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Postprandial Lipemia as a Risk Factor for Cardiovascular Disease in Patients with Hypothyroidism

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Postprandial lipoprotein metabolism is suggested to play a role in the pathogenesis of atherosclerosis. In this study, we investigated postprandial lipemia and its relationship to cardiovascular risk factors in patients with overt and subclinical hypothyroidism. Twenty-nine female patients with TSH levels greater than 5 µIU/mL and 12 euthyroid control female subjects were included in the study. Fifteen patients had subclinical hypothyroidism and 14 had overt hypothyroidism. All subjects underwent an oral lipid tolerance test. If triglyceride levels increased by 80% or more, subjects were considered postprandial lipemia positive. Control, overt hypothyroid, and subclinical hypothyroid groups were not statistically different with respect to anthropometric measurements, fasting blood C-reactive protein, uric acid, homocysteine, glucose, insulin, lipoprotein (a), apolipoprotein B levels, and homeostasis model assessment index. Fasting triglyceride levels correlated positively with TSH levels. Postprandial lipemia frequency was higher in overt hypothyroid subjects than in the control group. The subclinical hypothyroid group did not differ from the hypothyroid group with respect to postprandial lipemia frequency. In subjects with TSH levels higher than 5 µIU/mL, PPL risk was increased sevenfold. The results of this study show that postprandial triglyceride metabolism is affected in hypothyroidism.

Key Words: Hypothyroidism; subclinical; overt; postprandial lipemia; cardiovascular risk; triglyceride.

Introduction

It is well established that abnormalities of lipid metabolism are very important factors in the development of atherosclerosis. Elevated serum total cholesterol and low-density lipoprotein cholesterol (LDL-C), and decreased serum concentrations of high-density lipoprotein cholesterol (HDL-C) are of great significance in coronary artery disease *(1,2)*. Elevated serum triglyceride was also considered a risk factor for coronary heart disease in several studies *(3–5)*. It has long been thought that atherosclerosis is strongly associated with nutritional intake and postprandial lipemia (PPL) *(6,7)*. 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 *(8,9)*.

Patients with overt or subclinical hypothyroidism typically show abnormal fasting lipid and lipoprotein levels, and these disturbances are reversed by L-thyroxine therapy *(10–14)*. However, to our knowledge no study to date has investigated postprandial lipid metabolism in the setting of hypothyroidism. Our aims were to assess the prevalence of PPL after a standardized fat-containing mixed test meal in patients with overt and subclinical hypothyroidism, and to investigate possible relationships between PPL and other cardiovascular risk factors in this patient group.

Results

As noted, the study included a total of 29 patients with hypothyroidism (15 in the subclinical group and 14 in the overt group) and 11 control subjects. There were no significant differences among the three groups with respect to mean age, height, weight, BMI, waist circumference, hip circumference, or waist/hip (WHR) ratio (Table 1). There were also no statistical differences among the groups with respect to fasting levels of total cholesterol, LDL-C, HDL-C, VLDL-C, and triglyceride (Table 1). However, as TSH levels increased, a parallel nonsignificant increase was noted in fasting triglyceride levels. In the correlation analysis, a positive correlation between TSH values and fasting triglyceride values was observed, and this result was found to be statistically significant (Fig. 1).

Comparisons of groups for other cardiovascular risk factors, fasting blood glucose, insulin, homeostasis model index (HOMA) index, C-reactive protein (CRP), uric acid, homocysteine, lipoprotein (a), and lipoprotein B, revealed no sig-nificant differences (Table 2).

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Table 1
Clinical, Demographic, and Anthropometric Features of the Participants at Baseline Evaluation

	Control (n = 11)	Subclinical (n = 15)	Overt (n = 14)	p
Age (yr)	54.6 ± 6.2	52.2 ± 6.9	58.2 ± 7.0	NS
Height (cm)	155 ± 5	157 ± 4	158 ± 7	NS
Weight (kg)	76 ± 18	77 ± 12	72 ± 13	NS
BMI (kg/m^2)	31.5 ± 6.8	31.2 ± 5.2	28.6 ± 3.9	NS
Waist (cm)	91 ± 12	92 ± 12	92 ± 13	NS
Hip (cm)	114 ± 15	114 ± 9	106 ± 10	NS
WHR	0.80 ± 0.06	0.81 ± 0.08	0.87 ± 0.08	NS
T3 (ng/mL)	1.06 ± 0.20	1.06 ± 0.25	0.90 ± 0.32	NS
T4 (μg/dL)	8.74 ± 1.71	6.34 ± 1.09	4.80 ± 1.99	**0.001**
TSH (μIU/mL)	1.96 ± 0.99	6.87 ± 1.52	28.11 ± 24.06	**0.001**
Total cholesterol (mg/dL)	226 ± 31	222 ± 40	245 ± 53	NS
LDL-C (mg/dL)	133 ± 33	134 ± 38	152 ± 39	NS
HDL-C (mg/dL)	66 ± 22	57 ± 14	56 ± 14	NS
VLDL-C (mg/dL)	28 ± 9	31 ± 8	37 ± 22	NS
Triglyceride (mg/dL)	109 ± 43	146 ± 46	169 ± 97	NS

