Associations Between High Triglycerides and Arterial Stiffness in a Population-Based Sample: Results from the Kardiovize 2030 Study

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Research

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Abstract

**Background** The term arterial stiffness (ArSt) describes the reduced capability of an artery to expand and contract in response to pressure changes and is recognized as an independent predictor of cardiovascular diseases (CVD). The evidence relating ArSt and triglycerides (TG) shows contradictory results. The aim of this paper is to assess the association between high TG and ArSt, using the cardio-ankle vascular index (CAVI).

**Methods** Subjects aged between 25 and 64 years from a random population-based sample were evaluated between 2013–2016. Data from questionnaires, blood pressure, anthropometric measures and blood samples were collected to identify the metabolic syndrome (MetS). CAVI was measured using VaSera VS-1500N devise (Fukuda Denshi Co., Ltd., Japan). Subjects with history of CVD or chronic renal disease were excluded.

**Results** 1934 participants, 44.7% males, were included. Median age was 48 (Interquartile Range [IQR] 19) years, TG levels were 1.05 (0.793) mmol/L, and CAVI 7.24 (1.43) points. Prevalence of high CAVI was 10.0% (14.5% in males and 6.4% in females; p < 0.001). Correlation between TG and CAVI was 0.136 (p < 0.001). High CAVI values were more prevalent among participants with MetS, high blood pressure, dysglycemia, abdominal obesity, and high total cholesterol. Using binary regression analysis, high TG were associated with high CAVI, even after adjustment for other MetS components, age, gender, smoking status and cholesterol (OR = 1.630, 95% CI = 1.061–2.505, p = 0.026).

**Conclusion** TG levels were correlated with ArSt, measured as CAVI. High TG was associated with high CAVI independent of multiple cardiometabolic risk factors.

**Background:**

Cardiovascular disease (CVD) was the leading cause of mortality worldwide in 2017, with 17.9 million deaths, representing 31.8% of deaths worldwide and 49.1% in Central Europe [1], demanding an urgent call for preventive strategies, including the development of novel biomarkers related to arteriosclerosis in the early detection of possible atherosclerosis. A main factor in the development of the arteriosclerosis is arterial stiffness (ArSt) [2, 3]. ArSt describes structural changes in arterial wall related to the loss of elasticity and is a strong predictor of CVD events and all-cause mortality [2, 3]. Measuring ArSt is one of the methods of quantitative estimation of arteriosclerosis extent [4], and can be measured both invasively and non-invasively. Pulse wave velocity (PWV) is considered the “gold standard” method to assess ArSt [4, 5].

Pulse wave moves along the arterial tree faster in the stiffer tube than in the elastic one. Nevertheless, at the moment of measurement, PWV is affected by acute blood pressure (BP) changes [2], e.g., stress induced rise in BP can lead to the overestimation of PWV. The cardio-ankle vascular index (CAVI) may eliminate this limitation, by adjusting the formula for BP value [4]. Experimental studies have shown that administration of α1 and β1 adrenoreceptor blockers to reduce BP does not change CAVI values despite
the significant and acute changes in BP [6]. Majority of the studies used PWV as biomarker of ArSt [2–4, 6–9], but CAVI is easy to measure and is suitable for clinical use [4, 10]. Studies indicate that CAVI might be superior to PWV, as an ArSt parameter [2, 7].

Metabolic syndrome (MetS) is a cluster of cardiometabolic risk factors including abdominal obesity, high BP, impaired blood glucose, high triglycerides (TG), and low high density lipoprotein cholesterol (HDL-c) [11]. The presence of MetS has been related to high CAVI as a surrogate of ArSt [12–14], a higher number of MetS components were associated with higher CAVI values [12]. When MetS components are analyzed individually, high BP [12, 15–18], impaired blood glucose [12, 13, 15–17], abdominal obesity [14, 15, 19], and HDL-c [13, 14, 17, 20], were associated with ArSt, however, the association between high TG and ArSt shows contradictory results. Many studies report no association between high TG and ArSt [12–14, 17–20], and many others report positive independent association between them [8, 9, 15, 21–25]. Most of these studies are not evaluating randomly selected population-based samples [8, 12, 13, 15, 19, 20, 23], mostly including high-risk individuals [9, 17, 18, 21], older age groups [9, 15, 19, 21, 24], and adjusting for components that are not specifically designed to evaluate the association between both parameters [13, 15, 19, 23, 24]. According to the best of our knowledge, none previous study was focused specifically on providing the answer to the question if high TG are associated with ArSt.

