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ORIGINAL ARTICLE

Postprandial lipaemia suppresses endothelium-dependent arterial dilation in patients with hypothyroidism

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Abstract Endothelial dysfunction represents an early step in the development of atherosclerosis. The purpose of this study was to investigate the relationship between postprandial lipaemia and endothelial dysfunction in patients with overt hypothyroidism (oHT) and subclinical hypothyroidism (sHT). Female subjects with oHT and sHT, as well as female healthy subjects with euthyroid state were enrolled (10 cases in each group). The examination of flow-mediated dilation (FMD) was performed before and after an oral fat-loading by high resolution ultrasound. Endothelial dysfunction after an oral fat challenge was related to the extent of hypertriglyceridemia and free radicals. FMD decreased significantly at 4-h point in 3 groups, ($p < 0.05$) and then FMD in control and sHT restored to baseline at 8-h point, it was lower than baseline in sHT group at 6-h point ($p = 0.042$). However, FMD continued to decrease at 6-h point ($p < 0.001$), and then increased toward to baseline at 8-h point, which was still lower than baseline ($p = 0.039$) in oHT. Spearman's analysis showed a negative correlation between FMD and triglyceride, a negative correlation between FMD and thiobarbituric acid reactive substances (TBARS), and a positive correlation between triglyceride and TBARS levels during oral lipid-loading test in hypothyroid patients ($p < 0.001$) and controls ($p < 0.05$). In hypothyroid subjects including oHT and sHT, even in healthy individuals, FMD was impaired after an oral fat challenge. The endothelial dysfunction observed after an oral fat challenge was related to the extent of hypertriglyceridemia and oxygen-derived free radicals.

Keywords Hypothyroidism · Postprandial lipaemia · Endothelial dysfunction

Abbreviations

PPL	Postprandial lipaemia
oHT	Overt hypothyroidism
sHT	Subclinical hypothyroidism
FMD	Flow-mediated dilation (endothelium-dependent vasodilation)
TPO-Ab	Anti-thyroid peroxidase antibody
Tg-Ab	Anti-thyroglobulin antibody
fT4	Free T4
fT3	Free T3
TSH	Thyroid-stimulating hormone
BMI	Body mass index
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
FBS	Fasting blood sugar
TBARS	Thiobarbituric acid reactive substances
Lp(a)	Lipoprotein (a)
CRP	C-reactive protein
GTN	Glyceryl trinitrate
SBP	Systolic blood pressure
DBP	Diastolic blood pressure

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Introduction

It is well established that fasting abnormalities of lipid metabolism are very important factors in the development of atherosclerosis. Also, it has long been recognized that atherosclerosis is strongly associated with postprandial lipaemia (PPL) [1, 2]. Research on these connections has suggested that alterations in postprandial lipid metabolism, particularly the number, size, and density of particles containing triglyceride-rich lipids, may lead to atherosclerosis [3, 4].

Previous studies showed that overt hypothyroidism (oHT), even subclinical hypothyroidism (sHT), were associated with increased morbidity from cardiovascular disease [5–7], and both fasting and PPL played important roles in the development of atherosclerosis in patients with oHT and sTH [5–9].

Flow-mediated dilation (FMD, endothelium-dependent vasodilation) of the brachial artery is a marker of endothelial function and an association with mortality and cardiovascular morbidity has been demonstrated [9–12]. Recently, several studies showed that FMD is impaired in patients with oHT and sHT [9–13] and abnormal fasting lipid and lipoprotein levels are associated with this endothelial dysfunction in hypothyroidism [9, 10, 13–16]. However, to the best of our knowledge no study to date has investigated the relationship between PPL and endothelial dysfunction in the setting of hypothyroidism. The purpose of this study was to investigate the relationship between PPL and endothelial dysfunction in patients with oHT and sHT.

