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Original Article

Triglyceride to HDL-C ratio and increased arterial stiffness in apparently healthy individuals

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Abstract: Objectives: High triglycerides and low high density lipoprotein cholesterol are important cardiovascular risk factors. Triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) has been reported to be useful in predicting cardiovascular disease. Brachial-ankle pulse wave velocity (baPWV) is a valid and reproducible measurement by which to assess arterial stiffness and a surrogate marker of atherosclerosis. However, there is limited evidence about the relationship between them. Therefore, we tested the hypotheses that TG/HDL-C is associated with baPWV in healthy individuals. Methods: Fasting lipid profiles, baPWV and clinical data were measured in 1498 apparently healthy, medication-free subjects (926 men, 572 women) who participated in a routine health screening from 2011 to 2013. Participants were stratified into quartiles of TG/HDL-C ratio. BaPWV > 1400 cm/s was defined as abnormal baPWV, Multivariable logistic regression was used to identify associations of TG/HDL-C quartiles and baPWV, after adjusting for the presence of conventional cardiovascular risk factors. Results: In both genders, we observed positive relationships between TG/HDL-C quartiles and BMI, systolic BP, diastolic BP, fasting glucose, total cholesterol, LDL-C, triglycerides, uric acid, and percentages of high baPWV. Multivariable logistic regression revealed that baPWV abnormality OR value of the highest TG/HDL-C quartiles was 1.91 (95% CI: 1.11-3.30, $P < 0.05$) and 2.91 (95% CI: 1.02-8.30, $P < 0.05$) in male and female after adjusting for age, systolic BP, diastolic BP, BMI, fasting plasma glucose, LDL-C, uric acid and estimated glomerular filtration rate when compared with the lowest TG/HDL-C quartiles. Conclusion: Increased TG/HDL-C was independently associated with baPWV abnormality in apparently healthy individuals.

Keywords: Arterial stiffness, pulse wave velocity, triglyceride to HDL-C Ratio

Introduction

The pathogenesis of atherosclerosis remains incompletely understood, but dyslipidemia is thought to play an important role [1, 2]. Increased serum concentrations of LDL-cholesterol (LDL-C) and triglycerides (TG) are recognized as risk factors for cardiovascular disease, whereas increased HDL-cholesterol (HDL-C) is considered cardioprotective [3, 4]. However, several epidemiologic studies demonstrated that the triglyceride to HDL-C ratio (TG/HDL-C) was a better predictor of atherosclerosis and cardiovascular disease than any other single lipid marker [5-8]. Previous reports have shown that TG/HDL-C correlate independently with atherosclerotic coronary artery disease among men and women [9, 10], even after adjustment for traditional risk factors, including diabetes [11]. However, the exact mechanism linking TG/HDL-C and atherosclerosis is still unclear.

Arterial stiffness represents one of the major risk factors of atherosclerosis even at an early stage of disease. Pulse wave velocity (PWV) is considered to be the 'gold standard' method for the measurement of arterial stiffness [12]. Aortic PWV has not only been reported to be a marker of vascular damage but also a significant predictor of mortality in patients with end-stage renal failure, hypertension, diabetes, and older otherwise healthy individuals, independently of known confounding factors [13-16]. In addition, Brachial-ankle PWV (baPWV), which correlates well with invasively measured aortic

