CLINICAL STUDY

Lipid profile in subclinical hypothyroidism: is L-thyroxine substitution beneficial?

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Abstract

Objective: The significance of dyslipidemia in subclinical hypothyroidism (SH) and the effect of thyroid substitution on lipids remain controversial. The present study aimed to assess the association of SH with lipid abnormalities and to quantify the effect of L-thyroxine therapy on serum lipid profiles.
Design: Serum lipid parameters of 66 patients with SH and 75 age- and sex-matched euthyroid controls were evaluated in a cross-sectional study.
Results: Patients with SH had higher total cholesterol (TC) (222 ± 45 (S.D.) vs 190 ± 32 mg/dl), low-density lipoprotein cholesterol (LDL-C) (139 ± 28 vs 118 ± 39 mg/dl), apolipoprotein B (149 ± 21 vs 139 ± 18 mg/dl) and lipoprotein (a) (Lp(a)) (median 12.5 (0.8–101) mg/dl vs 7 (0.8–44) mg/dl) levels compared with euthyroid controls ($P < 0.05$ for all comparisons). In a follow-up study including 37 patients with SH, all measurements were repeated after restoration of a euthyroid state with incremental doses of L-thyroxine. No significant changes in serum lipid profiles were observed except for a decrease in high-density lipoprotein cholesterol (59 ± 15 to 55 ± 14 mg/dl, $P < 0.05$). However, patients with high pre-treatment TC (≥240 mg/dl) showed a significant reduction in both TC (278 ± 28 vs 257 ± 36 mg/dl, $P < 0.05$) and LDL-C (192 ± 23 vs 173 ± 28 mg/dl, $P < 0.01$) levels. Similar but more pronounced changes were observed in a subgroup of patients with pre-treatment levels of TSH $\geq10\,\mu U$/ml. Thyroid autoimmunity had no effect on either the baseline or the post-treatment lipid profile.
Conclusion: Although patients with subclinical hypothyroidism exhibit increased levels of the atherogenic parameters (mainly LDL-C and Lp(a)), thyroid substitution therapy does not seem to significantly improve dyslipidemia in the whole group of patients.

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Introduction

Overt hypothyroidism is associated with abnormalities of lipid metabolism, which may predispose to the development of atherosclerotic coronary artery disease (CAD) (1, 2). However, a precise relationship between overt hypothyroidism and CAD has not been confirmed, although data linking these two conditions have been demonstrated in autopsy studies (1, 2). Subclinical hypothyroidism (SH), defined as the clinical status of elevated serum thyrotropin (TSH) levels, with normal levels of thyroxine (T_4) and triiodothyronine (T_3), is a more common disorder than overt hypothyroidism with a prevalence of 1.4–7.8% in older populations and even greater percentiles among women (3, 4). Some studies have associated this subtle change in thyroid function with increased risk of CAD (1, 4–6). Lipid

abnormalities would offer the most obvious explanation for this phenomenon, but several studies have shown conflicting results concerning not only the degree of lipid changes in SH but also the effect of L-thyroxine substitution therapy (2, 4, 7).

The aim of the present study was to determine the effect of SH on fasting serum lipids and to quantify the effect of L-thyroxine therapy on serum lipid profile.

Materials and methods

Subjects

Sixty-six subjects (61 women and 5 men) aged 47.6 ± 13 (S.D.) years with SH were studied. The mean body mass index (BMI) was 28.2 ± 5.6 kg/m^2. SH was established in terms of TSH levels $\geq4.5\,\mu U$/ml and normal

free T_4 and total T_3 levels, in two consecutive measurements. There was no history of thyroidectomy (total or subtotal), and prior exposure to radioiodine or external radiation was not recorded in any of the patients included in the study. A physical examination was performed in all subjects and a detailed history with emphasis on symptoms related to impaired thyroid function was recorded at each visit (particularly in those subjects with TSH > 10 µU/ml). Forty-three of the female patients were post-menopausal but none was receiving hormone replacement therapy at the time of the study. At the time of the study, 39 patients had significantly raised thyroid autoantibodies.

Seventy-five age- and sex-matched healthy individuals were used as controls in baseline measurements. The control group consisted of 66 women (44 post-menopausal) and nine men. The mean age of the controls was 48 ± 12 years and mean BMI $27\pm1.2\,\mathrm{kg/m^2}$.

None of the participants was diagnosed with neoplastic, renal, liver disease, diabetes mellitus or familial hypercholesterolemia. Subjects receiving drugs known to affect lipid metabolism were excluded from the study. Smoking habits were comparable in both the patient and the control group.