Mean value ± standard deviation. BMI, body mass index; WHR, waist/hip ratio; NS, not significant; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

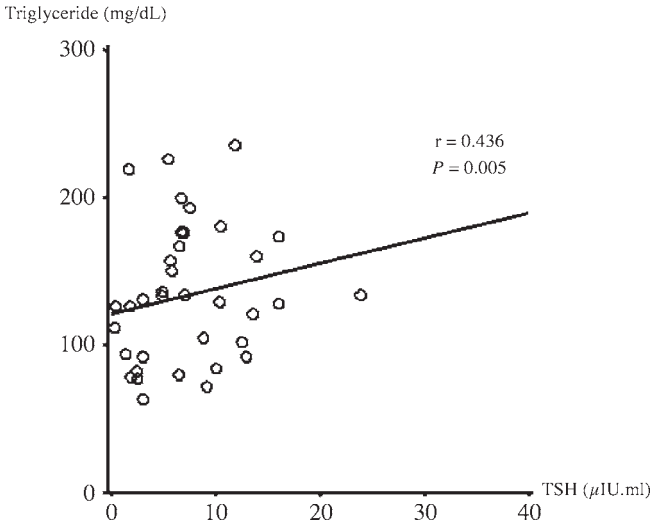

Fig. 1. Relationship between TSH and fasting triglyceride using data from all participants.

Table 2
Other Cardiovascular Risk Factors Measured in Participants at Baseline

	Control (n = 11)	Subclinical (n = 15)	Overt (n = 14)	p
FBG (mg/dL)	86 ± 15	84 ± 16	85 ± 8	NS
Insulin (μIU/mL)	7.8 ± 4.4	10.6 ± 5.5	9.7 ± 3.8	NS
HOMA-IR	1.7 ± 1.1	2.2 ± 1.2	2.0 ± 0.8	NS
CRP (mg/L)	3.2 ± 3.8	5.8 ± 3.6	5.4 ± 3.8	NS
Uric acid (mg/dL)	4.2 ± 1.2	5.0 ± 0.9	4.9 ± 1.1	NS
Homocysteine (μmol/L)	11.6 ± 2.0	11.9 ± 1.9	13.6 ± 5.3	NS
Lipoprotein (a) (mg/dL)	45.5 ± 32.3	39.8 ± 33.9	25.2 ± 23.1	NS
Apoprotein B (mg/dL)	98.6 ± 23.7	101.3 ± 24.9	112.2 ± 29.1	NS

Mean value ± standard deviation. NS, not significant; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment–insulin resistance; CRP, C-reactive protein.

Figure 2 shows the postprandial serum triglyceride concentrations (0, 2, 4, 6, and 8 h) after oral lipid loading. As expected, all three groups showed a significant postprandial rise in serum triglycerides above baseline. In the control group and the subclinical hypothyroidism group, triglyceride levels peaked at 4 h. However, in the overt hypothyroidism group, triglyceride levels continued to rise and reached a maximum at the 6-h time point. Curves indicating the changes in serum triglyceride levels in the three groups during the oral lipid-loading test were similar, as shown in Fig. 2 (with repeated measure one-way ANOVA, f= 1.318; p = 0.283).

To compare the triglyceride increases after oral lipid loading in the three groups, we calculated the area under curve (AUC) for the triglyceride using the trapezoidal method. Although a tendency to increase was observed in subclinical hypothyroidism and overt hypothyroidism groups compared to controls, no statistical difference was determined among the 3 groups (Fig. 3).

As detailed above, if an individual's triglyceride level at 4 or 6 h after lipid loading was increased (above baseline) by 80% or more, the subject was considered to have PPL.

