Original Article

Association between γ-Glutamyltransferase, Adiponectin and Arterial Stiffness

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***Aim*: Serum γ-glutamyltransferase (GGT) is used as a marker of hepatic dysfunction. Recently, several studies reported that GGT is significantly associated with cardiovascular mortality and atherosclerosis. Adiponectin is known to play an important role in the development of atherosclerosis, but its physiologic role has yet to be fully determined. In this study, we investigated the relationships among serum GGT, adiponectin and arterial stiffness.**

***Methods*: Of 4236 subjects recruited from 17 different medical centers in Seoul, Korea, 2846 subjects were enrolled in our study. The parameters of metabolic syndrome (MetS) were assessed in these subjects, and their plasma adiponectin levels and pulse wave velocity (PWV) were measured along with anthropometric and biochemical profiles, including GGT.**

***Results*: The subjects were stratified into 3 groups according to GGT values. PWV values gradually increased and the adiponectin level decreased with GGT tertiles. Aortic PWV showed a significant correlation with age, SBP, FPG, but there was no correlation among aortic PWV, GGT and adiponectin. Peripheral PWV demonstrated a significant correlation with age, SBP, DBP, BMI, WC, FPG and GGT, but there was no correlation between peripheral PWV and adiponectin. In multiple logistic regression analysis after adjusting for risk factors, GGT was a significant contributor to increased peripheral PWV.**

***Conclusions*: These findings indicate that serum GGT is independently associated with increased arterial stiffness, but there was no correlation between adiponectin and arterial stiffness in both males and females.**

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Key words; γ-Glutamyltransferase, Adiponectin, Pulse wave velocity

Introduction

Serum γ-glutamyltransferase (GGT) is used as a marker of hepatic dysfunction and alcohol consumption[1)]. Recently, several studies reported that GGT is significantly associated with cardiovascular mortality and atherosclerosis[2-4)]. These associations can be explained by the correlation of GGT with several metabolic risk factors, including obesity, dyslipidemia, hypertension, diabetes and metabolic syndrome[5-9)].

Adiponectin, a peptide specifically synthesized in adipose tissue, plays an important role in glucose and lipid metabolism and vascular biology[10, 11)]. Adiponectin levels are lower in metabolic syndrome, obesity, coronary heart disease and type 2 diabetes[12)]. Although its physiological functions have yet to be fully determined, adiponectin plays an important role in the development of atherosclerosis[13)]. Some studies have begun to evaluate the relationship between GGT and adiponectin[14, 15)], but this relationship has not been fully investigated.

Arterial stiffness represents vascular damage and is a measure of the degree of atherosclerosis[16)]. Pulse wave velocity (PWV) measurement is a non-invasive

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technique for assessing atherosclerosis related to arterial stiffness. PWV is strongly associated with cardiovascular diseases[17, 18], and recent longitudinal studies have demonstrated that it is an independent predictor of not only cardiovascular events but also mortality[19, 20]. There are a few reports on the relationship between GGT and PWV[21]; however, this correlation has not been well studied. In this study, we therefore investigated the relationships among serum GGT concentrations, adiponectin and arterial stiffness.

Methods

Study Population

This study was part of a population-based, multicenter, cross-sectional study, designed to evaluate the prevalence and characteristics of metabolic syndrome in inhabitants of Seoul, Korea. The study included 4,236 participants recruited from 17 different tertiary medical centers in Seoul, Korea.

Subjects were excluded if they had a history of alcohol consumption higher than 20 g/day, a known history of viral liver disease, cirrhosis, or malignancy, liver enzyme levels higher than three times the upper limit of the normal value, or if they were taking insulin-sensitizing medication. We also excluded subjects who had a history of cardiovascular or cerebrovascular disease. A total of 2846 subjects were included in the final analyses. The Institutional Review Board at Yonsei University College of Medicine approved the study protocol, and written informed consent was obtained from all participants.