Research design and methods

Subjects

From May 2010 to May 2011, 10 female subjects with oHT and 10 female subjects with sHT who were referred to our hospital were studied. During the same period, age matched 10 female healthy subjects with euthyroid state (from the medical staff in our hospital) were recruited as controls. All patients were newly diagnosed with Hashimoto's thyroiditis and were positive for both anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin (Tg-Ab) antibodies. The diagnosis of oHT was established on the basis of reduction of serum-free T4 (fT4) and free T3 (fT3) to below the normal lower limit and elevation of serum TSH to above the normal upper limit, and sHT was defined as the elevated serum TSH levels and normal fT3 and fT4 values. Control subjects were negative for both TPO-Ab and Tg-Ab, and without goiter by sonograms. All individuals in this study were pre-menopausal, with regular menses, and none was pregnant. Obese [body mass index (BMI) >30 kg/m^2] subjects, smokers and those with hypertension, clinical detectable coronary artery disease, malignant neoplasms, renal or liver diseases, diabetes mellitus, familial hypercholesterolemia, or endocrinological disease other than oHT or sHT were excluded from the study. Also, no subject was taking any drugs, such as oral contraceptives, estrogen supplements, diuretics, hypolipidemic drugs, and β-blockers. All individuals enrolled in the study gave informed consent. The study protocol was in agreement with the guidelines of the ethics committee at our hospital.

Methods

Oral lipid-loading protocol

All venous blood samples were collected from the antecubital vein via a small indwelling intravenous catheter. Each subject's first sample ("zero time" before the lipid-loading test meal) was drawn between 8:00 a.m. and 9:00 a.m. after a minimum 12-h fast. Then the test meal was consumed [the test meal (breakfast) was prepared in our hospital's Nutrition Division such that it would provide a total of 800 kcal, comprising 62% fat, 26% carbohydrates, and 12% protein] and blood samples for triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), nitrite/nitrate, thiobarbituric acid reactive substances (TBARS) were obtained every 2 h for a total of 8 h.

Laboratory methods

Serum total cholesterol (normal range, 3.10–5.69 mmol/L), LDL-C (normal range, 2.10–3.10 mmol/L), triglyceride (normal range, 0.41–1.88 mmol/L), and HDL-C (normal range, 1.16–1.82 mmol/L) were measured enzymatically. Serum lipoprotein(a) [Lp(a)] concentrations (normal range, 0–300 mg/L) were measured by an ELISA method. Blood glucose levels were measured by a glucose oxidase procedure. Creatinine was measured enzymatically. C-reactive protein (CRP) concentrations were measured by using the CRP (Latex) ultrasensitive assay (normal range, 0–3 mg/L). The concentrations of fT3 (normal range, 3.20–9.20 pmol/L) and fT4 (normal range, 9.10–25.60 pmol/L) were measured by radioimmunoassay, and thyroid-stimulating hormone (TSH) levels (normal range, 0.3–5.5 mU/L) were determined with an ultrasensitive immunoradiometric assay. Tg-Ab was measured by specific immunoradiometric assay (normal range, <50 U/mL), TPO-Ab was measured by specific radioimmunoassay (normal range, <50 U/mL). Nitrite/nitrate, stable metabolites of NO, was measured using

methods reported by Kawano et al. [17]. The plasma lipid peroxide content was determined using TBARS as markers [18, 19]. In brief, 2.0 mL of trichloroacetic acid–thiobarbituric acid–HCl reagent was added to 1.0 mL of sample and vortexed. To minimize peroxidation during the assay procedure, butylated hydroxytoluene was added to the thiobarbituric acid reagent mixture. Results were expressed as malondialdehyde equivalent content (nmol MDA/mL plasma). The intra-assay coefficients of variation for these assays were 1–2% (total cholesterol, triglyceride, HDL-C, blood sugar, creatinine, CRP, fT3, fT4, TSH), 2–3% (LDL-C, nitrite/nitrate), 2–4% (TBARS), and 4–7% [Lp(a), Tg-Ab and TPO-Ab].