Thirty-seven patients (35 women (17 post-menopausal) and two men) eventually completed the study protocol. These patients were treated with incremental daily doses of L-thyroxine $(50-75-100-150\,\mu g)$, each dose given for at least 1 month, until euthyroid status was achieved. No selection was made with regard to the severity of dyslipidemia or the TSH levels.

Methods

Blood samples were drawn after overnight fasting under basal conditions and 3 months after dose titration was completed.

Total T_3 (normal range $0.6-1.7\,\mathrm{ng/ml}$), free T_4 (normal range $0.7-2.7\,\mathrm{ng/dl}$) and TSH (normal range $0.2-4.8\,\mu U/ml$) were measured by immunoassay on an AxSYM analyzer (Abbott Laboratory, Abbott Park, IL, USA). The sensitivities of the assays were calculated to be $0.3\,\mathrm{ng/ml}$, $0.4\,\mathrm{ng/dl}$ and $0.03\,\mu U/ml$ respectively. Anti-thyroid peroxidase and anti-thyroglobulin antibodies were detected by hemagglutination; samples providing agglutination to a dilution of 1/100 and 1/200 respectively were regarded as positive [8].

Serum total cholesterol (TC) and triglycerides (TG) were determined by enzymatic colorimetric assay (Olympus AU560; Diagnostica, Hamburg, Germany). High-density lipoprotein (HDL) cholesterol (HDL-C) was determined enzymatically in the supernatant after dextran–magnesium-induced precipitation of other lipoproteins. Low-density lipoprotein (LDL) cholesterol (LDL-C) was calculated using the Friedewald formula [9]. Serum apolipoprotein (Apo) A-I and Apo B were measured by immunonephelometry in a Behring Nephelometer BN100 (Behring Diagnostics, Frankfurt,

Germany). The assays were calibrated according to the International Federation of Clinical Chemistry standards.

Lipoprotein (a) (Lp(a)) was measured using a monoclonal anti-Lp(a) antibody technique by the enzyme immunoassay Macra Lp(a) (Terumo Medical Corporation Division, Elkton, MD, USA). The lower limit of detectability was $0.8\,\mathrm{mg/dl}$. The intra- and interassay coefficients of variation were less than 6.0 and 10.3% respectively [8].

Statistical analysis

Statistical analysis was carried out using a paired Student's t-test for all variables except for Lp(a), where a Wilcoxon signed-rank test was used due to its skewed distribution. The program Statistica (1998, Statsoft, Inc, Tulsa, OK, USA) was used for the analysis.

Results

Patients with SH had significantly higher levels of TC, LDL-C, Apo B and Lp(a) compared with controls, whereas levels of TG, HDL-C and Apo A-I were similar in the two groups (Table 1).

In patients who received L-thyroxine replacement therapy $(n = 37)$, a significant decrease of TSH levels (from 11.9 ± 7.1 to $1.6\pm1.2\,\mu U/ml$, $P < 0.00001$) was observed after treatment, accompanied by a significant increase in free T_4 levels (from 0.9 ± 0.2 to $1.4\pm0.4\,\mu U/ml$, $P < 0.000001$). L-Thyroxine resulted in a non-significant reduction in total and LDL-C levels (by 3.8 and 4.6% respectively). However, L-thyroxine replacement therapy was associated with a significant reduction in HDL-C concentration by 6.8% (59 ± 15 to $55\pm14\,\mathrm{mg/dl}$, $P < 0.05$) (Table 2).

There were 14 patients with SH whose pre-treatment TC levels exceeded $240\,\mathrm{mg/dl}$. In this subgroup, after L-thyroxine substitution, a significant fall in both TC and LDL-C levels was observed and it was not accompanied by significant decrease in HDL-C levels (Table 3).

Table 1 Lipid parameters in patients with subclinical hypothyroidism vs controls. Values represent means±S.D., except for Lp(a) where median and ranges are shown.

Parameters	Patients ($n = 66$)	Control population ($n = 75$)	P
TC (mg/dl)	222 ± 45	190 ± 32	<0.05
LDL-C (mg/dl)	139 ± 28	118 ± 39	<0.05
HDL-C (mg/dl)	57 ± 16	55 ± 12	NS
TG (mg/dl)	104 ± 56	99 ± 44	NS
TC/HDL-C	4.2 ± 1.1	3.8 ± 1.2	<0.05
Apo A-I (mg/dl)	148 ± 12	144 ± 16	NS
Apo B (mg/dl)	149 ± 21	136 ± 18	<0.05
Lp(a) (mg/dl)	12 (0.8–101)	7 (0.8–44)	<0.05

Table 2 Thyroid and lipid parameters before and after treatment with L-thyroxine in patients with subclinical hypothyroidism ($n = 37$). Values represent means±S.D., except for Lp(a) where median and ranges are shown.