Clinical Characteristics

Height, weight and waist circumference (WC) were measured, and body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m^2). WC was measured at the midpoint between the lower border of the rib cage and the iliac crest. Lifestyle, a personal medical history of acute and chronic illnesses and medication history were assessed using a standard questionnaire. Systolic and diastolic blood pressures were measured after a five-minute rest period. Metabolic syndrome (MetS) was defined according to the updated National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP ATP Ⅲ) criteria applying Asia Pacific WHO guidelines for waist circumference. Accordingly, subjects with three or more of the following characteristics were diagnosed with MetS: fasting plasma glucose ≥100 mg/dL or diabetes diagnosis, WC ≥90 cm for males and ≥80 cm for females, blood pressure (BP) ≥130/85 mmHg or currently taking BP medication, triglycerides (TG) ≥150 mg/dL or currently taking TG lowering medication, and high density lipoprotein cholesterol (HDL-C) <40 mg/dL for males and <50 mg/dL for females.

Biochemical Parameters

Blood samples were taken from all subjects after 8 hours of fasting. Samples were immediately centrifuged, and plasma and serum samples were stored at −80℃ until analysis. Glucose was measured by a standard glucose oxidase method (747 Automatic Analyzer; Hitachi, Tokyo, Japan). Total cholesterol (TC), HDL-C, TG, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and GGT were measured enzymatically using a chemical analyzer (Hitachi 747; Daiichi, Japan). Low density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald formula. Fasting serum insulin was determined by chemiluminescence (RIA Kit; Daiichi, Japan), and insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index, calculated with the following formula: HOMA-IR = fasting insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5. Plasma adiponectin was measured by the enzyme linked immunosorbent assay (ELISA; Mesdia, Seoul, Korea)[22].

Pulse Wave Velocity (PWV)

Aortic and peripheral PWV's were measured using a PP-1000 pulse wave analyzer (Hanbyul Meditech Co., Jeonju, Korea) as previously described[23]. Regional PWV values for the aorta and leg were calculated automatically after ten seconds of data had been collected. For aortic PWV, carotid-femoral transit time and PWV were calculated from the carotid-femoral distance divided by transit time. Peripheral PWV data were collected from the femoral-dorsalis pedis distance.

Statistical Analysis

Data are expressed as the means ± S.D. Intergroup comparisons were performed using ANOVA or Chi-square tests. Pearson's correlation analysis was also performed to evaluate the relationship between PWV and various clinical factors, where indicated. Linear correlations were analyzed after logarithmic transformation of the variables (TG, HOMA-IR, adiponectin and GGT) that were not normally distributed. Odds ratios for a high PWV were calculated using multivariate logistic regression analysis after adjusting for confounding variables across GGT tertiles. High PWV was designated as a value greater than the cut-off between the third and fourth tertiles.

Statistical analyses were carried out using SPSS for Windows 15.0 (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered significant.

Results

The clinical and laboratory characteristics of the study population are summarized in **Table 1**. The study included 1321 men, aged 54.04 ± 11.09 years, and 1525 women, aged 54.58 ± 10.66 years. The subjects were stratified into three groups according to their GGT values. There were significant differences in metabolic parameters among the groups. The mean age, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, WC, fasting plasma glucose (FPG), TC, TG, LDL-C, AST, ALT, insulin, HOMA-IR, aortic PWV and peripheral PWV increased according to tertiles of GGT in males and females, whereas HDL-C and adiponectin levels decreased (**Table 2**, **3**).

The subjects were subsequently categorized into five groups according to the number of MetS components they satisfied. There were significant differences in metabolic parameters among the groups, including age, SBP, DBP, BMI, WC, FPG, TG, AST, ALT, insulin level, and HOMA-IR, which all increased in parallel with the number of MetS components, and HDL-C and adiponectin levels, which decreased sequentially with an increasing number of MetS components. We found that more MetS components indicated a greater aortic and peripheral PWV and GGT, but a lower adiponectin level. In contrast, we found that TC and LDL-C were not significantly correlated to the number of MetS components (**Table 4**, **5**). In terms of medication history among the five groups, there was also a sequential increase in the percentage of subjects taking lipid-lowering drugs (1.72% vs. 3.25% vs. 9.58% vs. 13.26%, for 1, 2, 3, and >4 MetS components, respectively), antihypertensive drugs (2.31% vs. 7.25% vs. 12.43% vs. 17.34%, for 1, 2, 3, and >4 MetS components, respectively) and anti-diabetic drugs (1.15% vs. 3.05% vs. 3.28% vs. 12.76% vs. 19.22%, for 1, 2, 3, and >4 MetS components, respectively).

