance is a proposed pathophysiologic mechanism of MS, we consider that our results are plausible. However, the difference between both genders was not explained exactly. Further study is needed to ascertain whether gender difference really exists and the mechanism of that difference.

Study Limitations

First, identification of medications (eg, statins, antihypertensive drugs) was impossible. Second, self-reported alcohol consumption as a variable was of questionable because of its reliability and validity. Third, because a cut-off value of baPWV is not available, the results could change according to the characteristics and number of enrolled subjects, Last, though baPWV is convenient and reproducible, baPWV itself has some limitation in reflecting arterial stiffness. Despite these limitations, our results confirm that the role of GGT as an additional marker of arterial stiffness could be considered.

In conclusion, although it is necessary in the future to elucidate the role of GGT and the relationship was very weak, GGT might be an additional marker of arterial stiffness, at least in men. In the future, larger cohorts studies will be needed to confirm this result.

References

1. 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.
2. Meisinger C, Doring A, Schneider A, Lowel H; KORA Study Group. Serum gamma-glutamyltransferase is as predictor of incident coronary events in apparently healthy men from the general population. *Atherosclerosis* 2006; **189:** 297–302.
3. Ruttmann E, Brant LJ, Concin H, Diem G, Rapp K, Ulmer H; Vorarlberg Health Monitoring and Promotion Program Study Group. Gamma-glutamyltransferase as a risk factor for cardiovascular disease mortality: An epidemiological investigation in a cohort of 162,944 Austrian adults. *Circulation* 2005; **112:** 2130–2137.
4. Pomperlla A, Emdin M, Passino C, Paolicchi A. The significance of serum γ-glutamyltransferase in cardiovascular disease. *Clin Chem Lab Med* 2004; **42:** 1085–1091.
5. Paolicchi A, Minotti G, Tonarelli P. Gamma-glutamyltranspeptidase-dependent iron reduction and LDL oxidation: A potential mechanism in atherosclerosis. *J Invest Med* 1999; **47:** 151–160.
6. Cohn J. Arterial compliance to stratify cardiovascular risk: More precision in therapeutic decision making. *Am J Hypertens* 2001; **14:** 258S–263S.
7. Matsui Y, Kario K, Ishikawa J, Eguchi K, Hoshide S, Shimada K. Reproducibility of arterial stiffness indices (pulse wave velocity and augmentation index) simultaneously assessed by automated pulse wave analysis and their associated risk factors in essential hypertensive patients. *Hypertens Res* 2004; **27:** 851–857.
8. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, et al. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. *Hypertens Res* 2002; **25:** 359–364.
9. Nagano M, Nakamura M, Sato K, Tanaka F, Segawa T, Hiramori K. Association between serum C-reactive protein levels and pulse wave velocity: A population-based cross-sectional study in a general population. *Atherosclerosis* 2005; **180:** 189–195.
10. Ohya Y, Iseki K, Iseki C, Miyagi T, Kinjo K, Takshita S. Increased pulse wave velocity is associated with low creatinine clearance and proteinuria in a screened cohort. *Am J Kidney Dis* 2006; **47:** 790–797.
11. Matthews DR, Hosker JP, Rudensk AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: Insulin resistance and beta-cell function from fasting plasma glucose and insulin concentration in man. *Diabetologia* 1985; **28:** 412–419.
12. Levey AS, Greene T, Kusek J, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). *J Am Soc Nephrol* 2000; **11:** A0828.
13. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; **285:** 2486–2497.
14. Steering Committee of the WHO Western Pacific Region, IASO & IOTF. The Asia-Pacific perspective: Redefining obesity and its treatment, Australia, 2000.
15. Wannamethee G, Ebrahim S, Shaper AG. Gamma-glutamyltransferase: Determinants and association with mortality from ischemic heart disease and all causes. *Am J Epidemiol* 1995; **142:** 699–708.
16. Frey A, Mechelein B, Weiler-Guttler H, Mockel B, Flach R, Gassen HG. Pericytes of the brain microvasculature express γ-glutamyl transpeptidase. *Eur J Biochem* 1991; **202:** 421–429.
17. Brenner H, Rothenbacher D, Arndt V, Schuberth S, Fraisse E, Fliedner TM. Distribution, determinants and prognostic value of gamma-glutamyltransferase for all-cause mortality in a cohort of constuction workers from southern Germany. *Prev Med* 1997; **26:** 305–310.
18. Lee DH, Jacobs DR, Gross M, Kiefe CI, Roseman J, Lewis CE, et al. γ-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,
19. Bots ML, Salonen JT, Elwood PC, Nikitin Y, Freire de Concalves A, Inzitari D, et al. Gamma-glutamyltransferase and risk of stroke: The EUROSTROKE project. *J Epidemiol Community Health* 2002; **56**(Suppl 1)**:** i25–i29.
20. Lee DH, Ha MH, Kim JH, Christiani DC, Gross MD, Steffes M, et al. Gamma-glutamyltransferase and diabetes: A 4 year follow-up study. *Diabetologia* 2003; **46:** 359–364.
21. Kang YH, Min HK, Son SM, Kim IJ, Kim YK. The association of serum gamma glutamyltransferase with components of the metabolic syndrome in the Korean adults. *Diabetes Res Clin Pract* 2007; **77:** 306–313.
22. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, et al. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement-a survey of 12517 subjects. *Atherosclerosis* 2003; **166:** 303–309.
23. Yamashina A, Tomiyama H, Arai T, Hirose K, Koji Y, Hirayama Y, et al. Brachial-ankle pulse wave velocity as a marker of atherosclerotic vascular damage and cardiovascular risk. *Hypertens Res* 2003; **26:** 615–622.
24. Sipila K, Koivistoinen T, Moilanen L, Nieminen A, Jula A, Salomaa V, et al. Metabolic syndrome and arterial stiffness: The Health 2000 Survey. *Metabolism* 2007; **56:** 320–326.