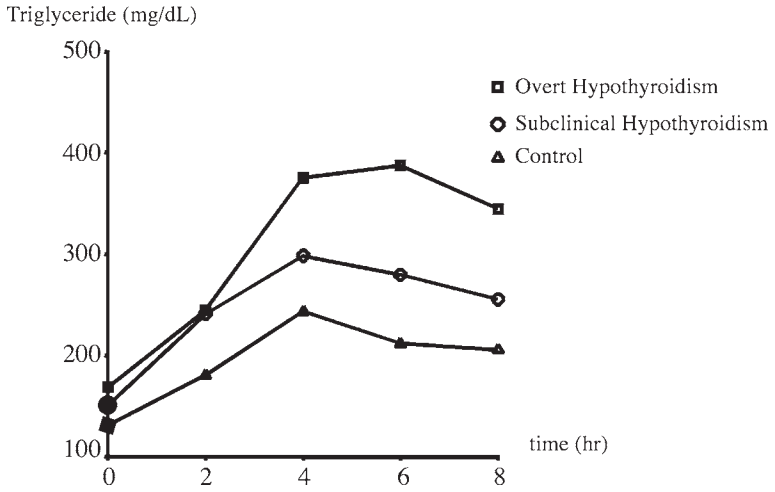

Fig. 2. Curves indicating the changes in serum triglyceride levels in the 3 groups during the oral lipid-loading test were similar (With repeated measure one way ANOVA, $F = 1.318$; $p = 0.283$).

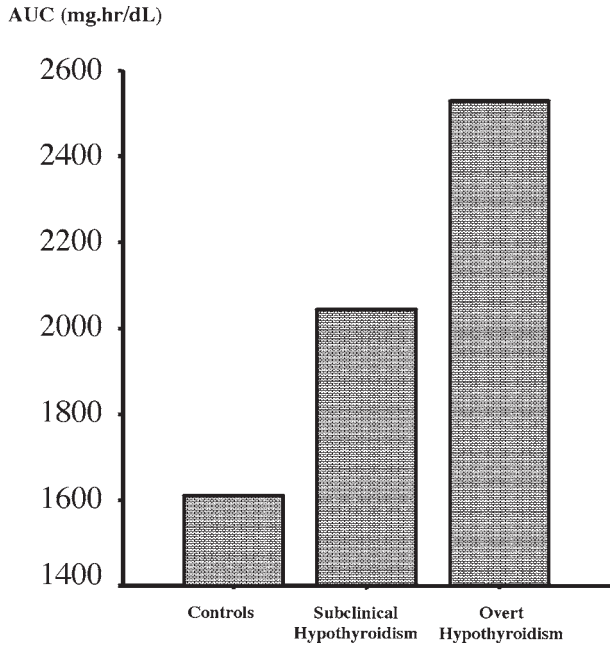

Fig. 3. Comparison of area under curve for the groups' triglyceride levels during the oral lipid-loading test. There was a trend towards higher AUC values from controls to subclinical hypothyroidism to overt hypothyroidism, but there were no significant differences among the 3 groups ($p = 0.271$). AUC, area under curve.

PPL was noted in 11 patients with overt hypothyroidism (79%), 10 patients with subclinical hypothyroidism (67%), and 3 of the controls (27%). The incidence rates of PPL were not significantly different between patients with overt hypothyroidism and patients with subclinical hypothyroidism, both of which were higher than the rate in the healthy controls ($p < 0.05$). When data for the subclinical and overt hypothyroidism groups were combined, risk analysis indicated that patients with above-normal TSH levels (> 5 μIU/mL) had sevenfold higher risk of developing PPL than those in the normal range ($p = 0.009$).

When the 29 patients were grouped according to underlying thyroid disorder (Hashimoto's disease vs all others), there were no statistical differences between these two groups with respect to incidence of PPL after lipid loading.

The subjects who developed PPL had a significantly higher mean fasting triglyceride level than those who did not (164 ± 79 vs 113 ± 40 mg/dL, respectively; $p = 0.022$). The group that developed PPL also had a higher mean TSH level ($p = 0.041$). Free T3, TSH, and fasting triglyceride level were entered into the simple logistic regression model, and fasting triglyceride was identified as the only independent risk factor for PPL ($p = 0.017$).