Aortic PWV showed a significant correlation with age, SBP and FPG in males (correlation coefficients: 0.14, 0.13 and 0.10, respectively; $p<0.01$) and females (correlation coefficients: 0.16, 0.14 and 0.07, respectively; $p<0.01$), but there was no correlation among aortic PWV, GGT and adiponectin in males or females. Peripheral PWV was significantly correlated with age, SBP, DBP, BMI, WC, FPG and GGT in males (correlation coefficients: 0.29, 0.23, 0.22, 0.14, 0.10 and 0.14, respectively; $p<0.01$) and females (correlation coefficients: 0.23, 0.18, 0.14, 0.08, 0.07 and 0.18, respectively; $p<0.01$), but there was no correlation between peripheral PWV and adiponectin in males or females.

Table 1. Baseline physical and metabolic characteristics of subjects

	Male	Female
N	1,321	1,525
Age (years)	54.04 ± 11.09	54.58 ± 10.66
SBP (mmHg)	127.05 ± 13.66	125.78 ± 14.34
DBP (mmHg)	81.49 ± 9.89	79.57 ± 9.43
BMI (kg/m^2)	25.35 ± 3.23	25.17 ± 3.52
WC (cm)	90.27 ± 8.25	80.84 ± 8.09
FPG (mg/dL)	108.77 ± 33.36	107.95 ± 31.84
TC (mg/dL)	189.05 ± 37.02	185.83 ± 36.9
TG (mg/dL)	161.11 ± 103.12	138.30 ± 84.08
LDL-C (mg/dL)	98.20 ± 33.75	103.69 ± 33.31
HDL-C (mg/dL)	48.58 ± 11.75	54.48 ± 13.12
AST (IU/L)	25.88 ± 12.08	23.11 ± 13.22
ALT (IU/L)	27.85 ± 19.12	21.32 ± 14.56
GGT (IU/L)	47.03 ± 37.57	24.86 ± 30.55
Insulin (μIU/mL)	6.02 ± 7.31	6.42 ± 7.74
HOMA-IR	1.64 ± 1.98	1.80 ± 2.74
Adiponectin (μg/mL)	6.55 ± 3.64	9.53 ± 5.45
Aortic PWV (m/s)	8.02 ± 1.22	7.56 ± 1.28
Peripheral PWV (m/s)	9.93 ± 1.44	9.35 ± 1.44

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; PWV, pulse wave velocity. Data are the mean ± SD.

Logistic regression analysis after adjusting for age revealed that the odds ratio for high peripheral PWV in the highest tertile of sex-specific GGT was significantly increased compared to the lowest tertile. These relationships remained significant after further adjustments for other risk factors (**Table 6**).

Discussion

In this study, we found a significant association between serum GGT and arterial stiffness, but there was no correlation between adiponectin and PWV in any subjects.

GGT is a glycoprotein with a molecular weight of 68,000 daltons. It consists of two proteins, a larger chain (46,000 daltons) and a smaller chain (22,000