Aim

Aim of this study is to evaluate the association between high TG and ArSt, measured by CAVI, adjusting for MetS components and other traditional risk factors, in a random population-based sample of European adults.

Methods:

Design and Population:

The study design, sampling, and implementation were described previously [26]. In brief, Kardiovize Brno 2030 is a prospective population-based study with a random stratified by sex and gender sample of 25 to 64 year-old residents of the city of Brno [26]. The recruitment and core baseline examinations were completed in 2014. Follow-up will be carried out regularly at 5-year intervals, the first one is being conducted and expected to in 2020, It is envisioned that the study will run until 2030 [26].

Brno is the second largest city in the Czech Republic (after Prague). As of 1 January 2013, Brno had a general population of 373,327 residents [27]. The study aimed to enroll 1% of the adult population of Brno randomly selected and stratified by sex and age. Eligibility criteria included permanent residence in Brno, and registration (required by the law) with any of the five state-run health insurance companies operating in the Czech Republic [26].

Sampling and Recruitment:
Survey sampling was done in January 2013 with the technical assistance from the largest (state-run) health insurance company using the registries of all health insurance companies, except one that declined to cooperate (thus excluding 8.9% of the population). A random stratified sample of 3300 persons adjusted for a response rate of 64.4% was drawn from the registries. The health insurance companies mailed invitation letters with a description of the study goals while ensuring the confidentiality of personal information. The invitation letters were mailed in January 2013, with two reminder mailings. Following the same procedure, another random sample of 3077 was selected in April 2014; the study target of 1% of the adult urban population was met on 19 December 2014. Based on the two samplings with a total of 6,377 randomly selected invitees, the overall response rate was 33.9%. No information on non-respondents was available due to confidentiality restrictions. Despite the relatively low response rate, the number of enrolled participants was large enough to ensure optimal representativeness of sociodemographic strata in the sample [26]. A total of 2160 individuals were enrolled in the study and 226 records were excluded from the present analysis due to either missing information on ArSt or MetS components, or presence of self-reported history of CVD, defined as stroke or chronic ischaemic disease, or chronic renal disease. Figure 1 summarizes recruitment of the participants and further exclusion of non-eligible records.

Data Collection:

The baseline health assessment face-to-face health interview, and comprehensive questionnaire was performed by trained nurses and physicians at the International Clinical Research Center of the St Anne's University Hospital in Brno, who also entered the collected data into the web-based research electronic data capture (REDCap) database. The questionnaire included demographics, socioeconomic status (age, gender, education, household income, and occupation), cardiovascular risk behaviors (smoking status, nutrition, alcohol consumption, and physical activity), history (family and personal, medications, and hospitalizations), mental health (depression, stress level) and a food frequency questionnaire. CAVI was measured using VaSera VS-1500N device (Fukuda Denshi Co., Ltd., Japan). Laboratory analyses were performed with 12-hour fasting blood samples. TG levels were assessed by a well-established enzymatic calometric method (Roche Diagnostics GmbH, Germany), using a Modular SWA P800 analyzer (Roche, Basel, Switzerland). Blood pressure was measured with the patient alone using an automated office measurement device (BpTRU, model BPM 200; Bp TRU Medical Devices Ltd., Canada). Smokelyzer (Micro Smokerlyzer; BedFont Scientific Ltd., UK) was used to determine the amount of carbon monoxide in expired breath in order to validate self-report smoking status. The anthropometric assessment included height and weight measurements using a medical digital scale with meter (SECA 799; SECA, GmbH and Co. KG, Germany) and manual tape measurement of waist, hip, and neck circumference [26].