Discussion

Substantial evidence suggests that hypothyroidism is associated with increased cardiovascular morbidity and mortality *(15,16)*. Coronary artery disease is more common in patients with overt hypothyroid, which warrants L-thyroxine replacement *(10,17)*. However, the need to treat subclinical hypothyroidism has been discussed for years. The main concern with not treating this condition might be associated with an atherogenic lipid profile, a hypercoagulable state, a subtle cardiac defect with mainly diastolic dysfunction, impaired vascular function, and reduced submaximal exercise capacity *(15)*. In patients with overt hypothyroidism, it is well known that increased plasma homocysteine, increased serum CRP, and abnormalities of lipoprotein metabolism can increase cardiovascular risk *(11–14,18–20)*. However, relationships between subclinical hypothyroidism and cardiovascular risk factors such as homocysteine and CRP levels are still under debate. The present study compared healthy individuals with subclinical and overt hypothyroidism patients with respect to homocysteine and CRP levels, but we could not determine any significant differences.

Although overt hypothyroidism has been shown to be associated with dyslipidemia, a less-recognized relationship also exists with subclinical hypothyroidism. Studies have

shown that both overt and subclinical hypothyroid patients can exhibit elevated serum levels of total cholesterol, LDL-C, triglyceride, intermediate-density lipoprotein cholesterol, apoprotein A-1, and apoprotein B concentrations *(10–14,21, 22)*. We could not determine any differences in total cholesterol, LDL-C, HDL-C, VLDL-C, and triglyceride measurements of the patients with subclinical and overt hypothyroidism compared to the control group when the baseline measurements were considered. Likewise, we could not find any statistical differences between the groups in terms of lipoprotein(a) and apolipoprotein B measurements. One explanation for this discrepancy might be related to the small population size in our study.

A recent meta-analysis of 17 prospective studies reported that a 1 mmol/L increase in fasting plasma triglyceride levels caused a 30% increase in cardiovascular disease (CVD) risk in men and a 75% increase in women *(23)*. Those findings are consistent with the results of the Copenhagen Male Study, which involved 8 yr of observation and concluded that elevated baseline triglyceride level is associated with increased risk of CVD *(5)*.

Twenty years ago, Zilversmit described atherosclerosis as a postprandial phenomenon and suggested a possible connection between triglyceride-rich lipoprotein metabolism disorders and CVD *(6)*. Since then, the importance of triglyceride-rich lipoprotein metabolism as a cardiovascular risk factor has become widely recognized *(7–9)*. PPL has been defined as a physiological transient alteration, lasting 6–12 h, in lipoprotein metabolism after a fatty meal. Fasting plasma triglyceride concentration has long been known to predict the severity and duration of PPL *(24)*. Postprandial dyslipidemia results when there is overproduction of intestinal and/or hepatic triglyceride-rich lipoproteins combined with decreased clearance of these lipoproteins *(7)*. The speed of increase of serum triglycerides following fat intake depends on gastric emptying, intestinal absorption, production and excretion of chylomicrons, lipoprotein metabolism, and hepatic clearance of chylomicron remnants. However, studies also show the significant contribution of hepatic VLDL triglycerides to the development of late responses. These investigations have demonstrated that elevated triglyceride levels in the postprandial period do not necessarily originate entirely from the intestine *(7,25,26)*.

The present study analyzed participants' triglyceride levels in the fasting state and every 2 h after oral lipid loading. The healthy individuals and those with subclinical hypothyroidism reached maximum serum triglyceride concentration at 4 h. In contrast, the triglyceride levels in the patients with overt hypothyroidism peaked at 6 h and remained elevated longer than in the other groups. The literature suggests that this difference may be associated with prolonged gastric emptying, increased intestinal absorption, increased production and excretion of chylomicrons, decreased lipoprotein activity, or decreased hepatic clearance of triglycerides in the setting of overt hypothyroidism *(25,26)*. Our study did not identify which one of these factors was the main defect; however, the analysis did indicate that patients with TSH levels exceeding 5 μIU/mL have a sevenfold higher incidence of PPL. The high risk for PPL in this group suggests that these individuals need to start L-thyroxine replacement as early as possible. One study has shown that L-thyroxine enhanced the clearance of chylomicron remnants in patients with hypothyroidism *(27)*.

In conclusion, the data from this study show that postprandial triglyceride metabolism is disturbed in overt and subclinical hypothyroidism, and that PPL may be another risk factor for coronary artery disease in these patient groups.

Material and Methods

Selection of Subjects

This cross-sectional cohort study was conducted at a thyroid outpatient clinic. The Baskent University Ethics Committee for Human Studies approved the study protocol and informed consent was obtained from all participants. The target groups for the study were female patients with untreated subclinical (n = 15) and overt hypothyroidism (n = 14). The control group (n = 11) consisted of healthy asymptomatic female individuals who were matched for age and body mass index (BMI), and who had normal serum levels of thyroid-stimulating hormone (TSH) and anti-thyroglobulin and anti-thyroid peroxidase antibodies.

