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Lipoprotein Profile in Subclinical Hypothyroidism: Response to Levothyroxine Replacement, a Randomized Placebo-Controlled Study

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The relationship between subclinical hypothyroidism (SCH) and an atherogenic lipoprotein profile is still controversial. We measured lipoproteins in 49 SCH patients by comparison with 33 euthyroid controls. Total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDLc), apolipoprotein A_1, apolipoprotein B, and lipoprotein (a) [Lp(a)] were measured after an overnight fast. Patients were randomly assigned to levothyroxine therapy or placebo and re-evaluated after 6 months of euthyroidism. SCH patients showed significantly higher TC ($P < 0.01$), LDLc ($P = 0.01$), and apolipoprotein B ($P = 0.001$) levels than controls, positively correlated with baseline TSH levels ($P = 0.003$, $P = 0.01$, and $P = 0.03$, respectively). Elevated Lp(a) levels were significantly more frequent in SCH ($P < 0.05$) and associated with familial diabetes mellitus and/or coronary heart disease ($P < 0.01$). Levothyroxine treatment resulted in a significant decrease of both TC and LDLc concentrations ($P = 0.003$), in direct proportion to the respective baseline values ($P < 0.05$ and $P < 0.01$, respectively), whereas no change in Lp(a) level was observed. No changes occurred in the placebo group. In conclusion, only serum LDLc levels are increased specifically and reversibly in association with SCH. Altered Lp(a) values reflect a genetic influence rather than a reduced thyroid hormone action. (*J Clin Endocrinol Metab* 87: 1533–1538, 2002)

SUBCLINICAL HYPOTHYROIDISM (SCH) is defined by the finding of elevated serum TSH concentrations associated with normal free thyroid hormone levels (FT_4 and FT_3). The prevalence of this condition is higher in women than men and increases with age, reaching a peak of 21% in women and 16% in men over 74 yr of age (1–4). After 20 yr of follow-up, the incidence of progression to overt hypothyroidism was 4.3% per year in women with both elevated serum TSH levels (>6 mIU/liter) and positive antithyroid antibody titers, 2.6% if raised serum TSH was present alone, and 2.1% if antithyroid antibodies alone were positive (5). Because SCH is often regarded as a solely biochemical abnormality, the need for lifelong levothyroxine (L-T_4) replacement therapy is still under debate. L-T_4 treatment is generally considered in two prospects: 1) to prevent progression to overt hypothyroidism, and 2) to reduce symptoms of thyroid hormone deficiency (which appear to be reversible in at least 25% of patients suffering from SCH) (6–9). A reversible impairment of systolic and diastolic myocardial function has also been reported in SCH (10, 11), and the condition has been claimed to be a risk factor for coronary heart disease and peripheral arterial disease (1, 12–14). However, whether this risk is conveyed by an altered lipid profile is uncertain because the relationship between SCH and serum lipid levels is controversial (15–19).

Some cross-sectional studies have reported that serum cholesterol levels are significantly elevated in SCH patients (4, 8, 13, 16, 18, 20), but in other reports the differences from euthyroid subjects were not significant (1, 15, 21). A meta-analysis of 13 intervention studies showed that, in SCH patients L-T_4 therapy lowered serum total cholesterol (TC) by 0.20 mmol/liter (or 5%) and low-density lipoprotein cholesterol (LDLc) by 0.26 mmol/liter (22). However, in a recent study, none of the serum lipoproteins were found to differ between SCH patients and euthyroid controls, and no significant changes were seen after the euthyroid stage was reached (23). These conflicting results might be, at least in part, explained by different patient selection (age, inclusion of patients with unstable SCH, and smoking status) and different diagnostic criteria (too large a range of TSH levels, inclusion of patients with low serum FT_4 levels).

The aim of the present study therefore was to evaluate the lipoprotein profile in a group of rigorously selected patients with stable SCH and positive antithyroid antibody titers. A possible genetic influence was also investigated by recording familial disposition to diabetes mellitus and/or premature coronary heart disease. To verify the potential beneficial effect of L-T_4 therapy, the patients were then randomized to a placebo-controlled, L-T_4 treatment course.