Definition of Variables:

MetS was defined as simultaneous presence of 3 or more of the following components: elevated TG level $\geq$ 1.7 mmol/l, or treatment with fibrates or nicotinic acid; low HDL level (< 1 mmol/l in men and < 1.3 mmol/l in women), or treatment with fibrates or nicotinic acid; previously diagnosed diabetes
mellitus, treatment of elevated glucose, or fasting plasma glucose ≥ 5.6 mmol/l; systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg or treatment of elevated BP; presence of abdominal obesity, identified as high waist circumference ≥ 94 cm in men and ≥ 80 in women [11].

CAVI is defined as stiffness derived from the β coefficient, obtained from the Bramwel-Hill equation:

$$\beta = 2\rho \frac{1}{Ps - Pd} ln \frac{P_s}{P_d} PWV$$

Where PWV is pulse wave velocity, ρ is blood density, Ps and Pd are systolic and diastolic BP values in mmHg [4]. High CAVI group was defined as those subjects with ≥ 9 points and normal as those with CAVI < 9, based on the presence of advance arteriosclerosis [4–6, 28–32]. Levels of carbon monoxide in the expired breath < 10 ppm were compatible with the definition of non-smoker. Smoking status was divided into: never smoker as those having smoked fewer than 100 cigarettes in a lifetime; former smokers as those having stopped smoking in the past year; current smokers as those smoking either daily or less than daily in the past year, and smoker-liar as those who reported to smoke less than 100 cigarettes through his/her life, denied passive smoking, but his/her Smokelyzer values were ≥ 10 [26].

**Statistical analysis**

Analyses were performed using the SPSS software (SPSS, version 23.0, Armonk, NY: IBM Corp.). Kolmogorov-Smirnov test was conducted in order to assess the normality of the continuous variables. Variables were non-normally distributed and presented as median (interquartile range), their differences were evaluated using Mann-Whitney U test. Correlation Spearman analysis between TG and CAVI was assessed. Proportions were presented as percentage and differences were determined by χ² test. Univariate analysis was used to assess risk factors related with CAVI as a binary outcome (High ≥ 9 or normal < 9) and was presented as OR and 95% CI. A multivariate analysis was done using CAVI as a binary outcome and TG as a dichotomic variable (high ≥ 1.7 mmol/l and normal < 1.7 mmol/l), and adjusted by multiple confounders (See Directed Acyclic Graph in Supplementary files). In model 1 by age and gender, and in subsequent models by high waist circumference, elevated fasting glucose, systolic and diastolic BP levels, HDL values, smoking status, and total cholesterol. In multicollinearity test with CAVI as outcome, the values of the variance inflation factors in these models were ≤ 4.0. Statistical significance was considered p < 0.05.

**Results:**

Subject characteristics

In total 1934 participants were included (Fig. 1). Participants were 44.7% males, median age of 48 (19) years (Table 1). Men had higher BP, blood glucose, TG, waist circumference, and CAVI than women, but lower age, HDL-c and total cholesterol. TG and CAVI were 1.0 (0.7) and 7.2 (1.4), respectively, and were significantly and positively correlated (r = 0.136; p < 0.001).
### Table 1
Characteristics of subjects by gender

| Variables                    | All          | Male          | Female        | p          |
|------------------------------|--------------|---------------|---------------|------------|
| n (%)                        | 1934 (100.0) | 864 (44.7)    | 1070 (56.3)   |            |
| Age (years)                  | 48.0 (19.0)  | 46.5 (20.0)   | 49.0 (20.0)   | 0.002      |
| Systolic blood pressure (mmHg) | 118.4 (19.6) | 121.2 (17.6) | 115.6 (19.4) | < 0.001    |
| Diastolic blood pressure (mmHg) | 79.4 (12.6)  | 82.2 (12.0)   | 77.0 (11.8)   | < 0.001    |
| Fasting plasma glucose (mmol/L) | 4.9 (0.7)    | 5.0 (0.7)     | 4.8 (0.7)     | < 0.001    |
| Triglycerides (mmol/L)       | 1.0 (0.7)    | 1.2 (0.9)     | 0.9 (0.6)     | < 0.001    |
| HDL – Cholesterol (mmol/L)   | 1.4 (0.5)    | 1.3 (0.3)     | 1.6 (0.4)     | < 0.001    |
| Waist Circumference (cm)     | 88.0 (20.0)  | 95.0 (17.0)   | 82.0 (18.0)   | < 0.001    |
| CAVI                         | 7.2 (1.4)    | 7.3 (1.5)     | 7.1 (1.3)     | < 0.001    |
| Total Cholesterol (mmol/L)   | 5.1 (1.3)    | 5.0 (1.3)     | 5.1 (1.3)     | 0.007      |

Data are presented as median (Interquartile range) and differences were assessed using Mann-Whitney U test.

