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High triglyceride to high-density lipoprotein cholesterol ratio and arterial stiffness in postmenopausal Korean women

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The ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL) is positively linked to insulin resistance, and it has emerged as an independent predictor of cardiovascular disease. Menopause is characterized by various detrimental metabolic and vascular changes that may lead to high TG with low HDL cholesterol and arterial stiffness. Several epidemiological studies have reported that high TG/HDL ratio has a positive association with arterial stiffness in both adult and adolescent populations; it is not known whether TG/HDL ratio is related to brachial-ankle PWV (baPWV) in postmenopausal women. Thus, the authors aimed to investigate the association between TG/HDL ratio and arterial stiffness as measured by baPWV in 434 postmenopausal women. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for high baPWV were calculated after adjusting for confounding variables across TG/HDL ratio quartiles using multiple logistic regression analysis. The mean values of meaningful cardiometabolic variables increased with TG/HDL ratio quartiles. The adjusted baPWV (SEs) significantly increased with TG/HDL quartiles: Q1 = 1412 (22.1), Q2 = 1469 (21.4), Q3 = 1482 (21.0), and Q4 = 1505 (21.6) cm/s after adjusting for age, body mass index (BMI), and systolic blood pressure. The OR (95% CI) of the highest TG/HDL ratio quartile as compared to the lowest TG/HDL ratio quartile for high PWV was 2.77 (1.16-6.63) after adjusting for age, BMI, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, total cholesterol level, hypertension, log-transformed C-reactive protein, and the use of antihypertensive and lipid-lowering drugs. The TG/HDL ratio was positively and independently associated with arterial stiffness in postmenopausal Korean women.

1 | INTRODUCTION

The pathophysiology of atherosclerotic cardiovascular disease (CVD) is only partially understood. Dyslipidemia, such as elevated low-density lipoprotein (LDL) cholesterol and triglycerides or low levels of high-density lipoprotein (HDL) cholesterol, is an established risk factor and plays a crucial role in the development and progression of vascular disease, such as CVD and ischemic stroke.[1,2] Serum lipid profiles are frequently evaluated in general clinical practice. Among lipid profile parameters, the ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL) is positively linked to insulin resistance, and it has emerged as an independent predictor of CVD.[3,4]

For women, menopause is an additional risk factor due to the loss of hormonal protection to traditional risk factors. The reason for this is that high TG/HDL ratio is associated with increased atherosclerotic arterial disease and hypertension in premenopausal women as well.[5] Postmenopausal women are more susceptible to increased weight gain and fat redistribution accompanied by marked changes in estrogen level.[6] Decreased estrogen levels also influence lipid metabolism in vascular smooth muscle and the endothelium.[7] Thus, menopause is characterized by various detrimental metabolic and vascular changes that may lead to high TG with low HDL cholesterol and arterial stiffness.

Arterial stiffness is caused by structural and functional changes within the arterial walls, resulting in an increased pulse wave velocity (PWV). The PWV is a noninvasive and useful measure of arterial stiffness[8,9] and is also a reliable indicator of vascular damage and early atherosclerosis.[9] Increased arterial stiffness as measured by PWV has been reported as a significant predictor of cardiovascular events and mortality.[10] Carotid-femoral PWV (cfPWV), a measure of arterial PWV through the entire aorta, is the most recognized and established index of central arterial stiffness. However, from a practical point of view, cfPWV has some limitations, such as a long time for measurement, examiner variability, and inconvenience of exposing the femoral site. Recently, a simple, automated device has become available to measure brachial-ankle PWV (baPWV), an index of peripheral arterial stiffness, using a volume rendering method. Measuring baPWV is easier and more time-effective than conventional measurement of cfPWV with a high correlation with cfPWV particularly in East Asian populations.[11]

Several epidemiological studies have reported that a high TG/HDL ratio has a positive association with arterial stiffness in both adult and adolescent populations[12,13]; it is not known whether TG/HDL ratio is related to baPWV in postmenopausal women. Thus, in this study, the authors aimed to investigate the association between TG/HDL ratio and arterial stiffness as measured by baPWV in postmenopausal women.