Lipid parameters	Before L-thyroxine replacement	After L-thyroxine replacement	P
TSH (μU/ml)	11.9±7.1	1.6±1.2	<0.000001
Free-T_4 (ng/dl)	0.9±0.2	1.4±0.4	<0.000001
T_3 (ng/ml)	1.1±0.2	1.1±0.2	NS
TC (mg/dl)	232±47	223±45	NS
LDL-C (mg/dl)	152±42	145±35	NS
HDL-C (mg/dl)	58±15	55±14	<0.05
TG (mg/dl)	115±61	114±52	NS
TC/HDL-C	4.2±1.3	4.3±1.1	NS
Apo A-I (mg/dl)	147±14	142±15	<0.05
Apo B (mg/dl)	163±34	159±39	NS
Lp(a) (mg/dl)	8 (0.8−64)	9 (0.8−60)	NS

Table 3 Thyroid and lipid parameters before and after treatment with L-thyroxine in patients with subclinical hypothyroidism and initial total cholesterol levels ≥240 mg/dl ($n = 14$). Values represent means±S.D., except for Lp(a) where median and ranges are shown.

Lipid parameters	Before L-thyroxine replacement	After L-thyroxine replacement	P
TSH (μU/ml)	13.2±8.5	1.3±1.2	<0.001
Free-T_4 (ng/dl)	0.8±0.1	1.4±0.3	<0.0001
T_3 (ng/ml)	1.1±0.1	1.1±0.2	NS
TC (mg/dl)	278±28	257±36	<0.05
LDL-C (mg/dl)	192±23	173±28	<0.01
HDL-C (mg/dl)	61±12	56±11	NS
TG (mg/dl)	129±40	139±57	NS
TC/HDL-C	4.8±1.0	4.6±0.9	NS
Apo A-I (mg/dl)	149±15	144±18	NS
Apo B (mg/dl)	174±36	156±33	<0.05
Lp(a) (mg/dl)	8.3 (0.8−64)	8.1 (0.8−60)	NS

Table 4 Lipid parameters before and after treatment with L-thyroxine in patients with subclinical hypothyroidism and initial thyrotropin levels ≥10 μU/ml ($n = 18$). Values represent means±S.D., except from Lp(a) where median and ranges are shown.

Lipid parameters	Before L-thyroxine replacement	After L-thyroxine replacement	P
TSH (μU/ml)	17.2±7.1	1.5±1.4	<0.000001
Free-T_4 (ng/dl)	0.8±0.1	1.5±0.3	<0.000001
T_3 (ng/ml)	1.1±0.2	1.1±0.2	NS
TC (mg/dl)	237±51	215±49	<0.01
LDL-C (mg/dl)	155±43	141±38	<0.05
HDL-C (mg/dl)	57±15	50±12	<0.01
TG (mg/dl)	120±57	121±57	NS
TC/HDL-C	4.4±1.2	4.4±1.1	NS
Apo A-I (mg/dl)	149±14	141±12	<0.05
Apo B (mg/dl)	151±31	139±28	<0.05
Lp(a) (mg/dl)	8 (0.8−64)	7 (0.8−43)	NS

In the subgroup of patients ($n = 18$) with original TSH levels ≥10 μU/ml, L-thyroxine substitution resulted in a significant reduction in TC concentration (9.3%, $P < 0.01$) and LDL-C (8.4%, $P < 0.05$). HDL-C also decreased significantly by 12.3% ($P < 0.01$) (Table 4).

L-Thyroxine replacement did not produce any significant changes in Lp(a) concentrations in any of the studied groups.

There were no significant differences in lipid profiles between patients with positive thyroid antibodies and

those without any evidence of thyroid autoimmunity (data not shown).

Discussion

The nature and degree of dyslipidemia in overt hypothyroidism has been demonstrated in many studies and there is no doubt about the beneficial effects of thyroid substitution on serum lipids and on the risk for CAD (1, 2, 10). However, the possible effects of subtle alterations of thyroid function on lipid profile and atherogenesis remain unclear (7). There is, in fact, doubt as to whether SH should be treated (4). The evidence provided by different authors is controversial and concerns different aspects of this condition. There is growing evidence, however, that SH is an indicator of increased risk for atherosclerosis and myocardial infarction in elderly women (6).