The underlying thyroid disorders in the patient cases were Hashimoto's thyroiditis (n = 21), Graves' disease treated with radioiodine (n = 2), and hypothyroidism after thyroidectomy (n = 6). The exclusion criteria were pregnancy or lactation; hepatic or renal dysfunction; history of heart failure; diabetes mellitus; stroke or ischemic heart disease; significant neurological or psychological disease such as depression, epilepsy, or schizophrenia; malignancy; and alcohol or drug abuse. Patients were also excluded if they had been on any special lipid-lowering diet or used any medication that might affect study parameters within the 6 mo prior to the study. Such drugs included thyroid hormone preparations, lipid-lowering agents, anti-thyroid medications, amiodarone, multivitamins, oral contraceptives, antidepressants, anti-serotonergics, oral corticosteroids, antifolates, and anti-convulsant agents.

All patients and controls underwent an initial screening assessment that included collection of medical history and a physical examination. Each subject was then asked to revisit the clinic on a day that suited them for an oral lipid-loading test after a 12-h fast.

Anthropometric Measurements

Before the oral lipid-loading test, subjects' height, weight, and waist and hip measurements were recorded by the same doctor. Waist circumference was measured with a folding tape at the natural waistline (the level of the umbilicus) in

a horizontal plane. Hip circumference was measured as the diameter at the level of the greater trochanters in a horizontal plane. BMI was calculated by dividing body weight in kilograms by the square of height in meters.

Laboratory Investigations and 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" prior to 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 (see below) and blood samples for triglyceride were obtained every 2 h for a total of 8 h.

The parameters measured in fasting serum sample were glucose, insulin, CRP, uric acid, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies, total cholesterol, HDL-C, LDL-C, triglycerides, homocysteine, lipoprotein(a), and apolipoprotein B. Serum glucose was measured using the glucose oxidase technique (Roche Diagnostics GmbH, Mannheim, Germany). Insulin levels were measured by microparticle enzyme immunoassay (Abbott, Weisbaden-Delkenheim, Germany). Total cholesterol, HDL-C, and triglyceride concentrations were measured by enzymatic assay (Boehringer-Mannheim, Mannheim, Germany). LDL-C and VLDL-C was calculated using the Friedewald formula (LDL-C = total cholesterol – (HDL-C + triglyceride/5). CRP and apolipoprotein B were analyzed by the immunoturbidimetric method (Boehringer-Mannheim). Levels of free T3, free T4, TSH, anti-thyroglobulin antibodies, and anti-thyroid peroxidase antibodies were determined using immunometric assays (Diagnostic Products Corporation, Los Angeles, CA, USA). Each subject's level of insulin resistance was estimated based on the HOMA index, which was calculated as follows:

(Fasting Insulin [μU/mL] – Fasting Glucose [mmol/L]) ÷ 22.5.

Test Meal

The test meal (breakfast) was prepared in our hospital's Nutrition and Dietetic section such that it would provide a total of 800 kcal, comprising 62% fat, 26% carbohydrates, and 12% protein. The content was as follows: one glass whole/homogenized milk containing an additional 30 g milk powder; 10 g walnuts; 20 g butter; 50 g cream cheese; two thin slices of white bread.

Postprandial Lipemia

Subjects who showed an 80% or greater rise in triglyceride (compared to baseline) at 4 or 6 h after lipid loading were considered PPL positive *(28)*.

Statistical Methods

All continuous data were expressed as mean ± SD. Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows version 11.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was applied to assess for normal distribution. The area under the curve representing the triglyceride measurements obtained every 2 h was calculated using the trapezoidal method. One-way ANOVA testing was used to compare means for the three groups' (overt hypothyroid, subclinical hypothyroid, controls) normally distributed parameters. The Kruskal–Wallis *H* test was used for parameters that did not show normal distribution. Repeated measurements of the ANOVA *F* test were used to assess triglyceride changes in each group after oral lipid loading. Frequency analyses were done using chi-square and Bonferroni multiple comparison tests with the aid of cross-tables. Subclinical and overt hypothyroidism groups were merged to calculate relative risk for PPL. Correlation analysis was assessed with the Pearson or Spearman correlation analysis. Paired *t* tests were used to assess parameter changes that occurred between groups. A simple logistical regression model was used to identify independent risk factors for development of PPL. p values < 0.05 were considered statistically significant.

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