2 | METHODS

2.1 | Study participants

From January 1, 2015, through July 31, 2015, researchers retrospectively reviewed the medical records of 615 postmenopausal women who voluntarily visited the health promotion center of Yonsei University Gangnam Severance Hospital in Seoul, South Korea, for regular healthcare checkups. Menopause was defined as having no menstrual periods for 12 consecutive months following a final menstrual period in the absence of a clear biological or physiological cause. We excluded participants who met at least one of the following criteria: a history of exogenous estrogen or tamoxifen therapy; a history of induced menopause due to bilateral oophorectomy, radiation, or drug use; a history of ischemic heart disease, stroke, or thyroid or hepatobiliary disease; an ankle-brachial index <0.9; and C-reactive protein (CRP) ≥ 10.0 mg/L, and those with missing data or those who did not fast for 12 hours prior to testing. Following these exclusions, 434 participants aged 46 years or older were included in the final analysis. Each participant provided informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the institutional review board of Yonsei University College of Medicine, Seoul, Korea.

2.2 | Data collection

Each participant completed a questionnaire about her lifestyle and medical history. Self-reported cigarette smoking, alcohol consumption, and physical activity characteristics were taken from the questionnaires. Smoking status was categorized as non-smoker, ex-smoker, and current smoker. Alcohol drinking was defined as alcohol consumption ≥two times per week. Participants were also asked about the type and frequency of leisure-time physical activity on a weekly basis. Regular exercise was defined as exercise ≥three times per week. Body mass and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice in the sitting position after at least 10 minutes of rest using the patient's right arm with a standard mercury sphygmomanometer (Baumanometer; WA Baum Co Inc, Copiague, NY). Mean arterial pressure was calculated using the equation $(SBP + 2 \times DBP)/3$. All blood samples were obtained from the antecubital vein after 12 hours overnight fast. Fasting plasma glucose, total cholesterol, triglyceride, and HDL cholesterol levels were measured by enzymatic methods using a Hitachi 7600 automated chemistry analyzer (Hitachi Co., Tokyo, Japan). High-sensitivity CRP concentrations were measured using the Roche/Hitachi 912 System (Roche Diagnostics, Indianapolis, IN), a latex-enhanced immunoturbidimetric method with a lower limit of detection of 0.02 mg/L. Hypertension was defined as SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg, or use of hypertension medication. Type 2 diabetes was defined as a fasting plasma glucose level ≥126 mg/dL or a use of diabetes medication.

2.3 | BaPWV measurement

An automatic waveform analyzer (model BP-203RPE; Colin Medical Technology Corp., Komaki, Japan) was used to measure PWV. This instrument simultaneously records blood pressure, phonocardiogram, electrocardiogram, and arterial blood pressure at both the left and right brachial arteries and ankles. Subjects were examined in the supine position after 10 minutes of bed rest. Electrocardiogram electrodes were placed on both wrists, and a microphone for the phonogram was placed on the left edge of the sternum. Pneumonic cuffs were wrapped around both the upper arms and ankles and connected to a plethysmographic sensor to determine the volume pulse waveform. Waveforms for the upper arm (brachial artery) and ankle (tibial artery) were stored for 10-second sample times with automatic gain analysis and quality adjustment. An oscillometric pressure sensor was attached to the cuffs to measure blood pressure at the four extremities. The baPWVs were recorded using a semiconductor pressure sensor (1200 Hz sample acquisition frequency) and calculated using the equation $(La-Lb)/\Delta Tba$. La and Lb were defined as the distance from the aortic valve to the elbow and to the ankle, respectively, and are expressed as follows: $La = 0.2195 \times$ height of subject (cm) − 2.0734 and Lb = 0.8129 × height of subject (cm) + 12.328. The time interval between the arm and ankle distance (ΔTba) was defined as the pulse transit time between the brachial and tibial arterial pressure waveforms. La and Lb were automatically estimated based on the subjects' heights. The coefficients of variation for inter- and intra-observer reproducibility were 7.4% and 5.8%, respectively.