Table 2. Clinical characteristics of male subjects divided into GGT groups

	I	II	III	*p*
N	441	440	440	
Age (years)	53.43 ± 11.95[a]	54.14 ± 11.85[b]	54.30 ± 11.72[b]	0.01
SBP (mmHg)	125.23 ± 13.23[a]	126.78 ± 13.62[a, b]	128.96 ± 14.53[b]	< 0.01
DBP (mmHg)	79.63 ± 9.09[a]	81.20 ± 9.59[b]	83.62 ± 10.66[c]	< 0.01
BMI (kg/m^2)	24.26 ± 2.95[a]	25.43 ± 3.10[b]	26.23 ± 3.29[c]	< 0.01
WC (cm)	87.38 ± 7.65[a]	90.51 ± 8.02[b]	92.53 ± 7.71[c]	< 0.01
FPG (mg/dL)	109.91 ± 30.12[a]	115.89 ± 34.75[b]	119.07 ± 33.80[c]	< 0.01
TC (mg/dL)	170.37 ± 34.94[a]	180.54 ± 34.79[b]	186.59 ± 39.03[b]	< 0.01
TG (mg/dL)	126.02 ± 76.93[a]	158.29 ± 86.34[b]	204.77 ± 133.63[c]	< 0.01
LDL-C (mg/dL)	96.49 ± 30.98[a]	98.19 ± 32.17[b]	99.55 ± 38.07[b]	< 0.01
HDL-C (mg/dL)	50.11 ± 11.47[a]	48.89 ± 12.55[b]	47.49 ± 11.07[b]	< 0.01
AST (IU/L)	20.61 ± 6.23[a]	24.40 ± 8.44[b]	33.21 ± 17.72[c]	< 0.01
ALT (IU/L)	20.86 ± 11.04[a]	26.79 ± 13.07[b]	38.93 ± 17.54[c]	< 0.01
GGT (IU/L)	17.95 ± 4.08[a]	33.29 ± 5.77[b]	70.80 ± 12.56[c]	< 0.01
Insulin (μIU/mL)	5.00 ± 5.91[a]	5.67 ± 6.69[a]	6.11 ± 6.24[b]	0.037
HOMA-IR	1.35 ± 1.56[a]	1.59 ± 1.94[b]	1.87 ± 1.90[c]	< 0.01
Adiponectin (μg/mL)	7.37 ± 3.88[a]	6.29 ± 3.42[b]	5.91 ± 3.50[b]	< 0.01
Aortic PWV (m/s)	7.64 ± 1.16[a]	7.98 ± 1.19[a, b]	8.16 ± 1.36[b]	0.03
Peripheral PWV (m/s)	9.08 ± 1.51[a]	9.51 ± 1.50[a, b]	10.10 ± 1.46[b]	0.02

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; PWV, pulse wave velocity. Data are the mean ± SD.
[a, b, c]: Groups were separated by Tukey's post-hoc test.

Table 3. Clinical characteristics of female subjects divided into GGT groups

	I	II	III	*p*
N	508	509	508	
Age (years)	53.34 ± 11.40[a]	54.80 ± 11.00[b]	56.93 ± 10.06[c]	< 0.01
SBP (mmHg)	123.09 ± 14.05[a]	125.32 ± 14.27[a]	129.41 ± 14.38[b]	< 0.01
DBP (mmHg)	76.65 ± 9.20[a]	78.05 ± 8.80[a]	81.01 ± 9.81[b]	< 0.01
BMI (kg/m^2)	24.18 ± 3.04[a]	25.19 ± 3.56[b]	26.14 ± 3.69[c]	< 0.01
WC (cm)	82.15 ± 8.33[a]	84.59 ± 9.16[b]	87.26 ± 9.46[c]	< 0.01
FPG (mg/dL)	102.78 ± 24.75[a]	111.09 ± 30.80[b]	119.37 ± 31.51[c]	< 0.01
TC (mg/dL)	178.56 ± 32.86[a]	183.55 ± 33.15[a]	194.24 ± 42.07[b]	< 0.01
TG (mg/dL)	111.87 ± 61.21[a]	136.62 ± 66.76[b]	165.36 ± 66.46[c]	< 0.01
LDL-C (mg/dL)	100.05 ± 29.82[a]	102.18 ± 30.64[a, b]	107.84 ± 37.60[b]	< 0.01
HDL-C (mg/dL)	56.05 ± 13.41[a]	54.43 ± 12.80[a, b]	53.48 ± 13.23[b]	< 0.01
AST (IU/L)	18.95 ± 5.35[a]	21.93 ± 8.98[b]	29.91 ± 11.24[c]	< 0.01
ALT (IU/L)	16.66 ± 5.88[a]	21.26 ± 13.69[b]	28.91 ± 17.89[c]	< 0.01
GGT (IU/L)	11.32 ± 2.23[a]	18.21 ± 2.52[b]	46.59 ± 47.05[c]	< 0.01
Insulin (μIU/mL)	5.22 ± 6.41[a]	6.01 ± 7.47[a]	7.48 ± 8.12[b]	0.037
HOMA-IR	1.33 ± 1.62[a]	1.67 ± 1.28[b]	2.40 ± 1.89[c]	< 0.01
Adiponectin (μg/mL)	10.39 ± 6.25[a]	9.39 ± 5.27[b]	8.43 ± 4.70[c]	< 0.01
Aortic PWV (m/s)	7.44 ± 1.37[a]	7.57 ± 1.36[a, b]	7.74 ± 1.31[b]	0.02
Peripheral PWV (m/s)	8.98 ± 1.43[a]	9.34 ± 1.42[a, b]	9.61 ± 1.48[b]	0.02

