SCIENTIFIC LETTER

Fasting hypertriglyceridaemia increases carotid intima–media thickness and impairs coronary microvascular functions in non-obese middle aged women but not in men

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The effect of triglyceride concentration on coronary artery disease risk has long been controversial. In this study, we investigated possible effects of hypertriglyceridaemia on carotid intima–media thickness (IMT) and coronary flow reserve (CFR), and thereby coronary microvascular functions in otherwise healthy hypertriglyceridaemic patients and healthy controls with normal triglyceride concentration.

METHODS

Forty six patients with increased triglyceride concentrations (mean age 41.4 (6.9) years; serum triglyceride concentration $\geqslant$ 1.7 mmol/l) and 46 healthy volunteers with normal cholesterol and triglyceride concentrations (mean age 40.9 (8.4) years; serum triglyceride concentration $<$ 1.7 mmol/l) were studied. Inclusion criteria were good health and being free of coronary risk factors. All of the women were premenopausal and on a regular menstrual cycle. Patients with ECG changes suggesting coronary artery disease, total cholesterol $>$ 5.2 mmol/l, high density lipoprotein (HDL) cholesterol $<$ 0.78 mmol/l, low density lipoprotein cholesterol $>$ 4.16 mmol/l, triglyceride $>$ 4.56 mmol/l, vasoactive drug use within two weeks, family history of coronary artery disease, and body mass index $>$ 30 kg/m^2 were excluded. Also excluded were current smokers and patients who drank alcohol, had hypertension, or had diabetes mellitus. The institutional ethics committee approved the study protocol and each participant provided written informed consent.

A high resolution 7.5 MHz linear array transducer (attached to an EUB 6500; Hitachi, Tokyo, Japan) were used to scan the two common carotid arteries longitudinally. Images were obtained from the far wall of the common carotid artery 1–2 cm proximal to the carotid bulb and stored on S-VHS videotape. IMT was measured as the distance from the main edge of the first bright echogenic line to the main edge of the second one.[1] Each measurement was repeated three times and averaged. The same observer blinded to the clinical and biochemical data recorded all the scans.

A high resolution transducer with second harmonic capability (5V2c, attached to a Sequoia C256 echocardiography system; Acuson Corp, Mountain View, California, USA) was used to visualise the distal left anterior descending coronary artery in a modified, foreshortened two chamber view obtained by sliding the transducer on the upper part and medially from an apical two chamber view. Subsequently, coronary flow in the distal left anterior descending artery was examined by colour Doppler flow mapping with the colour Doppler velocity set in the range of 8.9–24.0 cm/s.[2] Coronary diastolic peak velocity was measured at baseline and after dipyridamole infusion (0.56 mg/kg over four minutes) by averaging the highest three Doppler signals for each measurement. CFR was defined as the ratio of hyperaemic diastolic mean peak flow velocity (DPFV) to baseline DPFV.[2] Images were recorded on VHS videotapes. Two echocardiographers blinded to the clinical data analysed the records off line.

For comparisons Student's *t* test or Mann-Whitney U test were used and for correlation analyses Pearson or Spearman's analyses were used as appropriate. Linear regression analysis was used for multivariate analyses. A probability value of $p < 0.05$ was regarded as significant.

RESULTS

The two groups were similar in demographic, clinical, and biochemical characteristics (table 1). HDL cholesterol concentration was significantly lower in hypertriglyceridaemic patients than in controls (1.05 (0.26) *v* 1.34 (0.30) mmol/l, $p < 0.01$). Carotid IMT was higher in hypertriglyceridaemic patients than in controls (0.54 (0.1) *v* 0.49 (0.1) mm, $p = 0.03$). CFR was significantly lower in hypertriglyceridaemic patients than in controls (2.8 (0.6) *v* 3.1 (0.7), $p = 0.03$). Hyperaemic DPFV was lower in hypertriglyceridaemic patients than in controls (66.2 (14.7) *v* 72.8 (17.2) cm/s, $p = 0.04$). However, the two groups were similar in baseline DPFV. Left ventricular mass index (LVMI) and systolic and diastolic functions were similar in the two groups.[3] Serum triglyceride concentration correlated inversely with HDL cholesterol ($r = -0.363$, $p < 0.01$).

