DIABETES, LIPIDS AND METABOLISM

Triglyceride level is associated with wave reflections and arterial stiffness in apparently healthy middle-aged men

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Objective: To investigate the relationship of arterial stiffness and wave reflections, which are predictors of cardiovascular risk, with serum triglyceride level in healthy adults.
Design: Cross-sectional study at the University Department of Cardiology. 213 healthy individuals (141 men and 72 premenopausal women) not taking any medication and without known cardiovascular disease and risk factors, except for smoking.
Main outcome measures: Central (aortic) augmentation index (AIx, a composite measure of arterial stiffness and wave reflections), fasting lipid profile (including triglycerides) and 10-year Framingham Risk Score (FRS).
Results: Compared with women, men had higher serum triglyceride level (median (interquartile range) (89 (67–117) vs 73 (54–96) mg/dl, $p<0.01$) and lower AIx (17.7 (1.0) vs 26.3 (1.4), $p<0.001$). In both genders, serum triglyceride levels were significantly associated with FRS (men: $r=0.43$, $p<0.001$; women: $r=0.37$, $p<0.01$) and AIx (men: $r=0.21$, $p<0.05$; women: $r=0.26$, $p<0.05$). In men, multivariate linear regression analysis showed an association between triglyceride level and AIx (standardised β coefficient = 0.19, $p=0.009$), independent of age, blood pressure, heart rate, height, weight, smoking habits, total cholesterol and HDL-cholesterol levels. On the other hand, in women, the unadjusted correlation between triglyceride level and AIx was largely explained when the abovementioned confounders were taken into account ($\beta=-0.016$, $p=0.86$).
Conclusion: In healthy men, serum triglyceride levels are associated with indices of arterial stiffness and wave reflections, which are important determinants of cardiovascular function and risk. The role of triglycerides in the vascular function of women warrants further investigation.

Although the association of triglycerides (TGLs) with cardiovascular disease has been debated, accumulating evidence suggests that hypertriglyceridaemia may indicate an independent increased risk of atherosclerotic disease.[1] A subclinical impairment of arterial elastic properties often precedes overt atherosclerotic disease and predicts the corresponding risk.[2] The clinical significance of arterial performance is further highlighted by the recent Conduit Artery Function Evaluation study, which showed that a beneficial alteration of central (aortic) haemodynamics and wave reflections is independently related to reduced cardiovascular outcomes.[3] In the present study we investigated the relationship of the central (aortic) augmentation index (AIx), a composite measure of arterial stiffness and wave reflections, with fasting serum TGL level in healthy adults.

METHODS

We studied 213 healthy individuals (141 men and 72 premenopausal women) without known cardiovascular disease and risk factors, except for smoking. They were clinically well and were not taking any medication. Venous blood was drawn and arterial function studies were performed after an overnight fast in all participants. Total cholesterol, high-density lipoprotein (HDL)-cholesterol and TGL levels were measured using standard methods. The 10-year risk of atherosclerotic disease was calculated using the Framingham Risk Score (FRS).

AIx of the central (aortic) waveform was measured as an index of wave reflection. AIx is a determinant of left ventricular afterload. Higher values of AIx indicate increased wave reflections from the periphery and/or earlier return of the reflected wave as a result of increased arterial stiffness.[2] Tr represents the time to the merging point of the incident and reflected wave, and is inversely correlated with arterial stiffness. AIx and Tr were measured using a validated, commercially available system (Sphygmocor, AtCor Medical, Sydney, Australia) as we have described previously. The protocol was approved by our institutional research ethics committee and all subjects gave written informed consent.

RESULTS

Between the two genders, there were no significant differences (p = NS by unpaired t test) with regard to age (mean (SE) (41.6 (0.7) years in men vs 41.0 (1.0) years in women), resting heart rate (66.6 (0.8) vs 66.5 (0.9) beats/min), incidence of smoking (61% vs 50%) or serum cholesterol level (196 (3) vs 191 (5) mg/dl). On the other hand, men had higher weight (84.0 (0.9) vs 63.9 (1.3) kg, $p<0.001$), body mass index (26.7 (0.3) vs 24.1 (0.5) kg/m^2, $p<0.001$), systolic blood pressure (122.1 (1.0) vs 108.3 (1.6) mm Hg, $p<0.001$), diastolic blood pressure (75.1 (0.7) vs 64.9 (1.4) mm Hg, $p<0.001$), serum TGL level (median (interquartile range) (89 (67–117) vs 73 (54–96) mg/dl, $p<0.01$) total cholesterol/HDL-cholesterol ratio (4.7 (0.1) vs 4.1 (0.2), $p<0.001$), FRS (3.4 (0.2) vs −2.1 (0.9), $p<0.01$) and lower HDL-cholesterol level (43 (1) vs 50 (2) mg/dl, $p<0.001$). In women, AIx was higher (26.3 (1.4) vs 17.7 (1.0) in men, $p<0.001$) and Tr was lower (143 (2) vs 154 (1) msec, $p<0.001$) compared with men. In both genders, serum TGL levels (after logarithmic transformation) were significantly associated with FRS (men: Pearson's $r=0.43$, $p<0.001$; women: $r=0.37$, $p<0.01$).