**Associations between CAVI and Triglycerides**
The prevalence of high CAVI was 10.0%, higher in men than women, 14.5% and 6.4% (p < 0.001), respectively (Table 2). The prevalence of MetS was 23.2%, higher in men than in women, 28.9% and 18.7% (p < 0.001), respectively. Subjects with high CAVI were more likely to have MetS (OR = 3.6, 95% CI 2.70–4.96), high TG (OR = 2.5, 95% CI 1.86–3.51), abdominal obesity (OR = 2.2, 95% CI 1.58–3.06), dysglycemia (OR = 3.5, 95% CI 2.58–4.98), high BP (OR = 7.0, 95% CI 4.81–10.19), and high total cholesterol (OR = 1.7, 95% CI 1.32–2.43). High CAVI was more prevalent in males (OR = 2.4, 95% CI 1.80–3.34) and increasing with age. Among others, age older than 45 years and elevated BP were the risk factors associated with the higher chance of high CAVI. Smoking status and low HDL-c were not related to high CAVI (Table 2).
Table 2
Prevalence of high CAVI and risk factors related using a Univariate Analysis

|                          | High CAVI (%) | OR  | 95% CI          | p       |
|--------------------------|--------------|-----|-----------------|---------|
| All subjects             | 10.0         |     |                 |         |
| Age 25–44/Age 45–64      | 1.1 /17.1    | 19.2| 9.78–37.79      | < 0.001 |
| Male/Female              | 14.5 /6.4    | 2.4 | 1.80–3.34       | < 0.001 |
| MetS                     | 20.9         | 3.6 | 2.70–4.96       | < 0.001 |
| Without MetS             | 6.7          | 1.0 |                 |         |
| High TG                  | 18.2         | 2.5 | 1.86–3.51       | < 0.001 |
| Normal TG                | 8.0          | 1.0 |                 |         |
| Abdominal Obesity        | 12.9         | 2.2 | 1.58–3.06       | < 0.001 |
| Without Abdominal obesity| 6.3          | 1.0 |                 |         |
| Dysglycemia              | 23.1         | 3.5 | 2.58–4.98       | < 0.001 |
| Without Dysglycemia      | 7.7          | 1.0 |                 |         |
| Low HDL                  | 10.2         | 1.0 | 0.66–1.58       | 0.911   |
| Normal HDL               | 10.0         | 1.0 |                 |         |
| High BP                  | 19.1         | 7.0 | 4.81–10.19      | < 0.001 |
| Normal BP                | 3.3          | 1.0 |                 |         |
| Smoker                   | 12.0         | 1.3 | 0.94–1.80       | 0.133   |
| Non-Smoker               | 9.5          | 1.0 |                 |         |
| High TC                  | 12.8         | 1.7 | 1.32–2.43       | < 0.001 |
| Normal TC                | 7.5          | 1.0 |                 |         |

Abbreviations:

OR, odds ratio; CI, confidence interval; MetS, metabolic syndrome; TG, triglycerides; HDL, HDL cholesterol; BP, blood pressure; TC, total cholesterol. Proportions were presented as percentage and differences were determined by $\chi^2$ test. Univariate analysis was used to assess risk factors related with CAVI as a binary outcome (High $\geq$ 9 or normal $\leq$ 9) and was presented as OR and 95% CI. Risk factors are presented as dichotomic variables. To estimate the OR past smokers with non-smokers were merged into a Non-smoker category; smokers and smokers-liars were merged into current Smoker category.
Three models were created to assess the association between high TG and high CAVI (Fig. 2). In the model 1, adjusting by age and gender, subjects with high TG had 70% higher odds of having high CAVI than those with normal TG (OR = 1.703, 95% CI = 1.188–2.442, p = 0.004). In the model 2, adjusted by age, gender and individual components of MetS the odds of having high CAVI were 62% (OR = 1.622, 95% CI = 1.083–2.428). Finally, in the model 3, adding smoking status and total cholesterol to model 2, the odds of having high CAVI remained 63% (OR = 1.630, 95% CI = 1.061–2.505).