Table 1. Clinical and biochemical characteristics of the male subjects

	TG/HDL-C quartiles in males				
	Q1 (< 0.77) (n = 239)	Q2 (0.77-1.18) (n = 224)	Q3 (1.19-1.86) (n = 231)	Q4 (> 1.86) (n = 232)	*P*-value
Age (years)	41 (37-48)	41 (37-50)	40 (36-48)	42 (38-49)	0.145
BMI (kg/m^2)	22.3 ± 2.9	24.1 ± 3.1	24.9 ± 3.2	25.9 ± 2.9	0.001
Systolic BP (mmHg)	115.3 ± 9.2	117.3 ± 9.6	118.5 ± 9.6	118.9 ± 9.2	0.001
Diastolic BP (mmHg)	69.9 ± 7.7	72.1 ± 8.3	73.6 ± 8.1	73.9 ± 7.6	0.001
Fasting glucose (mmol/l)	5.17 ± 0.43	5.24 ± 0.48	5.18 ± 0.45	5.32 ± 0.52	0.005
Total cholesterol (mmol/l)	5.32 ± 0.92	5.37 ± 0.97	5.52 ± 1.06	5.62 ± 1.04	0.008
LDL-C (mmol/l)	3.09 ± 0.75	3.26 ± 0.80	3.39 ± 0.81	3.18 ± 0.88	0.001
HDL-C (mmol/l)	1.57 (1.32-1.81)	1.33 (1.14-1.53)	1.15 (1.04-1.34)	1.05 (0.95-1.19)	0.001
Triglycerides (mmol/l)	0.84 (0.68-1.00)	1.27 (1.10-1.46)	1.77 (1.50-2.03)	2.77 (2.30-3.64)	0.001
Uric acid (mg/dl)	374.3 ± 75.1	391.5 ± 81.2	419.7 ± 80.5	433.4 ± 89.6	0.001
eGFR	83.9 ± 17.1	88.6 ± 16.7	92.3 ± 20.0	94.1 ± 19.9	0.001
Mean ABI	1.11 ± 0.07	1.13 ± 0.07	1.12 ± 0.06	1.12 ± 0.07	0.102
High baPWV (%)	18.8%	23.4%	28.4%	31.9%	0.007

BMI, Body mass index; BP, blood pressure; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity.

Table 2. Clinical and biochemical characteristics of the female subjects

	TG/HDL-C quartiles in females				
	Q1 (< 0.47) (n = 151)	Q2 (0.47-0.66) (n = 139)	Q3 (0.67-1.02) (n = 140)	Q4 (> 1.02) (n = 142)	*P*-value
Age (years)	39 (35-45)	40 (36-44)	40 (36-47)	44 (38-53)	0.001
BMI (kg/m^2)	21.0 ± 2.7	21.7 ± 2.7	22.9 ± 3.2	24.1 ± 3.2	0.001
Systolic BP (mmHg)	109.6 ± 10.6	113.1 ± 11.4	113.0 ± 10.1	116.4 ± 10.9	0.001
Diastolic BP (mmHg)	65.3 ± 8.2	67.2 ± 8.2	67.5± 7.7	70.1 ± 8.2	0.001
Fasting glucose (mmol/l)	4.96 ± 0.38	5.02 ± 0.38	5.12 ± 0.45	5.22 ± 0.50	0.001
Total cholesterol (mmol/l)	5.04 ± 0.99	5.05 ± 0.89	5.23 ± 0.96	5.46 ± 1.04	0.001
LDL-C (mmol/l)	2.66 ± 0.74	2.79 ± 0.66	3.00 ± 0.72	3.08 ± 0.79	0.001
HDL-C (mmol/l)	1.79 (1.51-2.06)	1.54 (1.34-1.76)	1.40 (1.25-1.63)	1.20 (1.08-1.36)	0.001
Triglycerides (mmol/l)	0.6 (0.53-0.71)	0.9 (0.74-1.02)	1.12 (0.98-1.35)	2.02 (1.61-2.6)	0.001
Uric acid (mg/dl)	279.8 ± 67.8	280.5 ± 63.3	299.5 ± 65.2	311.8 ± 76.6	0.001
eGFR	77.6 ± 15.3	81.8 ± 16.6	82.7 ± 18.4	81.1 ± 17.0	0.054
Mean ABI	1.07 ± 0.06	1.08 ± 0.08	1.07 ± 0.07	1.10 ± 0.07	0.004
High baPWV (%)	7.3%	12.8%	15.1%	26.5%	0.001

BMI, Body mass index; BP, blood pressure; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index; baPWV, brachial-ankle pulse wave velocity.

PWV, has been regarded as a conventional, reproducible and noninvasive screening tool for identifying subjects at risk of cardiovascular diseases [17].

A recent study reported that high TG/HDL-C was associated with increased arterial stiffness in diabetic Japanese men [18]. However, whether there is any relationship between TG/HDL-C and baPWV in healthy individuals is unclear. Therefore, the aim of the present study was to evaluate the relationships between TG/HDL-C and baPWV in apparently healthy Chinese adults who participated in a general medical check-up between 2011 and 2013.