Brachial arterial study

The vascular studies of the brachial artery were performed noninvasively, as described by us previously [9–12, 14–16]. High resolution ultrasound was used to measure changes in arterial diameter in response to reactive hyperemia (with increased flow producing an endothelium-dependent stimulus to vasodilation) and to glyceryl trinitrate (GTN, an endothelium-independent vasodilator) (128XP/10 with a 7.0 MHz linear array transducer: Acuson, Mountain View, California). The intra- and inter-observer variabilities in our laboratory for repeated measurements of artery diameter are 0.09 ± 0.10 and 0.08 ± 0.13 mm, respectively.

The subjects rested in supine position for 10 min before the first scan and remained supine throughout the study. The target artery (the brachial 2–15 cm above the elbow) was scanned in longitudinal section and the center of the vessel was identified when the clearest images of anterior and posterior walls of the artery were obtained. The transmit zone was set to the level of the anterior vessel wall. Depth and gain settings were optimized to identify the lumen to vessel wall interface. Images were magnified with the resolution box function leading to a television line width of $\sim$0.05 mm. Machine settings were kept constant during each study.

Flow increase was induced by inflation of a blood pressure tourniquet placed around the forearm distal to the target artery, to 300 mmHg. The cuff was released after 5 min, and after cuff deflation the artery was scanned continuously for 90 s. Fifteen minutes were allowed for vessel recovery, sublingual GTN (400-μg spray) was then administered, and 5 min later the last scan was done. The electrocardiogram was monitored continuously.

Vessel diameter was measured by two observers, unaware of clinical details and the stage of the experiment. The arterial diameter was measured at a fixed distance from an anatomical maker, such as a bifurcation, with ultrasonic calipers. Measurements were taken from the anterior to the posterior "m" line at end diastole, incident with the R-wave on the electrocardiogram. The mean diameter was calculated from four cardiac cycles. For the hyperemia scan, vessel diameter was measured 45–60 s after cuff release. Diameter changes were derived as percent change relative to the first baseline scan (100%). Baseline blood flow (measured during the first baseline scan) was estimated by multiplying angle-corrected, pulsed Doppler recordings of the flow-velocity integral by π and the square of the radius of the artery.

Statistical methods

Data are reported as the mean $\pm$ SD. Comparison between more than two groups was carried out by analysis of variance (ANOVA), and post hoc corrections were applied for multiple comparisons. Univariate analysis of the effects of each potential risk factor on FMD and nitroglycerin response was performed by linear regression for continuous variables [fasting blood sugar (FBS), total cholesterol, LDL-C, HDL-C, triglycerides, Lp(a), mean blood pressure, age, vessel size, blood flow, BMI, TSH, fT3, fT4, Tg-Ab, TPO-Ab, pulse rate, TBARS, and nitrite/nitrate] before oral fat-loading. Correlations between triglyceride levels and FMD, between triglyceride and TBARS levels, and between TBARS and FMD during the oral lipid-loading meal test were examined. Lp(a) concentrations were log transformed before analysis. All analyses were carried out by using the statistical package SPSS11.5.

Results

The clinical characteristics and biochemical results including blood lipids, thyroid function, and other parameters, of the hypothyroid patients and control subjects are given in Table 1. The data confirmed that these 3 groups were in oHT, sHT, and euthyroid status, respectively. Compared with control group, total cholesterol ($p = 0.035$), LDL-C ($p < 0.001$), Lp(a) ($p < 0.001$), CRP ($p < 0.001$), and TBARS ($p < 0.001$) levels in oHT patients, only LDL-C ($p = 0.011$), Lp(a) ($p = 0.047$), CRP ($p = 0.038$), and TBARS ($p = 0.020$) levels in sHT group were significantly higher, and pulse rate ($p = 0.034$) in oHT patients was significantly lower. Other parameters, such as BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), did not differ among different groups (Table 1).