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; PWV, pulse wave velocity. Data are the mean ± SD.
[a, b, c]: Groups were separated by Tukey's post-hoc test.

Table 4. Clinical characteristics of male subjects according to the number of features of metabolic syndrome

	0	1	2	3	>4	*p*
N	144	411	344	269	153	
Age (years)	51.59 ± 12.97	54.33 ± 12.10	55.51 ± 11.51	56.31 ± 11.68	57.06 ± 11.84	< 0.01
SBP (mmHg)	116.02 ± 8.88	122.54 ± 11.98	126.11 ± 12.09	130.27 ± 14.13	136.82 ± 12.61	< 0.01
DBP (mmHg)	75.59 ± 8.37	78.80 ± 8.46	81.07 ± 8.96	82.96 ± 10.43	86.93 ± 10.26	< 0.01
BMI (kg/m^2)	22.92 ± 1.96	23.93 ± 2.62	25.26 ± 3.09	26.34 ± 3.36	27.37 ± 2.92	< 0.01
WC (cm)	82.61 ± 4.94	85.96 ± 6.92	89.95 ± 7.78	93.43 ± 7.70	96.36 ± 6.73	< 0.01
FPG (mg/dL)	89.22 ± 6.88	104.67 ± 29.98	112.47 ± 31.28	119.85 ± 35.80	125.83 ± 36.01	< 0.01
TC (mg/dL)	174.72 ± 35.83	175.17 ± 33.40	178.09 ± 35.10	182.07 ± 41.25	184.95 ± 39.46	0.12
TG (mg/dL)	94.16 ± 28.46	108.09 ± 31.00	147.55 ± 56.58	193.35 ± 108.40	250.83 ± 110.95	< 0.01
LDL-C (mg/dL)	86.58 ± 32.98	96.67 ± 28.94	98.88 ± 31.32	97.72 ± 38.29	99.67 ± 28.94	0.53
HDL-C (mg/dL)	54.27 ± 10.13	53.71 ± 11.74	49.73 ± 11.41	45.51 ± 10.86	40.78 ± 8.64	< 0.01
AST (IU/L)	22.85 ± 7.89	24.26 ± 11.65	25.88 ± 10.36	27.38 ± 13.54	29.50 ± 14.59	< 0.01
ALT (IU/L)	22.84 ± 13.04	24.06 ± 16.23	26.33 ± 15.29	31.54 ± 24.63	33.58 ± 20.33	< 0.01
GGT (IU/L)	37.72 ± 49.99	40.58 ± 42.85	42.81 ± 40.07	55.95 ± 55.39	59.38 ± 48.66	< 0.01
Insulin (μIU/mL)	4.71 ± 5.53	4.87 ± 5.95	5.85 ± 6.77	6.68 ± 7.95	7.72 ± 9.31	< 0.01
HOMA-IR	1.04 ± 1.23	1.16 ± 1.35	1.58 ± 1.92	1.91 ± 2.17	2.28 ± 2.50	< 0.01
Adiponectin (μg/mL)	7.68 ± 3.69	7.18 ± 3.97	6.49 ± 3.42	6.13 ± 3.32	5.90 ± 3.91	< 0.01
Aortic PWV (m/s)	7.69 ± 1.17	7.86 ± 1.21	7.99 ± 1.21	8.06 ± 1.17	8.27 ± 1.22	< 0.05
Peripheral PWV (m/s)	9.77 ± 1.34	9.88 ± 1.38	9.99 ± 1.43	10.08 ± 1.49	10.26 ± 1.41	< 0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; PWV, pulse wave velocity. Data are the mean ± SD.