Materials and methods

Study subjects

This study included 2278 participants who participated in a routine health screening examina-

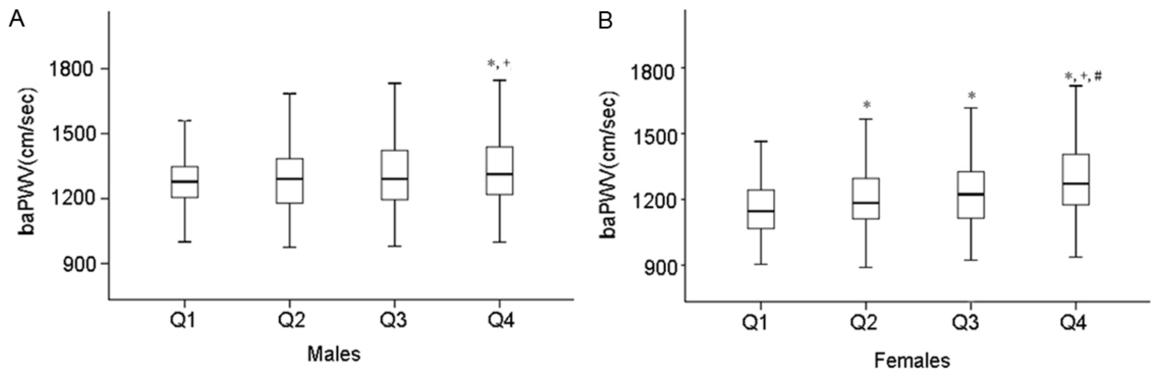

Figure 1. The box-whisker plots of baPWV according to TG/HDL-C quartiles in males and (A) in females (B). $^*P < 0.05$ vs Q1, $^+P < 0.05$ vs Q2, $^\#P < 0.05$ vs Q3.

tion at the Health Examination Centre of Jiangmen Central Hospital (GuangDong, China) from April, 2011 to August, 2013. Information including age, sex, weight, height, and history of previous diseases were collected. We excluded subjects with a history of diabetes mellitus or had a fasting glucose concentration ≥ 7.0 mmol/l, hypertension or blood pressure ≥ 140/90 mmHg, active infection, renal disease (defined as a clinical history, creatinine ≥ 150 μmol/L), or cardiovascular disease (defined as a clinical history or evidence on examination). Furthermore, those receiving lipid-lowering medication were also excluded to remove their confounding effect on dyslipidemia. After exclusion of ineligible subjects, it resulted in a final study population of 1498 apparently healthy subjects (926 men, 572 women).

Data collection

Blood pressure was measured using an automated sphygmomanometer (HBP-9021, Omron, Tokyo, Japan) after the subjects had rested for more than 5 min. Body mass index (BMI) was calculated as the ratio of weight to standing height squared (kg/m^2). Blood sample obtained from each subject in the morning after an overnight fast. Serum levels triglyceride, total cholesterol, HDL-C, LDL-C, glucose, creatinine, and uric acid were determined using standard methodology in an accredited laboratory. Estimated glomerular filtration rate (eGFR) was determined using the modified Modification of Diet in Renal Disease formula (MDRD). We classified TG/HDL-C into quartile groups as follows: Q1, < 0.77; Q2, 0.77-1.18; Q3, 1.19-1.85; Q4, ≥ 1.86 in men; Q1, < 0.47; Q2, 0.47-0.66; Q3, 0.67-1.02; Q4, ≥ 1.03 in women.

Measurement of baPWV

Brachial-ankle pulse wave velocity was used to assess arterial stiffness using an automatic device (VP-2000; Colin Co Ltd, Komaki, Japan). The subjects were examined in supine position after taking 5 minutes of rest. Pulse waves were recorded automatically by sensors in the cuffs. The transmission times and distances between the cuffs of arms and legs were recorded, then the bilateral ankle-brachial index (ABI) and baPWV were outputted. Although baPWV values were measured bilaterally, we used the higher value of baPWV in statistical analyses. In the present study, the cut-off value of high baPWV was > 1400 cm/sec for both sexes.