In oHT group, TBARS, LDL-C, and total cholesterol ($p < 0.05$) levels at 0-, 2-, 4-, 6-, and 8-h points, and triglyceride levels ($p < 0.05$) at 4-, 6-, and 8-h points were significantly higher than those in sHT and controls. However, FMD in oHT group ($p < 0.05$) at 0-, 2-, 4-, 6-, and 8-h points was significantly lower than those in sHT and

Table 1 Clinical and biochemical characteristics in oHT and sHT and control groups at baseline

	oHT	sHT	Controls	*p* Value
Number of subjects	10	10	10	
Age (years)	35.5 ± 6.5	34.2 ± 5.8	34.6 ± 5.3	0.532
BMI (kg/m^2)	24.3 ± 2.6	24.1 ± 2.3	23.8 ± 2.0	0.495
SBP (mmHg)	126.2 ± 5.8	121.1 ± 6.3	119.8 ± 5.6	0.227
DBP (mmHg)	75.7 ± 5.5	73.2 ± 5.8	72.7 ± 6.1	0.391
Pulse rate (beats/min)	65.5 ± 3.4†	70.7 ± 2.8	71.3 ± 2.6	0.014
FBG (mmol/L)	4.65 ± 0.52	4.78 ± 0.66	4.50 ± 0.59	0.187
Total cholesterol (mmol/L)	5.68 ± 0.55*	5.01 ± 0.49	4.52 ± 0.51	0.029
LDL-C (mmol/L)	3.54 ± 0.50**†	3.01 ± 0.61*	2.17 ± 0.54	<0.001
HDL-C (mmol/L)	1.17 ± 0.26	1.19 ± 0.23	1.22 ± 0.28	0.166
Triglyceride (mmol/L)	1.62 ± 0.76	1.48 ± 0.93	1.33 ± 0.70	0.301
Lp(a) (mg/L)	337(104, 645)**	295 (38, 603)*	136 (0, 255)	<0.001
Creatinine (mg/dL)	0.82 ± 0.28	0.84 ± 0.25	0.83 ± 0.23	0.252
CRP (mg/L)	2.48 ± 0.59**	2.27 ± 0.55*	1.29 ± 0.32	<0.001
fT3 (pmol/L)	1.74 ± 1.22**††	4.25 ± 1.07*	6.18 ± 2.14	<0.001
fT4 (pmol/L)	7.22 ± 3.21**†	10.85 ± 1.93**	16.42 ± 4.89	<0.001
TSH (mU/L)	31.35 ± 7.32**††	9.74 ± 1.92**	3.73 ± 1.05	<0.001
TPO-Ab (U/mL)	478 ± 208**	504 ± 195**	27 ± 11	<0.001
Tg-Ab (U/mL)	521 ± 217**	493 ± 238**	30 ± 9	<0.001
TBARS (nmol/mL)	2.97 ± 0.74**	2.51 ± 0.62*	1.38 ± 0.55	<0.001
Nitrite/nitrate (μmol/L)	61.68 ± 9.44	60.55 ± 8.52	63.43 ± 9.82	0.211

* $p < 0.05$, ** $p < 0.01$, compared with controls

† $p < 0.05$, $^{\dagger\dagger}p < 0.01$, compared with sTH subjects

controls. There were similar differences (FMD, TBARS, and LDL-C) between sHT and controls ($p < 0.05$) (Table 2). No difference existed in other parameters, such as plasma glucose, HDL-C among the 3 groups during oral lipid-loading meal test ($p > 0.05$) (Table 2).