In the whole study group (n = 92) IMT significantly correlated with age ($r = 0.389$, $p < 0.01$), systolic blood pressure ($r = 0.412$, $p < 0.01$), diastolic blood pressure ($r = 0.394$, $p < 0.01$), triglyceride concentration ($r = 0.289$, $p < 0.01$), and LVMI ($r = 0.423$, $p < 0.01$), but not with HDL cholesterol concentration. CFR was significantly inversely correlated with age ($r = -0{,}445$, $p < 0.01$), systolic blood pressure ($r = -0.223$, $p = 0.03$), triglyceride concentration ($r = -0.238$, $p = 0.02$), LVMI ($r = -0.208$, $p = 0.04$), and high sensitive C reactive protein concentration ($r = -0.295$, $p < 0.01$), but not with HDL cholesterol concentration. Linear regression analysis showed that triglyceride concentration was an independent predictor of increased IMT ($\beta = 0.247$, $p < 0.01$) but not of CFR.

The 49 women were divided into two subgroups of 22 with hypertriglyceridaemia and 27 with normotriglyceridaemia. HDL cholesterol was lower in hypertriglyceridaemic women (1.08 (0.30) *v* 1.40 (0.24) mmol/l, $p < 0.01$). Carotid IMT was greater in hypertriglyceridaemic women than in normotriglyceridaemic women (0.55 (0.10) *v* 0.46 (0.09) mm, $p < 0.01$). Baseline DPFV was similar; however, hyperaemic DPFV was lower in hypertriglyceridaemic than in normotriglyceridaemic

Abbreviations: CFR, coronary flow reserve; DPFV, diastolic mean peak flow velocity; HDL, high density lipoprotein; IMT, intima–media thickness; LVMI, left ventricular mass index

Table 1 Demographic, biochemical, and study characteristics of the two groups

	All subjects		Women		Men	
	High TG (n = 46)	Control (n = 46)	High TG (n = 22)	Control (n = 27)	High TG (n = 24)	Control (n = 19)
Age (years)	41.4 (6.9)	40.9 (8.4)	41.8 (6.7)	40.1 (8.2)	41.0 (7.1)	42.2 (8.6)
Body mass index (kg/m^2)	27.1 (2.6)	26.0 (2.9)	27.6 (2.6)	26.1 (2.8)	26.6 (2.5)	25.8 (2.6)
Total cholesterol (mmol/l)	4.68 (0.42)	4.73 (0.48)	4.69 (0.50)	4.75 (0.36)	4.67 (0.33)	4.69 (0.65)
HDL cholesterol (mmol/l)	1.05 (0.26)**	1.34 (0.30)	1.08 (0.30)**	1.40 (0.24)	1.04 (0.22)	1.24 (0.38)
LDL cholesterol (mmol/l)	2.95 (0.58)	2.95 (0.41)	2.99 (0.62)	2.97 (0.36)	2.91 (0.56)	2.92 (0.49)
TG (mmol/l)	2.22 (0.36)**	0.95 (0.26)	2.16 (0.35)**	0.90 (0.22)	2.28 (0.37)**	1.05 (0.29)
Glucose (mmol/l)	5.04 (0.47)	5.14 (0.37)	90.5 (9.3)	93.7 (7.2)	5.10 (0.43)	5.11 (0.35)
Haemoglobin (g/l)	142 (12)	141 (12)	134 (9)	134 (10)	149 (9)	151 (5)
hsCRP (mg/l)	2.4 (1.7)	2.0 (1.6)	3.0 (1.9)	2.2 (1.7)	1.8 (1.3)	1.7 (1.3)
LVEF (%)	67.7 (3.3)	69.0 (3.3)	67.7 (3.3)	69.0 (3.3)	67.9 (3.3)	68.2 (2.9)
LVMI (g/m^2)	87.6 (16.9)	85.0 (17.0)	87.6 (16.9)	85.0 (17.0)	91.1 (18.7)	92.3 (13.8)
Mitral E:A	1.25 (0.12)	1.28 (0.13)	1.19 (0.09)	1.22 (0.08)	1.26 (0.11)	1.37 (0.11)
Baseline HR (beats/min)	76.2 (10.1)	72.6 (10.1)	78.8 (11.4)	76.5 (12.10	72.3 (9.0)	67.2 (5.5)
Baseline SBP (mm Hg)	126.4 (14.3)	125.4 (16.8)	127.0 (13.8)	125.6 (15.5)	125.9 (15.0)	125.0 (19.4)
Baseline DBP (mm Hg)	74.2 (10.1)	75.0 (8.4)	78.2 (7.3)	78.5 (5.9)	78.3 (6.5)	80.0 (11.6)
Peak HR (beats/min)	97.6 (14.0)	95.4 (14.1)	97.6 (14.0)	95.4 (14.1)	92.7 (12.5)	88.3 (11.3)
Peak SBP (mm Hg)	127.8 (15.8)	127.0 (13.7)	127.8 (15.8)	127.0 (13.7)	124.8 (13.4)	128.6 (5.6)
Peak DBP (mm Hg)	78.4 (5.8)	77.5 (7.6)	78.4 (5.8)	77.5 (7.6)	80.0 (8.5)	82.1 (11.2)
Baseline DPFV (cm/s)	24.0 (2.6)	23.9 (4.1)	24.5 (2.5)	23.9 (3.7)	23.5 (2.8)	24.0 (4.8)
Hyperaemic DPFV (cm/s)	66.2 (14.7)*	72.8 (17.2)	67.5 (13.0)	75.4 (16.6)	64.9 (16.3)	69.3 (17.8)
Coronary flow reserve	2.76 (0.60)*	3.06 (0.65)	2.76 (0.49)*	3.17 (0.65)	2.77 (0.71)	2.90 (0.61)
Carotid IMT (mm)	0.54 (0.10)*	0.49 (0.10)	0.55 (0.10)**	0.46 (0.09)	0.53 (0.10)	0.54 (0.10)