Patients and Methods

Patients

Forty-nine SCH patients [7 men and 42 women; age, 35 ± 9 yr; range, 18–50 yr; body mass index (BMI), 24.3 ± 3.8 kg/m^2] were recruited from the outpatient clinic of the Department of Internal Medicine of the University of Pisa. Forty-eight patients had Hashimoto's thyroiditis; one with Graves' disease had developed SCH 1 yr after radioiodine therapy. All patients were positive for both antithyroid peroxidase and anti-Tg autoantibodies; their thyroid hormone profile is shown in Table 1. To be enrolled, patients had to have documented SCH (TSH > 3.6 mIU/liter) for at least 6 months before the study; 12 SCH women had serum TSH

Abbreviations: $ApoA_1$, Apolipoprotein A_1; ApoB, apolipoprotein B; BMI, body mass index; CI, confidence interval; FT_3, free T_3; FT_4, free T_4; HDLc, high-density lipoprotein cholesterol; IRMA, immunoradiometric assay; LDLc, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); L-T_4, levothyroxine; SCH, subclinical hypothyroidism; TC, total cholesterol; TG, triglyceride.

TABLE 1. Baseline lipoprotein profile, thyroid function, age, and BMI in the study subjects

	Controls (n = 33)	Patients (n = 49)
Age (yr)	32.3 ± 9.2	34.5 ± 9.1
BMI (kg/m^2)	22.9 ± 3.1	24.3 ± 3.8
TSH (mIU/liter)	1.36 (0.63–2.65)	5.43[a] (3.65–15.00)
FT_4 (pmol/liter)	13.1 ± 2.3	11.9 ± 2.2[e]
FT_3 (pmol/liter)	5.2 ± 0.6	4.8 ± 0.6[b]
TC (mmol/liter)	4.7 ± 0.6	5.4 ± 1.1[c]
HDLc (mmol/liter)	1.4 ± 0.3	1.5 ± 0.3
LDLc (mmol/liter)	2.9 ± 0.5	3.4 ± 1.0[d]
Triglyceride (mmol/liter)	1.2 ± 0.5	1.3 ± 0.5
$ApoA_1$ (mg/dl)	151.5 ± 28.8	160.0 ± 25.2
ApoB (mg/dl)	88.0 ± 19.7	107.4 ± 26.1[b]
Lp(a) (mg/dl)	13.1 ± 4.2	26.0 ± 24.0
Cholesterol/HDL	3.4 ± 0.6	3.8 ± 1.2
LDL/HDL	2.1 ± 0.5	2.4 ± 1.1
LDL/ApoB	1.3 ± 0.2	1.3 ± 0.2

TSH values are expressed as mean and range; the other data are expressed as mean ± SD.

[a] $P < 0.0001$; [b] $P = 0.001$; [c] $P < 0.01$; [d] $P = 0.01$; [e] $P < 0.05$ *vs.* controls.

levels greater than 6.00 mIU/liter, *i.e.* they were at highest risk for developing overt hypothyroidism. Thirty-three euthyroid subjects matched to the patient group for sex (27 women, 6 men), age (32 ± 9 yr, range 19–48 yr), and BMI (22.9 ± 3.1 kg/m^2) were recruited among staff and relatives of patients and served as the control group. Thyroid autoimmunity was detected in none of the controls; their thyroid hormone profile is given in Table 1. All subjects were in good health, all women were premenopausal with regular menses, and none was pregnant. Obese (BMI > 30 kg/m^2) subjects, smokers, and those with primary or secondary dyslipidemia, diabetes mellitus, renal and hepatic failure, or other systemic diseases were excluded from the study [the cut-off levels of TC and triglyceride (TG) used to exclude patients were 7.8 and 4.6 mmol/liter, respectively]. Routine laboratory chemistry was normal in all, and none was taking any drug. The presence of familial history of coronary heart disease and/or diabetes mellitus was recorded. All subjects were on a free diet and were advised to maintain their dietary habits throughout the study. All study subjects gave their signed informed consent to the study, which was approved by the Institutional Ethical Committee.

Protocol

At baseline, blood samples were drawn at 0800 h after an overnight fast for the determination of serum TC, TG, high-density lipoprotein cholesterol (HDLc), LDLc, apolipoprotein A_1 ($ApoA_1$), apolipoprotein B (ApoB), and lipoprotein (a) [Lp(a)] concentrations. Then, patients were randomly assigned to L-T_4 replacement (n = 24) or placebo (n = 25). Tablets containing L-T_4 (Eutirox, Bracco SpA, Milan, Italy) or placebo were accurately counted and given to each patient. L-T_4 treatment always started with 25 μg, the dose being then gradually increased. To confirm patient compliance and to adjust L-T_4 dose, serum TSH was measured every 3 months. The L-T_4 dose required to restore euthyroidism eventually averaged 67.5 μg/d. Patients treated with L-T_4 were re-evaluated after 6 months of stable euthyroidism (mean, 11 months; range, 6–15), whereas patients taking placebo (one or two tablets) were restudied after 6 months of treatment.