Discussion:

To the best of our knowledge, this may be the first analysis specifically designed to address the question if high TG are associated with ArSt, where previous reports show contradictory results. Using a randomly selected large population-based sample, high TG (≥ 1.7 mmol/l) increased the odds of having high CAVI (≥ 9) by 63%, independent of multiple confounding variables as age, gender, MetS components, total cholesterol, and smoking habits. The prevalence of high CAVI was 10.0% and was associated with male gender, higher age, high BP, dysglycemia, abdominal obesity, and total cholesterol, but not related to smoking and low HDL-c.

Consistent with this result, in Japan [23], in 23,257 urban residents, aged 47.1 ± 12.5 years, odds of having a high CAVI (≥ 90th percentile) per 1-standard deviation increment of TG were almost double (OR = 1.9, 95% CI = 1.81–1.99). In this population, a cut-off value of TG 1.05 mmol/l was more sensitive and specific predicting high CAVI (OR = 2.43, 95 CI 2.14–2.75) than the threshold, currently used in clinical practice (1.7 mmol/l) [11, 23]. In China [8], in 16,733 adults from the southern part of the country, aged 18 or older, subjects with high TG (≥ 1.7 mmol/l) and LDL-c below 1.8 mmol/l were 144% times more likely to have high PWV in comparison to subjects with normal TG and low LDL-C (OR = 2.44, 95% CI = 1.61–3.71) [8]. In 14,071 hypertensive patients from Jiangsu and Anhui Provinces of China [9], with the mean age of 64.4 ± 7.4 years, the association between TG and PWV, remained significant even after adjusting the results for gender, age, BMI, fasting blood glucose, smoking, alcohol consumption, BP, medical treatment etc. (β = 0.54, 95% CI = 0.44–0.65, p < 0.001) [9]. In a prospective observational study assessing 1,447 community-based residences from Beijing [24], followed by 4.8 years, baseline TG was strongly correlated with ArSt during the follow-up evaluation (carotid femoral PWV; β = 0.747, 95% CI = 0.394–1.100, p < 0.001 and carotid-radial PWV; β = 0.367, 95% CI = 0.140–0.593, p = 0.002). Moreover, changes in TGs were directly associated with changes in PWV, every standard deviation increase in TG levels between baseline and follow-up was associated with 29% higher risk for increased change in the PWV between baseline and follow-up (OR = 1.296, 95% CI = 1.064–1.580, p = 0.010) [24]. In Spain [15], in 2351 subjects with the mean age of 61.4 ± 7.7, all MetS components, except HDL-c, were associated with CAVI. TG values were significantly and positively related to CAVI using multivariate linear regressions models (r2 = 0.351; p = 0.002) [15].

On the contrary, in 18 countries from Europe [19], assessing 2224 subjects, aged 40 and older, PWV was higher in subjects with MetS compared with those without (9.57 ± 0.06 vs 8.65 ± 0.10; p < 0.001), but CAVI
was similar in those two groups (8.34 ± 0.03 vs 8.29 ± 0.04; p = 0.40). In the multivariate analysis, PWV was positively correlated with age, BP, glucose and HDL-c, but not with waist circumference and TG; CAVI was positively correlated with age, gender, BP, glucose, but not with TG and HDL, and negatively correlated with waist circumference. Authors don’t provide a clear explanation with contradictory results relating waist circumference and CAVI [19]. In a prospective evaluation of 2106 middle aged subjects with MetS from Lithuana [17], high CAVI values at the baseline was related with higher risk for CVD events after around four years. At the baseline, high CAVI values were related to worse cardiometabolic profile, but not with TG value (p = 0.891) [17]. In Korea, in 1144 adults, older than 18 years from Gyeonggi [12], assessing the association between MetS and CAVI reported that CAVI was independently related with age, sex, diastolic BP, and uric acid, but not with waist circumference, plasma glucose, HDL-c, and TG [12]. In two Chinese population studies [13, 20], TG were significantly correlated with CAVI, but this association disappeared after multiple adjustments.