Table 5. Clinical characteristics of female subjects according to the number of features of metabolic syndrome

	0	1	2	3	>4	*p*
N	128	452	418	329	198	
Age (years)	50.40 ± 11.25	53.36 ± 11.43	55.17 ± 9.73	56.93 ± 9.75	57.61 ± 10.70	< 0.01
SBP (mmHg)	115.82 ± 8.44	120.21 ± 11.51	123.93 ± 14.08	129.26 ± 14.18	132.84 ± 14.45	< 0.01
DBP (mmHg)	74.72 ± 7.69	76.19 ± 8.97	78.70 ± 9.33	80.18 ± 9.08	81.64 ± 9.08	< 0.01
BMI (kg/m^2)	21.63 ± 1.91	23.79 ± 3.09	25.54 ± 3.38	26.05 ± 3.37	26.72 ± 3.39	< 0.01
WC (cm)	73.18 ± 4.24	80.17 ± 8.49	85.02 ± 8.53	87.79 ± 8.11	89.56 ± 7.57	< 0.01
FPG (mg/dL)	88.68 ± 7.05	95.54 ± 11.50	104.17 ± 28.58	114.00 ± 33.51	124.60 ± 38.03	< 0.01
TC (mg/dL)	183.75 ± 32.46	185.86 ± 35.60	186.28 ± 33.99	188.78 ± 43.92	190.72 ± 35.57	0.37
TG (mg/dL)	79.69 ± 29.18	95.59 ± 39.12	116.70 ± 39.18	149.76 ± 50.74	193.99 ± 111.57	< 0.01
LDL-C (mg/dL)	102.42 ± 29.67	104.86 ± 33.11	103.18 ± 30.69	103.38 ± 38.49	105.11 ± 32.68	0.41
HDL-C (mg/dL)	65.33 ± 12.28	61.39 ± 11.71	56.63 ± 12.65	51.39 ± 11.68	44.78 ± 8.56	< 0.01
AST (IU/L)	20.03 ± 6.92	22.09 ± 9.42	23.56 ± 9.98	24.24 ± 10.92	25.61 ± 13.06	< 0.01
ALT (IU/L)	16.63 ± 9.09	19.43 ± 11.57	20.39 ± 14.28	23.02 ± 16.34	24.09 ± 16.16	< 0.01
GGT (IU/L)	16.14 ± 12.00	21.41 ± 14.56	24.75 ± 17.65	28.79 ± 27.94	30.36 ± 23.60	< 0.01
Insulin (μIU/mL)	4.27 ± 5.10	4.84 ± 5.32	6.28 ± 8.99	6.92 ± 7.65	8.36 ± 8.54	< 0.01
HOMA-IR	0.93 ± 1.08	1.13 ± 1.31	1.64 ± 2.36	2.04 ± 3.35	2.66 ± 3.47	< 0.01
Adiponectin (μg/mL)	10.99 ± 5.56	10.84 ± 6.13	9.90 ± 5.46	8.93 ± 5.20	7.94 ± 4.22	< 0.01
Aortic PWV (m/s)	7.27 ± 1.17	7.49 ± 1.23	7.53 ± 1.29	7.63 ± 1.26	7.76 ± 1.27	< 0.05
Peripheral PWV (m/s)	9.36 ± 1.44	9.50 ± 1.36	9.59 ± 1.46	9.66 ± 1.46	9.80 ± 1.49	< 0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; PWV, pulse wave velocity. Data are the mean ± SD.

Table 6. Odds ratios (95% CI) for high peripheral PWV according to GGT tertiles in subjects

		GGT tertiles		
		I	II	III
Males	Model 1[a]	1.00	1.32* (1.04-1.98)	1.48** (1.28-2.43)
	Model 2[b]	1.00	1.46* (1.05-2.05)	1.72** (1.22-2.42)
	Model 3[c]	1.00	1.44* (1.12-2.15)	1.87** (1.31-2.62)
Females	Model 1[a]	1.00	1.42* (1.05-2.12)	1.76** (1.19-2.60)
	Model 2[b]	1.00	1.43* (0.82-2.16)	1.80** (1.06-2.43)
	Model 3[c]	1.00	1.72** (1.21-2.93)	2.41** (1.39-4.62)