2.4 | Statistical analysis

TG/HDL ratio quartiles were categorized as follows: Q1: ≤1.11, Q2: 1.12-1.66, Q3: 1.67-2.69, and Q4: ≥2.70. The clinical characteristics of the study population according to TG/HDL ratio quartiles were compared using a one-way analysis of variance (ANOVA) or Kruskal-Wallis test for continuous variables according to the normality of distributions and chi-square test for categorical variables. Continuous data are presented as the mean (standard deviation, SD) or median (interquartile range, IQR), and categorical data are presented as the frequency. The mean differences between groups were determined using post hoc analysis of ANOVA test using Tukey corrections. Pearson correlation coefficients (*r*) were calculated to assess associations between baPWV and triglyceride or HDL cholesterol. The adjusted mean values of baPWV were calculated using analysis of covariance (ANCOVA) test after adjusting for age, BMI, and SBP. The high baPWV was determined as more than 1600 cm/s, which corresponded to the 75th percentile of the current sample. The odds ratios (ORs) and 95% confidence intervals (95% CIs) for high baPWV were calculated after adjusting for confounding variables across TG/HDL ratio quartiles using multiple logistic regression analysis. All analyses were conducted using the SAS statistical software (version 9.4; SAS Institute Inc, Cary, NC). All statistical tests were two-sided, and statistical significance was determined at $P < 0.05$.

3 | RESULTS

Table 1 shows the distribution of clinical characteristics across the TG/HDL ratio quartiles. The mean values of meaningful cardiometabolic variables, including age, BMI, blood pressure, and fasting plasma glucose levels, and the median CRP level increased proportionally with the TG/HDL ratio quartiles. The prevalence of hypertension

TABLE 1 Clinical characteristics of the study population according to TG/HDL ratio quartiles in postmenopausal women

	TG/HDL ratio quartiles						
	Total	Q1 (≤1.11)	Q2 (1.12-1.66)	Q3 (1.67-2.69)	Q4 (≥2.70)	*P*-value[a]	Post hoc
n	434	107	110	106	111		
Age (years)	58.3 (6.6)	56.3 (6.1)	58.4 (6.6)	58.3 (6.6)	60.2 (6.6)	<0.001	c
Body mass index (kg/m^2)	23.2 (3.0)	21.7 (2.3)	23.1 (3.3)	23.5 (3.0)	24.4 (2.8)	<0.001	a, b, c, d
Systolic blood pressure (mm Hg)	124.9 (19.3)	118.9 (15.5)	123.7 (22.0)	125.4 (18.2)	131.6 (18.7)	<0.001	c, e
Diastolic blood pressure (mm Hg)	76.2 (11.1)	73.3 (9.2)	74.9 (12.3)	76.2 (11.2)	80.3 (10.3)	<0.001	c, e, f
Mean arterial pressure (mm Hg)	92.4 (13.4)	88.5 (11.0)	91.2 (15.0)	92.6 (13.1)	97.4 (12.7)	<0.001	c, e, f
Fasting plasma glucose (mmol/L)	5.31 (0.99)	4.97 (0.74)	5.43 (1.01)	5.38 (0.94)	5.46 (1.18)	<0.001	a, b, c
Total cholesterol (mmol/L)	5.25 (0.96)	5.21 (0.88)	5.15 (0.91)	5.38 (1.15)	5.27 (0.88)	0.348	-
C-reactive protein (mg/L)	0.70 (0.34-1.50)	0.41 (0.30-0.90)	0.70 (0.30-1.50)	0.80 (0.30-1.50)	1.00 (0.50-2.08)	<0.001	-
Current smoking (%)	3.7	1.0	4.9	6.2	2.8	0.378	-
Alcohol drinking (%)[b]	11.8	13.7	11.1	12.1	10.4	0.899	-
Regular exercise (%)[c]	42.0	46.7	50.5	36.0	34.6	0.049	-
Hypertension (%)	59.4	28.9	40.0	40.6	59.5	<0.001	-
Type 2 diabetes (%)	7.1	3.7	8.2	8.5	8.1	0.476	-

Data are expressed as the mean (SD), median (IQR), or percentage.

[a]*P*-values were calculated using 1-way ANOVA test, Kruskal-Wallis test, or chi-square test.

[b]Alcohol drinking ≥twice/week.

[c]Regular exercise ≥three times/week. Post hoc analysis of ANOVA test for mean difference between groups: a, Q1 vs Q2; b, Q1 vs Q3, c: Q1 vs Q4; d, Q2 vs Q3; e, Q2 vs Q4, and f, Q3 vs Q4.