As shown in Table 2, all three groups showed significant postprandial rises in serum triglycerides above baseline. In sHT and control groups, triglyceride levels peaked at 4 h ($p < 0.001$ and $p = 0.01$, respectively). However, in the oHT group, triglyceride levels continued to rise and reached a maximum at 6-h time point ($p = 0.003$) during oral lipid-loading test meal. As expected, FMD in three groups showed significant postprandial decreases below baseline. In control and sHT group, FMD decreased significantly at 4-h time point after oral lipid loading ($p = 0.008$ and 0.014, respectively) and then restored to baseline levels at 8-h time point. However, in contrast to controls, it was still significantly lower than baseline in sHT group at 6-h time point ($p = 0.044$). Similarly, FMD significantly decreased from baseline at 4-h time point ($p < 0.001$), and continued to decrease at 6-h time point ($p < 0.001$), and then increased toward to baseline at 8-h time point, which was still significantly lower than baseline ($p = 0.039$) in oHT group. Also, all three groups showed significant postprandial rises in serum TBARS above baseline. In control and sHT groups, TBARS levels significantly increased at 4-h time point ($p < 0.001$ and $p = 0.015$, respectively) and then decreased toward to fasting levels at 6- and 8-h time point ($p > 0.05$) in controls. However, it was still higher than baseline at 6-h time point in sHT group ($p = 0.028$). In oHT group, plasma TBARS levels significantly increased at 4-h time point from baseline ($p < 0.001$), continued to rise and reached a maximum at 6-h time point ($p < 0.001$), and then decreased toward to baseline, which was still significantly higher than baseline ($p = 0.027$) at 8-h time point. Other parameters, such as baseline brachial arterial diameters, baseline blood flow, GTN-induced endothelium-independent arterial dilation, plasma glucose, and total cholesterol did not significantly differ among different time-points in three groups (Table 2).

Univariate analysis showed a correlation between FMD and TPO-Ab ($r = -0.26$, $p = 0.01$), LDL-C ($r = -0.24$, $p = 0.029$), triglyceride ($r = -0.23$, $p = 0.042$), Lp(a) ($r = -0.21, p = 0.047$), CRP ($r = -0.32, p < 0.001$), BMI ($r = -0.20$, $p = 0.049$), mean blood pressure ($r = -0.25$, $p = 0.025$), age ($r = -0.33$, $p < 0.001$), TBARS ($r = -0.26, p = 0.01$), fT3 ($r = 0.30, p < 0.001$), fT4 ($r = 0.28$, $p < 0.001$), TSH ($r = -0.34, p < 0.001$), and no correlation with other parameters (such as pulse rate, HDL-C, FBS and etc.) in hypothyroidism patients (including oHT and sHT) before oral fat-loading meal test.

Spearman's analysis showed that there was a negative correlation between FMD and triglyceride levels ($r = -0.572$, $p < 0.001$), a negative correlation between FMD and TBARS levels ($r = -0.583$, $p < 0.001$), and a positive

Table 2 Brachial arterial data, lipids, blood glucose, TBARS and serum nitrite/nitrate during the oral lipid-loading meal test