In a substantial number of studies, TC and/or LDL-C seem to be elevated in SH compared with controls (11–16). However, there are studies that do not confirm this observation (1, 17–23). In this respect, in our cohort, subjects with SH had significantly higher levels of TC, LDL-C, Apo B and Lp(a), thus displaying a more atherogenic lipid profile when compared with healthy individuals. The lipid response to L-thyroxine substitution is another, yet clinically very important matter. The results of previous studies have been inconsistent. A number of studies suggest a decrease of TC and LDL-C after L-thyroxine-substitution (11, 15, 24–27), whereas others report no significant changes (22, 28–34). It appears that the degree of change depends on two parameters: the initial levels of cholesterol (35, 36) and the degree of thyroid dysfunction (17). Indeed, in the subgroups of patients with 'more severe' hypothyroidism (namely TSH $\geq 10\,\mu$U/ml) or high baseline levels of TC (≥ 240 mg/dl), there was a significant response of TC and LDL-C to treatment. Even more contradictory results have been presented on HDL-C levels. They are reported as either lower (12, 14, 16, 22), or comparable (11, 13, 15, 17, 18–21) with control groups. Furthermore, the response of HDL-C levels to thyroid substitution remains obscure.

A few studies have shown an increase in HDL-C levels (22), whereas others showed either no change or decreases (15, 27–30). A recent meta-analysis including 13 studies showed no effect of L-thyroxine therapy on HDL-C and TG concentrations (36). In our study, a significant decrease in HDL-C levels was observed after initiation of L-thyroxine therapy both in the treated group as a whole and in the subgroup with higher initial TSH levels. To our knowledge, only a few studies have shown a post-treatment decrease in HDL levels (15, 27). It is well known that hepatic lipase activity is low in hypothyroid patients (13, 14, 37) and increases with thyroid substitution therapy, leading to an increased catabolism of HDL_2 and lower HDL-C plasma concentrations (37). Although decreased hepatic lipase activity has not been shown in SH, our finding could be attributed to an increase of hepatic lipase activity triggered by L-thyroxine. The percentage of the TC and LDL-C decreases after treatment found in our group of patients is comparable with previous observations (35).

Lp(a) is an independent risk factor for atherosclerosis (8). There is limited information with regard to the effect of SH on Lp(a) levels (Table 4). Lp(a) levels and their response to treatment in SH have been evaluated in five previous studies (11, 12, 20, 24, 38) (Table 5). All but one failed to demonstrate any significant changes in Lp(a) levels following L-thyroxine substitution therapy. In our study, a considerable number of subjects with SH were included. SH was associated with raised serum Lp(a). However, Lp(a) did not change after treatment with L-thyroxine. This suggests the predominance of genetic factors in Lp(a) metabolism, at least in SH, although thyroid hormones are proposed to play a role in Lp(a) metabolism (20). As stated before, changes in Lp(a) are more prominent in the transition from a hyper- to a euthyroid state, where possibly the catabolism of Lp(a) through the LDL receptor plays a more important role than its production (20, 39).

The question whether SH should be treated or not is still pending. Large randomized trials are necessary to determine whether treatment with L-thyroxine will beneficially influence the quality of life in otherwise asymptomatic subjects and by improving the lipid

Table 5 Studies on Lp(a) levels and changes after L-thyroxine substitution in subclinical hypothyroidism. Lp(a) values are expressed in mg/dl except from the study of Kung *et al.* where they are shown in U/l. Lp(a) values represent median and ranges except from the study of Yildirimkaya *et al.* where means±s.e.m. are shown.

Author#	Number	Before treatment	Controls	*P*-value	After treatment	*P*-value
Arem *et al.* (25)	14	23 (0.99–101.6)	—	—	29 (1.98–1003)	NS
Kung *et al.* (12)	32	296 (48–1650)	182 (19–1952)	<0.005	—	—
Yildirimkaya *et al.* (11)	20	16.3±1.5	13.1±1.5	NS	12.6±1.2	<0.001
Engle & Riesen *et al.* (20)	33	7.9 (1.6–39.1)	—	—	7.5 (1.7–32.6)	NS
Tzotzas *et al.* (38)	23	11.5 (5–155)	11.2 (5–73)	NS	9.7 (5–90)	NS
Efstathiadou *et al.* (this study)	67	12 (0.8–101)	7 (0.8–44)	0.05	9 (0.8–60)*	NS

*Comparison with pretreatment levels in 37 patients who received L-thyroxine substitution.

profile result in a reduction in the incidence of CAD in these patients. In the present study, although SH patients exhibit a more atherogenic lipid profile compared with healthy individuals, thyroid substitution therapy did not significantly improve dyslipidemia. A novel finding in this study is the significant reduction in HDL-C after thyroid substitution, which could undermine the beneficial effect of total and LDL-C reduction. Our findings suggest that thyroid substitution, if used, would be most beneficial in patients with prominent thyroid dysfunction (TSH levels >10 μU/ml) and greater initial cholesterol levels.

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