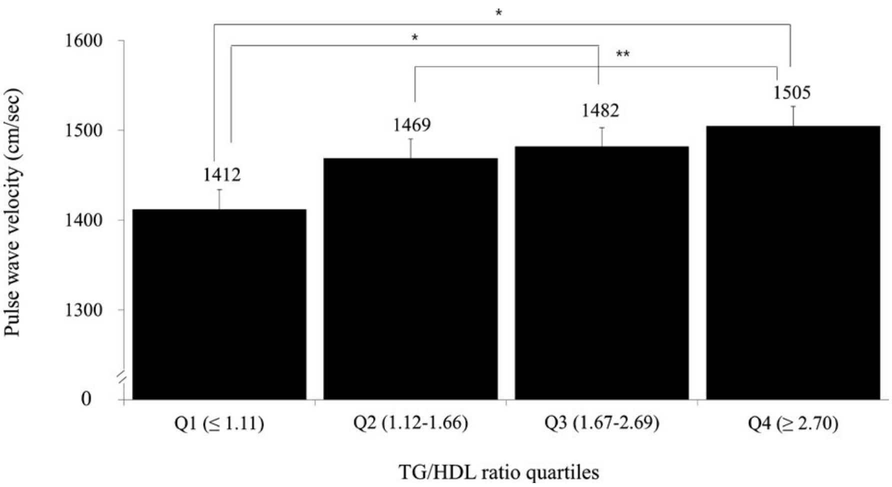

FIGURE 1 Adjusted mean values of brachial-ankle pulse wave velocity according to the TG/HDL ratio quartiles after adjusting for age, body mass index, and systolic blood pressure (bars mean standard errors, *P < 0.01, **P < 0.05)

TABLE 2 Odds ratios and 95% confidence intervals for high pulse wave velocity according to TG/HDL ratio quartiles

	TG/HDL ratio quartiles			
	Q1 (≤1.11)	**Q2 (1.12-1.66)**	**Q3 (1.67-2.69)**	**Q4 (≥2.70)**
Model 1	1.00 (Reference)	2.27 (1.03-5.05)	2.33 (1.04-5.24)	3.98 (1.81-8.77)
Model 2	1.00 (Reference)	1.94 (0.81-4.63)	2.03 (0.86-4.81)	2.84 (1.22-6.64)
Model 3	1.00 (Reference)	1.68 (0.68-4.13)	2.01 (0.83-4.89)	2.77 (1.16-6.63)

Model 1: adjusted for age, body mass index, and smoking status.
Model 2: adjusted for age, body mass index, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, total cholesterol level, and hypertension.
Model 3: adjusted for age, body mass index, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, total cholesterol level, hypertension, log-transformed C-reactive protein, and the use of antihypertensive and lipid lowering drugs.

increased in accordance with the TG/HDL ratio quartiles. When examined as continuous variables, baPWV was positively correlated with log-transformed triglyceride (r = 0.218 P < 0.001) and inversely correlated with HDL cholesterol (r = −0.187, P = 0.004) (data not shown).

Figure 1 shows the age, BMI, and SBP adjusted means and SE of baPWV according to the TG/HDL ratio quartiles. The adjusted baPWV (SEs) significantly increased with the TG/HDL quartiles: Q1 = 1412 (22.1), Q2 = 1469 (21.4), Q3 = 1482 (21.0), and Q4 = 1505 (21.6) cm/s.

Table 2 describes the ORs for high baPWV according to the TG/HDL ratio quartile. The OR (95% CI) of the highest TG/HDL ratio quartile as compared to the lowest TG/HDL ratio quartile for high PWV was 2.77 (1.16-6.63) after adjusting for age, BMI, smoking status, regular exercise, mean arterial pressure, fasting plasma glucose, total cholesterol level, hypertension, log-transformed CRP, and the use of antihypertensive and lipid-lowering drugs.

4 | DISCUSSION

In this cross-sectional study, researchers found that the TG/HDL ratio was positively and independently associated with arterial stiffness in postmenopausal women. Our findings are consistent with the results of previous studies that demonstrated that a high TG/HDL ratio has positive associations with arterial stiffness in adult populations.[13,14] A high TG/HDL ratio was significantly associated with increased arterial stiffness as measured by the cardio-ankle vascular index (>8.0) among Japanese diabetic men according to the Nagasaki Island Study.[14] In 1498, apparently healthy Chinese individuals (men n = 926 and women n = 572) participated in a routine health screening program. Wen et al[13] also found a similar positive relationship between the TG/HDL quartiles and high baPWV (>1400 cm/s) for both men and women. In a recent Japanese study, TG/HDL ratio was positively related with baPWV when the TG/HDL ratio was less than 5.6 in 912 individuals, aged 24-84 years, after adjusting for age, sex, and other potential confounding variables.[15]

This positive association between TG/HDL ratio and arterial stiffness as measured by cfPWV was also reported in adolescents and young adults, especially in obese youth among 894 children, adolescents, and young adults in the United States.[12] Consistent with previous findings in adults and adolescents, we found that high TG/HDL was significantly associated with increased arterial stiffness in postmenopausal women, suggesting that this positive association can be applied to all age-groups.