	Fasting	2 h	4 h	6 h	8 h
OHT group					
Baseline vessel (mm)	3.79 ± 0.52	3.81 ± 0.60	3.78 ± 0.63	3.75 ± 0.55	3.80 ± 0.57
Baseline flow (mL/min)	80.35 ± 35.43	82.43 ± 36.33	81.23 ± 33.50	80.49 ± 38.76	82.24 ± 33.78
FMD (%)	3.28 ± 0.65††§	2.91 ± 0.80††§	2.28 ± 0.73**††§	2.24 ± 0.76**††§	2.60 ± 0.67*††§
GTN-induced dilation (%)	22.04 ± 3.12	20.63 ± 2.94	20.83 ± 2.55	21.26 ± 2.93	22.38 ± 3.01
Triglyceride (mmol/L)	1.82 ± 0.76	2.29 ± 0.60§	2.96 ± 0.77**†§	3.14 ± 0.66**††§	2.53 ± 0.77*††§
Total cholesterol (mmol/L)	5.68 ± 0.55†	5.71 ± 0.62†	5.59 ± 0.65†	5.63 ± 0.58†	5.64 ± 0.60†
LDL-C (mmol/L)	3.54 ± 0.50††§	3.48 ± 0.48††§	3.51 ± 0.52††§	3.55 ± 0.47††§	3.52 ± 0.54††§
HDL-C (mmol/L)	1.17 ± 0.26	1.20 ± 0.24	1.17 ± 0.22	1.19 ± 0.19	1.17 ± 0.21
Blood glucose (mmol/L)	4.65 ± 0.52	5.03 ± 0.64	4.76 ± 0.56	4.77 ± 0.52	4.55 ± 0.49
TBARS (nmol/mL)	2.89 ± 0.70††§	3.28 ± 0.67††§	3.85 ± 0.75**††§	3.92 ± 0.58**††§	3.66 ± 0.85*††§
Nitrite/nitrate (μmol/L)	61.68 ± 9.44	60.56 ± 10.21	60.83 ± 9.15	62.26 ± 8.56	61.58 ± 8.48
sHT group					
Baseline vessel (mm)	3.82 ± 0.52	3.75 ± 0.63	3.83 ± 0.59	3.79 ± 0.64	3.87 ± 0.61
Baseline flow (mL/min)	79.44 ± 32.65	80.34 ± 30.65	81.32 ± 33.65	79.55 ± 35.62	80.83 ± 32.04
FMD (%)	3.88 ± 0.68†	3.52 ± 0.55†	2.96 ± 0.60**†	3.22 ± 0.50*†	3.70 ± 0.56†
GTN-induced dilation (%)	21.38 ± 2.75	20.36 ± 3.02	22.15 ± 2.84	19.92 ± 2.85	20.32 ± 2.90
Triglyceride (mmol/L)	1.41 ± 0.56	1.91 ± 0.55	2.72 ± 0.81**†	2.28 ± 0.84*†	1.90 ± 0.86†
Total cholesterol (mmol/L)	5.01 ± 0.49	5.21 ± 0.39	5.14 ± 0.47	5.26 ± 0.54	4.98 ± 0.59
LDL-C (mmol/L)	3.01 ± 0.61†	2.89 ± 0.56†	3.05 ± 0.63†	3.12 ± 0.52†	2.92 ± 0.62†
HDL-C (mmol/L)	1.19 ± 0.23	1.09 ± 0.31	1.15 ± 0.28	1.15 ± 0.27	1.17 ± 0.29
Blood glucose (mmol/L)	4.78 ± 0.66	5.11 ± 0.57	5.03 ± 0.63	4.96 ± 0.59	5.09 ± 0.60
TBARS (nmol/mL)	2.20 ± 0.87†	2.79 ± 0.67†	3.34 ± 0.80**†	2.95 ± 0.82*†	2.54 ± 0.68†
Nitrite/nitrate (μmol/L)	60.55 ± 8.52	61.04 ± 9.32	61.93 ± 8.59	60.72 ± 10.32	62.18 ± 9.04
Controls					
Baseline vessel (mm)	3.87 ± 0.62	3.82 ± 0.69	3.85 ± 0.57	3.83 ± 0.60	3.79 ± 0.66
Baseline flow (mL/min)	81.19 ± 34.45	80.38 ± 33.01	82.24 ± 35.92	81.73 ± 33.95	80.17 ± 32.84
FMD (%)	5.68 ± 0.51	5.34 ± 0.54	5.0 ± 0.50*	5.32 ± 0.63	5.64 ± 0.61
GTN-induced dilation (%)	20.93 ± 3.16	21.14 ± 2.78	20.43 ± 3.03	22.14 ± 2.96	21.79 ± 3.25
Triglyceride (mmol/L)	1.33 ± 0.70	1.83 ± 0.57	2.30 ± 0.69**	1.96 ± 1.02	1.48 ± 0.58
Total cholesterol (mmol/L)	4.52 ± 0.51	4.43 ± 0.43	4.74 ± 0.49	4.50 ± 0.53	4.67 ± 0.45
LDL-C (mmol/L)	2.17 ± 0.54	2.09 ± 0.49	2.32 ± 0.44	2.11 ± 0.50	2.14 ± 0.46
HDL-C (mmol/L)	1.22 ± 0.28	1.16 ± 0.22	1.20 ± 0.26	1.19 ± 0.25	1.23 ± 0.23
Blood glucose (mmol/L)	4.59 ± 0.45	5.05 ± 0.52	4.87 ± 0.58	4.63 ± 0.47	4.60 ± 0.49
TBARS (nmol/mL)	1.38 ± 0.55	1.85 ± 0.68	2.07 ± 0.68*	1.83 ± 0.67	1.46 ± 0.50
Nitrite/nitrate (μmol/L)	63.43 ± 9.82	60.49 ± 8.88	61.78 ± 9.05	62.21 ± 9.11	61.54 ± 8.83