Abbreviations: AIx, augmentation index; FRS, Framingham Risk Score; HDL, high-density lipoprotein; TGL, triglyceride

Table 1 Regression coefficients b and their SEs, standardised coefficients β and p values after linear regression analysis evaluating the association of augmentation index (dependent variable) with serum triglycerides in men and women, after adjusting for potential confounders

	Men (n = 141)			Women (n = 72)		
Independent variables	**b (SE)**	**β**	**p Value**	**b (SE)**	**β**	**p Value**
Age (years)	0.49 (0.10)	0.34	<0.001	0.72 (0.13)	0.50	<0.001
Mean blood pressure (mm Hg)	0.39 (0.08)	0.33	<0.001	0.12 (0.07)	0.13	0.08
Heart rate (beats/min)	−0.47 (0.07)	−0.40	<0.001	−0.46 (0.10)	−0.29	<0.001
Smoking (pack-years)	0.15 (0.04)	0.21	0.001	0.09 (0.06)	0.12	0.12
Height (cm)	−0.17 (0.12)	−0.10	0.16	−0.56 (0.17)	−0.27	0.001
Weight (kg)	−0.21 (0.08)	−0.20	0.006	−0.05 (0.09)	0.05	0.54
Total cholesterol (mg/dl)	0.01 (0.02)	0.04	0.51	0.04 (0.03)	0.13	0.16
HDL-cholesterol (mg/dl)	0.03 (0.08)	0.02	0.76	−0.16 (0.08)	−0.16	0.046
Log TGL (mg/dl)	10.49 (3.98)	0.19	0.009	−1.02 (5.76)	−0.016	0.86
Adjusted R^2	0.55			0.71		

HDL, high-density cholesterol; TGL, triglyceride.
TGL values were log-transformed before the analysis because of skewed distribution.

In men, TGL levels correlated with AIx ($r = 0.21$, $p<0.05$) and Tr ($r = -0.20$, $p<0.05$). In a subsequent multivariate linear regression model, we investigated the association of AIx (dependent variable) with TGL level after adjusting for potential confounding factors (independent variables) such as age, blood pressure, heart rate, height, weight, intensity of smoking (pack-years), total cholesterol and HDL-cholesterol levels. In this model, TGL levels were independently associated with AIx (table 1). However, in women, although TGL levels were also correlated with AIx ($r = 0.26$, $p<0.05$), multivariate analysis indicated that this was not an independent association (table 1).

DISCUSSION

Our study demonstrates an independent association between fasting TGL and AIx in apparently healthy middle-aged men, but not in women. Thus, our results imply that in men, increased—albeit within the normal range—TGL level may coexist with increased arterial wave reflections and left ventricular afterload. This finding may be clinically relevant, in as much as TGLs emerge as a marker of wave reflections. Wave reflections are involved in the pathogenesis of systolic hypertension, predict cardiovascular risk[2] and, importantly, represent an excellent independent therapeutic target.[3] The present study denotes that in men, enhanced wave reflections may mediate, at least partly, the estimated cardiovascular risk that accompanies high TGL level. In our population, we observed a significant correlation between TGL and FRS, and the prognostic role of TGL has been emphasised by prospective studies showing that TGL levels predict cardiovascular outcomes. Moreover, reduction of TGL level with treatment results in a decreased incidence of hard cardiovascular end points.[4] However, although this association between AIx and TGL is independent of other parameters that are well known to explain the variation of AIx, the present study does not prove any cause-and-effect relationship.

On the other hand, AIx did not correlate with TGL level in women, despite a significant correlation between TGL and FRS; reasons for this lack of association may include short stature, which causes an earlier return of the reflected wave and tends to increase AIx. An interaction between TGL and gender in predicting arterial elastic properties has also been reported in other studies that included premenopausal women. Inferences regarding the possible mediation of TGL-associated cardiovascular risk by wave reflections in premenopausal women are less clear. This is further supported by the discordance between AIx and FRS (high AIx but low FRS) and the lack of significant independent association of AIx with traditional risk factors such as smoking in our premenopausal female population.

Recently, an absence of association between AIx and TGL was reported in a subpopulation of the Framingham Heart Study.[5] However, >60% of the participants were women and gender-specific analysis was not performed.

Regarding the mechanisms underlying the relationship between TGL and risk, it has been reported that TGL may generate reactive oxygen species, induce insulin resistance and thus influence several proatherogenic signalling pathways. Importantly, TGL level is associated with smaller low-density lipoprotein particles, which are more atherogenic.[6] Regarding vascular function, increased TGL levels are accompanied by abnormal arterial smooth muscle and endothelial vasodilatory response.[7]

In conclusion, in healthy men, serum TGL, an inexpensive, readily available and widely used test, is associated with wave reflections and arterial stiffness, which are important determinants of cardiovascular function and risk. The role of TGL in the vascular function of women warrants further investigation.

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