Statistical analysis

Continuous variables are expressed as mean and standard deviations. Skewed variables are expressed as the median value (interquartile range) and categorical variables are expressed as numbers and percentages. Comparison between groups was made using the chi-square test for categorical data and analysis of variance or the Mann-Whitney U-test for continuous data. Multivariable logistic regression was applied to evaluate the association between TG/HDL-C and baPWV, after adjusting for several potential confounders. A two-sided $P < 0.05$ was considered statistically significant. All analyses were done using SPSS statistical software, version 16.0 (SPSS, Chicago, IL, USA).

Result

The clinical and biochemical characteristics of the study population according to TG/HDL-C

Table 3. Odds ratios and 95% confidence intervals for high brachial-ankle pulse wave velocity according to TG/HDL-C quartiles

	Q1	Q2	Q3	Q4	*P*-value*
TG/HDL-C quartiles in males					
Model 1[a]	1	1.18 (0.73-1.89)	1.92 (1.21-3.04)*	2.11 (1.34-3.30)*	< 0.05
Model 2[b]	1	1.04 (0.60-1.78)	1.59 (0.93-2.74)	1.91 (1.11-3.30)*	< 0.05
TG/HDL-C quartiles in females					
Model 1[a]	1	1.85 (0.69-4.90)	1.62 (0.62-4.23)	2.77 (1.15-6.69)*	< 0.05
Model 2[b]	1	1.30 (0.42-4.01)	2.06 (0.69-6.14)	2.91 (1.02-8.30)*	< 0.05

[a]Adjusted for age; [b]Adjusted for age, BMI, systolic BP, diastolic BP, LDL-C, fasting plasma glucose, uric acid and eGFR. *$P < 0.05$ vs Q1.

quartiles are shown in **Tables 1** and **2**. In both genders, we observed positive relationships between TG/HDL-C quartiles and BMI, systolic BP, diastolic BP, fasting glucose, total cholesterol, LDL-C, triglycerides, uric acid and percentages of high baPWV and a negative relationship between TG/HDL-C quartiles and HDL-C (*P* for trend < 0.01 each).

Figure 1A, **1B** shows the distributions of the baPWV according to TG/HDL-C quartiles in males and (A) in females (B). For men, the mean baPWV in quartiles Q1, Q2, Q3 and Q4 were 1299 cm/s, 1313 cm/s, 1319 cm/s and 1331 cm/s, while for women, the mean baPWV in these four quartiles were 1173 cm/s, 1225 cm/s, 1232 cm/s and 1311 cm/s. The ends of the whisker indicate the 5th and 95th percentiles of baPWV.

Table 3 shows the risk for high baPWV according to TG/HDL-C quartiles. In multivariable logistic regression model 2, after adjusting for confounding factors, including age, systolic BP, diastolic BP, BMI, fasting plasma glucose, LDL-C, UA and eGFR. The odds ratios (ORs) consistently showed the increasing trend across the TG/HDL-C quartiles. These ORs were higher in women than in men. The highest quartile of TG/HDL-C was associated with ORs (95% CI) of 1.91 (95% CI 1.11, 3.30) and 2.91 (95% CI 1.02, 8.30) for the high baPWV among men and women, respectively.

Discussion

To our knowledge, this is the first study investigating a direct relationship between TG/HDL-C and arterial stiffness by assessment of baPWV in apparently healthy Chinese adults. A major finding of the present study was that, after controlling for other confounding factors, the TG/HDL-C was significantly associated with the increased baPWV. This positive association between them was significant both in men and in women. These data suggest that using the TG/HDL-C may be helpful in predicting increased arterial stiffness in apparently healthy individuals.

Arterial stiffness occurs as a result of structural changes in the medial layer of the elastic arteries, including fragmentation and degeneration of elastin, increase of collagen, and thickening of the arterial wall, which are potentially related to the risk of development and progression of atherosclerosis [19]. Arterial stiffness has an important, independent predictive power with respect to cardiovascular mortality, coronary events and several atherosclerotic diseases [15, 16, 20]. Thus, early detection of arterial stiffness is useful in prevention of series of major CVD. Brachial-ankle pulse wave velocity (baPWV), which reflects the elasticity of both the aorta and middle arteries, has been developed as a noninvasive and convenient index of arterial stiffness and has been reported to be correlated well with aortic PWV obtained by invasive catheter manometer [17]. Apparently healthy subjects having abnormal baPWV most likely represented those with early stage of atherosclerosis [21]. In the present study, we defined high baPWV as > 1400 cm/sec in men and women because this cut-off value is an independent variable of the risk stratification according to the Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease [22]. We observed positive association between TG/HDL-C and increased baPWV, independent of conventional cardiovascular risk factors. This association between them appeared to be stronger in women in compared to men, which may be explained by the gender differences in the cardiovascular effects of sex hormones and the percentage of smoking behavior. However, further studies are required to address these hypotheses.