* $p < 0.05$, ** $p < 0.01$, compared with fasting

† $p < 0.05$, $^{\dagger\dagger}p < 0.01$, compared with controls

§ $p < 0.05$, compared with sHT group

correlation between triglyceride and TBARS levels ($r = 0.603, p < 0.001$) during oral lipid-loading meal test in hypothyroid patients including sHT and oHT (Figs. 1, 2, and 3). In control group, there were similar correlations [FMD and triglyceride ($r = -0.233, p = 0.018$), FMD and TBARS levels ($r = -0.353, p = 0.011$), as well as triglyceride and TBARS levels ($r = 0.214, p = 0.030$)], although the power of association decreased (Figs. 1, 2, and 3).

Discussion

In this study, we examined the changes in FMD and its association with plasma lipids levels before and after an oral lipid-loading meal test in hypothyroid patients including oHT and sHT as well as in healthy individuals. The results showed a significant postprandial decrease in FMD below baseline, which strongly depends on the

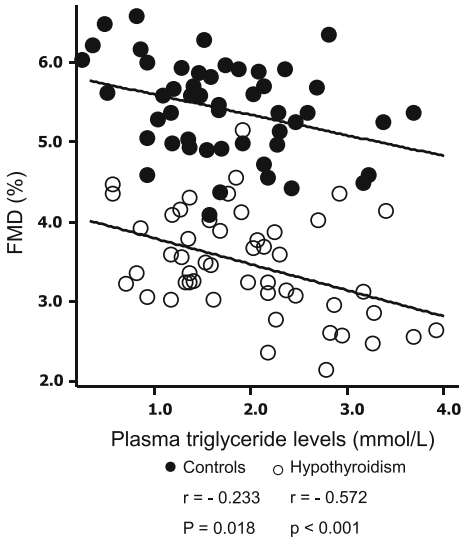

Fig. 1 Correlations between FMD and plasma triglyceride levels in hypothyroidism patients and controls. There were significant negative correlations between them

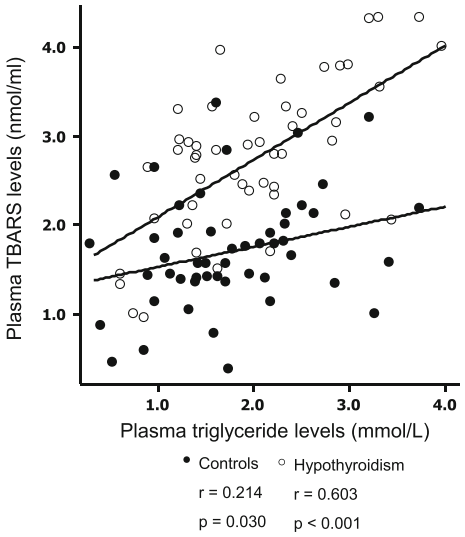

Fig. 3 Correlations between plasma triglyceride and plasma TBARS levels in hypothyroidism patients and controls. There were significant positive correlations between them

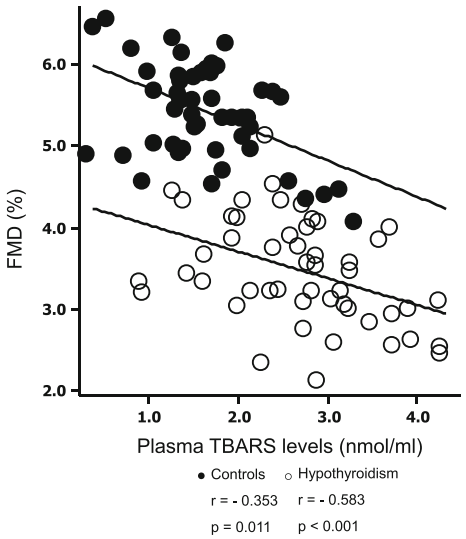

Fig. 2 Correlations between FMD and plasma TBARS levels in hypothyroidism patients and controls. There were significant negative correlations between them

magnitude of PPL, and a significant negative correlation between FMD and triglyceride levels in control subjects, especially in sHT and oHT patients, suggesting that PPL is an important factor in endothelial dysfunction. To the best of our knowledge, this is the first report on the relationship between PPL and endothelial dysfunction in hypothyroid patients, indicating that hypothyroid patients, even healthy individuals should have a low-fat diet.