High peripheral PWV was defined as more than 10.66 m/s in females and 10.95 m/s in males (>75th percentile).
[a]Model 1: adjusted for age
[b]Model 2: adjusted for age, SBP, DBP
[c]Model 3: adjusted for age, SBP, DBP, BMI, WC, FPG
*$p<0.05$, **$p<0.01$

daltons)[24]. GGT is a sensitive indicator of liver dysfunction or alcohol consumption and reflects other concomitant risk factors, such as obesity, insulin resistance, hypertension, diabetes and dyslipidemia[5-9]. In this study, we demonstrated that most of the metabolic parameters increased or decreased as expected with a rise in the GGT tertile. Moreover, significant relationships were observed among various metabolic parameters, including the correlation of GGT with an increase in the number of MetS components. The results suggest a strong correlation between GGT and MetS. Previous studies have shown that serum GGT is associated with MetS and its characteristic components in both genders[15, 25]. Although the detailed mechanism underlying the relationship between GGT levels and MetS is not completely understood, hepatic insulin resistance may be involved[26-28]. MetS represents a cluster of cardiovascular disease risk factors for which insulin resistance is believed to be of pathogenic importance. In our study, serum GGT levels were strongly associated with HOMA-IR, which is a marker of insulin resistance in both genders ($r=0.15$ in men, $r=0.17$ in women; $p<0.01$). Several recent studies have reported that the serum GGT level is a possible marker of oxidative stress[29-31], although the actual role that GGT plays in oxidative stress is controversial, GGT is surely related to oxidative stress. Oxidative stress may also play a role in the pathophysiology of MetS[32, 33]. Thus, oxidative stress may represent another possible mechanism of the relationship between GGT levels and MetS; however, we did not investigate oxidative stress markers, so the precise relationship among oxidative stress, GGT and MetS could not evaluated.

Previous studies did not clearly demonstrate a relationship between adiponectin and PWV. Araki *et al*. showed that adiponectin was significantly associated with arterial stiffness in a non-diabetic group, although they found no significant association between adiponectin and PWV in a group of diabetic subjects[34]. In another study of Japanese males, adiponectin levels did not appear to be a significant predictor of PWV[35], and our results also suggest that adiponectin is not correlated with PWV in either gender.

PWV of the aorta is the standard measure of arterial stiffness, but it can also be measured in other arterial segments. Previous studies investigated whether the effects of factors related to arterial stiffness varied among different parts of the arteries. Aortic PWV is a better predictor of cardiovascular risk and mortality than peripheral PWV[36], and peripheral PWV has been associated with peripheral vascular disease[37, 38]. The function and structure of the arterial system is heterogeneous and differs between central arteries (aorta and major branches) and muscular peripheral arteries (upper and lower limbs). The central arteries are characterized by high susceptibility to age and blood pressure, whereas the peripheral arteries are characterized by high susceptibility to vasoactive substances[39, 40]. Isabel *et al*. reported that blood pressure and glucose levels were the main determinants affecting arterial stiffness of central and peripheral arteries, whereas abdominal obesity was mainly associated with peripheral arterial stiffness[36]. Here we found that aortic PWV was associated with age, SBP and FPG, while peripheral PWV correlated with age, SBP, DBP, BMI, WC, FPG and GGT. This study corroborated previous findings that aortic arteries and peripheral arteries differ in composition, stiffness and susceptibility to risk factors[36-38].

Our results showed that GGT was correlated with peripheral PWV, but not with aortic PWV. Thus, we further investigated the relationships between GGT concentrations and peripheral PWV. In the final logistic regression analysis after adjustment for age, BP and other risk factors, although the relationship was weak, GGT was found to be an independent contributor to increased peripheral PWV.

Several limitations of our study need to be considered. First, the cross-sectional design cannot confirm causality, and more prospective studies are necessary to confirm the relationships. Second, medications and alcohol consumption were reported using a questionnaire, raising the possibility of questionable reliability. Finally, further studies are necessary to elucidate the mechanisms involved in the impact of different risk factors on the stiffness of central and peripheral arterial segments.

In conclusion, we found a significant association between serum GGT and arterial stiffness, but there was no correlation between adiponectin and PWV in any subjects.

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