Arterial stiffness is caused by structural and functional changes within the arterial walls, resulting in increased arterial stiffness. There are plausible mechanisms for the significant association between the TG/HDL ratio and increased PWV in postmenopausal women. First, an increased TG/HDL ratio is closely associated with arterial stiffness linked to insulin resistance in postmenopausal women.[16,17] A decrease in estrogen leads to an increase in abdominal visceral fat mass, which stimulates an influx of free fatty acid to the liver and consequently influences lipid metabolism, especially increased TG and decreased HDL cholesterol levels in postmenopausal women.[6,18] Additionally, advanced glycation end products, accompanied by insulin resistance, generate reactive oxygen and nitrogen species, which stimulate binding of the glycated LDL cholesterol to the arterial intima and excessive LDL cholesterol accumulation in the arterial wall, subsequently triggering arterial stiffness.[19,20] Second, TG/HDL and arterial stiffness may be linked by a low-grade inflammation in the vessel wall. Chronic low-grade inflammation plays a crucial role in initiating and propagating the atherosclerotic process. Stimulated leukocytes release a variety of cytokines and growth factors and have an increased tendency to adhere to vascular endothelium and easily penetrate the intima, which can induce further vascular damage and increased vascular resistance.[21] Indeed, in the present study, log-transformed CRP levels gradually increased with increasing TG/HDL quartiles.

The following limitations should be considered in the interpretation of this study. First, because of the cross-sectional design, caution should be used in causal and temporal interpretations; thus, it cannot be concluded whether the TG/HDL ratio is a risk factor actively involved in the development of arterial stiffness. Further prospective research is warranted to elucidate these positive correlations between TG/HDL ratio and arterial stiffness. Second, since study participants were limited to those who visited a single hospital for health promotion screening programs and appeared to be slightly healthier than most community-based cohorts, the study population may not be representative of the general population. Third, self-reporting of lifestyle data such as smoking, alcohol consumption, and physical activity may be an information bias in this study because the answers from participants could be arbitrary and incomplete. Fourth, central obesity indicated by waist circumference or visceral fat mass is more likely to be associated with baPWV; however, waist circumference was not evaluated at the beginning of this study. Finally, arterial stiffness as baPWV was assessed instead of cfPWV in the present study. Conventionally, cfPWV has been considered an accuracy and gold standard measure of arterial stiffness.[22] However, measurement of baPWV has been widely used particularly in East Asian populations and is easier and more time-effective than conventional measurement of cfPWV. Tanaka et al[11] reported a high correlation between baPWV and cfPWV ($r = 0.73$, $P < 0.001$) in 2287 Japanese individuals. Despite these potential limitations, our study also has strengths. We believe that this is the first study to evaluate the association between serum TG/HDL ratio and arterial stiffness in apparently healthy postmenopausal women. Our study was designed to clarify the associations between serum TG/HDL ratio and arterial stiffness in postmenopausal women with natural menopause and arterial stiffness by excluding those with induced or secondary menopause and estrogen replacement therapy. Early and premature menopause women result of an abrupt loss of ovarian function or total hysterectomy has a higher risk of CVD than natural menopause women.[23,24]

5 | CONCLUSIONS

The TG/HDL ratio was positively and independently associated with arterial stiffness in postmenopausal Korean women. These findings suggest that the TG/HDL ratio, a simple, general, and economical biomarker, may be a useful surrogate indicator of arterial stiffness in postmenopausal Korean women.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTION

Tae-Ha Chung researched data and wrote the manuscript. Jae-Yong Shim contributed to the discussion and review. Yu-Jin Kwon contributed to the discussion and review. Yong-Jae Lee analyzed data and reviewed/edited the manuscript.

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