PPL, representing triglyceride metabolic capacity under challenge, is considered to be more informative for assessing the role of triglyceride metabolism in the development of atherosclerosis [20, 21]. Consequently, a number of case–control studies showed impaired triglyceride metabolic capacity, defined as increased and prolonged postprandial hypertriglyceridemia, to be closely linked to the presence of cardiovascular diseases [21, 22]. Tanaci et al. [8] confirmed this association in oHT and sHT patients. Endothelial dysfunction represents a very early step in the development of atherosclerosis [23]. It has been proposed that postprandial hypertriglyceridemia can cause endothelial dysfunction, and that repeated episodes of hypertriglyceridemia may promote the development of atherosclerosis in patients with coronary artery disease and type 2 diabetes, [24, 25]. In this study, we got a tight association of increased PPL and impaired endothelial function in hypothyroid patients, which supports the notion that PPL is an important factor in the development of atherosclerosis [20, 21].

In studies of middle-aged healthy subjects impairment of FMD was strongly related to the extent of postprandial hypertriglyceridemia [26–28]. Here, we got similar results in healthy women. However, another report observed no correlation between endothelial dysfunction and magnitude of PPL [29]. The reasons for the contradictory results are not clear. We consider differences in the content of test meal to be partially responsible for the contradictory results.

Oxidative stress has been accused to represent the underlying mechanism responsible for the impaired endothelial function observed during PPL [25, 26, 30]. Plotnick et al. [30] has reported that pre-treatment with antioxidant vitamins C and E blocks this decrease in endothelial function, a finding which was confirmed by Vogel [31] who demonstrated that olive oil meals containing antioxidant vitamins or foods did not reduce endothelial function.

FMD has been shown to be mediated by the endothelium-derived relaxing factors, which are now identified as NO [32]. Previous studies have established that oxygen-derived free radicals interfere with or destroy FMD by inactivating NO in normal vessels [33, 34]. In this study, there was a significant positive correlation between triglyceride and TBARS levels, a marker of oxygen-derived free radicals during the oral lipid-loading meal test, and FMD of the brachial conduit artery decreased in association with an increase in plasma levels of TBARS. This is in a good agreement with previous studies in non-hypothyroid patients [25, 26, 30], indicating oxidative stress contributes to the decrease of endothelial dysfunction during PPL in hypothyroid patients. By contrast, the serum levels of nitrite/nitrate, the metabolites and the marker for production of NO did not change in any of the groups after oral lipid loading. As the nitrite/nitrate concentration includes the oxidative products of NO [35], PPL suppresses FMD, probably through an increase in oxygen-derived free radicals, and results in quenching of NO rather than a decrease in production/release of NO.

In accordance with other studies in healthy subjects [28, 36], we also found plasma total cholesterol, LDL-C, HDL-C, glucose, baseline vessel, baseline flow and GTN-induced dilation did not differ significantly among different time point during PPL. In addition, it has been suggested previously that impaired endothelial function exists in sHT, especially in oHT subjects [9, 10, 15, 16]. In this study, we got similar results. Likewise, compared with healthy subjects, we found higher CRP and TPO-Ab and Tg-Ab levels in hypothyroid patients; these are in a good agreement with our previous results [9, 10, 15, 16].

In conclusion, this cross-sectional study showed that PPL may be associated with endothelial dysfunction in patients with hypothyroidism, either subclinical or overt, in relation to the increase in oxygen-derived free radicals occurring in postprandial period. However, future studies with a larger number of patients are needed to confirm these preliminary results and to clarify the effectiveness of low-fat diet in preventing endothelial dysfunction in patients with hypothyroidism.

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