To date, there is growing interest in the TG/HDL-C as an easily obtainable atherogenic marker. Gaziano firstly reported a 16-fold increase in risk of myocardial infarction in the highest compared to the lowest quartile of the TG/HDL-C distribution [23]. Subsequent studies reported that high TG/HDL-C correlate independently with presence of angiographic coronary artery disease (defined as stenosis > 50%), CHD incidence and cardiovascular death, and total mortality [8, 10, 24]. However, only limited information exists about early atherosclerosis in people with high TG/HDL-C. Recently, Yuji et al. confirmed that high TG/HDL-C was a significant risk for atherosclerosis and increased arterial stiffness, evaluated by means of carotid intima-media thickness and cardio-ankle vascular index, in diabetic Japanese men [18]. Urbina et al. reported a relationship between TG/HDL-C arterial stiffness, measured by carotid-femoral PWV, in adolescents and young adults aged 10 to 26 years [25]. However, these subjects were significantly younger and lighter than our study population. In our study, we found that the highest quartile of TG/HDL-C was independently associated with an approximately 2-fold increased risk of arterial stiffness in men, and an approximately 3-fold increase in women, as compared with the lowest quartile of the TG/HDL-C distribution. Our data suggest that apparently healthy adults with high TG/HDL-C should be considered at high risk of cardiovascular disease, even in the absence of clinical manifestation.

Several potential mechanisms may explain the link between TG/HDL-C and arterial stiffness. Insulin resistance has been found to play a significant role in the pathogenesis of cardiovascular disease and it was independently associated with baPWV even in healthy individuals [26]. Insulin resistance causes increased assembly and secretion of triglyceride-rich VLDL and decreased HDL cholesterol [27]. McLaughlin et al. suggested that TG/HDL-C ratios were able to identify insulin-resistant overweight individuals with normal glucose tolerance and are markers of insulin resistance with specificities and sensitivities similar to those for fasting plasma insulin concentration [28]. In a cross-sectional study of 6,546 Korean adults who underwent routine health examinations, the TG/HDL-C was found to be significantly associated with insulin resistance in subjects without metabolic syndrome [29]. Since the TG/HDL-C has been available as a simple clinical indicator of insulin resistance, and thus probably provide a prediction of arterial stiffening related to insulin resistance. Further more, the association between TG/HDL-C and arterial stiffness is probably linked to the small-dense LDL particles, which are thought to be more atherogenic than LDL particles of normal size. Because these small-dense LDL particles are more easily enter the vessel wall and appear to be more prone to oxidative modification, which further increases their atherogenicity [9]. Taken together, these findings suggest that a high TG/HDL-C was a clinical indicator of insulin resistance and small-dense LDL particles, and could be used to evaluate early vascular damage, but further experiments will be necessary to elucidate the exact mechanism responsible for their relationship.

Some limitations of this study must be considered. First, this study was a cross-sectional study. We performed only association analysis and could not determine any causal relationships. Second, Participants were recruited at the time of their general health examination in only one location, which may not be a true representative of the general population. Third, we could not confirm the history of cigarette smoking and menopausal status of each individual, which may confound our findings somewhat. Finally, the baPWV measurement is a composed of the flexibility of both the aorta and medium arteries. Therefore, we could not separately evaluate PWV of central and peripheral arteries. However, baPWV, which can be measured more conveniently than aortic PWV, has been reported to be correlated well with aortic PWV assessed using a direct catheter method [17].

In summary, in a sample of apparently healthy Chinese adults, we found that high TG/HDL-C was a significant risk factor for arterial stiffness (baPWV > 1400 cm/sec). The data presented in the current study suggest that keeping a normal level of TG/HDL-C should be very important for cardiovascular disease prevention.

Disclosure of conflict of interest

None.

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