Discrepancies between results of the studies might be partially explained by the differences in the population sample sizes, inclusion criteria for the subject’s recruitment, way of ArSt quantification or the variety of adjustment variables. Studies, performed on large population samples tended to observe positive association between ArSt and TG, however, some of them used PWV as an ArSt marker [8, 9, 24]. Also, studies that failed to find an association between TG and ArSt, were often conducted on the population samples with MetS [17, 19] or diabetes [18], meanwhile studies that are indicating positive relationship included mostly healthy subjects [9, 22, 25]. More prospective studies are needed, in order to clarify the risk of elevated TG and it’s effect on the arterial wall state.

The whole spectrum of possible underlying pathophysiological mechanisms of the influence of lipid profile on ArSt has not been well established yet. However, abnormal lipid profile simultaneously influences several pathways – development of atherosclerotic plaques, oxidative stress, inflammation enhancement, endothelial dysfunction and low availability of nitric oxide [33]. From the point of view of atherosclerosis and CVD, there are four main mechanisms which can indirectly increase CVD risk. First, hydrolysis of postprandial chylomicrons or endogenously formed VLDL leads to further formation of cholesterol-rich remnants, which can enter the subendothelial space through the scavenger receptors and promote formation of the foam-cells [23]. Second, higher Apolipoprotein (Apo) CIII might also have an impact on the metabolism of TGs, through inhibition of TG hydrolysis and increased formation of dense, oxidation-prone low density lipoprotein particles [9, 34]. Liver fat mass was also directly associated with the amount of secreted very low density lipoprotein [34]. Third, high TG might disrupt the mechanism of reverse cholesterol transport [34]. Fourth, in vitro analysis indicates that high TG might also stimulate expression of endothelial mediators, such as endothelin-1, promoting endothelial dysfunction [23].

The main limitation of the present report is that the cross-sectional design doesn’t allow to establish causality between TG and ArSt. Independent association between TG and CAVI as continuous variables was not reported, because the assumptions of linear regression analysis were not met. The future prospective results of this study will allow us to examine the predictive value of lipid profiles on ArSt.
Conclusion

TG levels were correlated with ArSt, measured as CAVI. High TG were associated with high CAVI independently of age, gender, and the presence of additional MetS components, smoking status and total cholesterol. This result highlights the negative influence of high TG in the process of atherosclerosis.

Declarations

Ethics Approval:

Study protocol complied with the Helsinki declaration and all participants signed the informed consent. The Kardiovize Brno 2030 was approved by the ethics committee of St Anne’s University Hospital, Brno, Czech Republic (reference number 2 G/2012) [26].

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

PI, GRJP, MIJR, LJF, SGB contributed to the conception or design of the work. PI, GRJP, JJ, HJ, KS, SM, RSIM, MI JR, LJF, VR, GYE and SGB contributed to the acquisition, analysis, or interpretation of data for the work. PI and GR JP drafted the manuscript. All gave the final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Figures
Figure 1

Flow chart of the recruitment, baseline data collection and selection of participants for the analysis
Figure 2

Binary regression models associating high TG $\geq 1.7$ mmol/l and high CAVI $\geq 9$. * adjusted by age and gender. ** adjusted by age, gender, high waist circumference $\geq 80$ cm in females and $\geq 94$ cm in males, elevated fasting glucose $\geq 5.6$ mmol/l or treatment, systolic and diastolic BP levels, HDL values. *** as model 2, further adjusted by smoking status (4 categories) and TC levels. Abbreviations: BP – blood pressure, CAVI – cardio-ankle vascular index, CI – confidence interval, HDL – HDL cholesterol, OR – Odds ratio, TC – total cholesterol, TG – triglycerides

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