*p<0.05 versus control; **p<0.01 versus control.
DBP, diastolic blood pressure; DPFV, diastolic mean peak flow velocity; HDL, high density lipoprotein; HR, heart rate; hsCRP, high sensitive C reactive protein; IMT, intima–media thickness; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; SBP, systolic blood pressure; TG, triglyceride.

women (67.5 (13.0) *v* 76.2 (16.7) cm/s, p = 0.06). Accordingly, CFR was significantly lower in hypertriglyceridaemic than in normotriglyceridaemic women (2.7 (0.5) *v* 3.2 (0.7), p = 0.01). Linear regression analysis showed an independent association between triglyceride and IMT ($\beta = 0.525$, $p < 0.01$), but not between triglyceride and CFR.

When hypertriglyceridaemic men (n = 24) were compared with male controls (n = 19), the two subgroups were similar in HDL cholesterol, carotid IMT (0.53 (0.10) *v* 0.54 (0.10) mm, p = 0.8), baseline and hyperaemic DPFV, and, accordingly, CFR (2.77 (0.7) *v* 2.90 (0.6), p = 0.7).

In women, CFR had a significant inverse correlation with carotid IMT ($r = -0.398$, $p < 0.01$); however, in men, the correlation was weak ($r = -220$, p = 0.15).

DISCUSSION

Hypertriglyceridaemia, in decreasing nitric oxide bioavailability, can lead to endothelial dysfunction. Triglyceride rich lipoproteins stimulate leucocyte adhesion to the endothelial surface.[4] Accordingly, a meta-analysis showed that increased triglyceride concentration is associated with an increase in cardiovascular risk of 30% for men and 70% for women.[5] Our data showed that hypertriglyceridaemic women had increased carotid IMT and impaired CFR compared with female controls. However, the two subgroups of men had similar IMT and CFR. Pannacciulli *et al*[6] reported that carotid IMT positively correlated with fasting triglyceride concentration but, after multivariate analyses, the association disappeared. We found that fasting triglyceride concentration is independently associated with carotid IMT in totally healthy subjects. As a result, in women rather than men, increased triglyceride concentration may be regarded as an independent coronary risk factor.

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