Analytical measurements

Serum FT_3 and FT_4 concentrations were measured by specific RIA (Techno-Genetics Recordati, Milan, Italy). Serum TSH levels were determined by an ultrasensitive immunoradiometric assay (IRMA) method (Cis Diagnostici, Tronzano Vercellese, Italy). Anti-Tg antibodies were measured by a specific IRMA assay (TG-Ab IRMA, Biocode, Sclessin, Belgium); anti-TPO antibodies were measured by a specific RIA (AB-TPO; Sorin Biomedica, Saluggia, Italy). TC and TG were assayed using enzymatic methods (Roche Diagnostics, Mannheim, Germany). HDLc was measured enzymatically after precipitation of LDL and very LDL with Mg^{2+}-dextran (Roche Diagnostics). LDLc was calculated by Friedewald's formula. $ApoA_1$ and ApoB were determined immunochemically (Nephelometer, Behring Diagnostics, Marburg, Germany). Lp(a) concentrations were determined in serum by nephelometry (N latex Lp(a) reagent, Behring Diagnostics). Normal ranges in our laboratory are as follows: FT_4, 6.8–20 pmol/liter; FT_3, 4.3–8.6 pmol/liter; TSH, 0.30–3.6 mIU/liter; anti-Tg, less than 50 IU/ml; antithyroid peroxidase, less than 10 IU/ml; $ApoA_1$, 95–230 mg/dl; ApoB, 55–165 mg/dl; and Lp(a), less than 30 mg/dl.

Statistical analysis

Data were expressed as the mean ± SD. Unpaired or paired *t* test, χ^2 test, and two-way ANOVA for repeated measures were used as appropriate. Because of the highly skewed distribution of Lp(a) values, the nonparametric Mann-Whitney *U* test was applied to assess differences between groups. Linear regression analysis was carried out by standard techniques.

Results

Thirty-four per cent of the patients and 32% of the controls reported a positive family history for coronary heart disease and/or diabetes mellitus. BMI remained unchanged in all subjects throughout the study.

Thyroid hormones

At baseline, TSH levels were significantly higher in SCH patients than controls ($P < 0.0001$), whereas serum FT_3 and FT_4 levels, although still within the normal range, were significantly lower ($P = 0.001$ and $P < 0.05$, respectively) (Table 1). The only four SCH patients with serum TSH greater than 10 mIU/liter were randomized to the L-T_4-treated group. However, although the L-T_4-treated group tended to have higher TSH and lower FT_4 values at baseline, compared with the placebo group, there were no statistically significant differences in serum free thyroid hormone or TSH levels between the two groups (Table 2).

After therapy, serum TSH levels had returned within the normal range in the L-T_4-treated group and were now significantly lower than in the placebo group ($P < 0.0001$). Serum FT_3 and FT_4 levels remained within the normal range during the entire treatment period, both in placebo- and L-T_4-treated patients; however, FT_4 levels rose significantly in the L-T_4-treated group ($P = 0.0003$ *vs.* baseline) (Table 2).

Lipoprotein profile

At baseline, SCH patients showed significantly higher serum TC ($P < 0.01$), LDLc ($P = 0.01$), and ApoB ($P = 0.001$) levels than controls, whereas no differences were noted for HDLc, TG, or $ApoA_1$ concentrations, or the TC/HDL, LDL/HDL, and LDL/ApoB ratios. However, in the L-T_4-treated group, the LDL/HDL ratio was significantly different from controls (2.6 ± 1.2 *vs.* 2.1 ± 0.5; $P < 0.05$), and TC/HDL approached the statistical significance (3.9 ± 1.4 *vs.* 3.4 ± 0.6; $P = 0.052$) (Tables 1 and 2). Significant positive relationships were found between serum TSH and TC (r = 0.38; $P = 0.003$), ApoB (r = 0.33; $P = 0.02$), and LDLc (r = 0.40; $P = 0.005$) levels (Fig. 1). No differences were found for Lp(a) values between patients and controls; however, elevated Lp(a) levels (>30 mg/dl) were significantly more frequent in SCH (25% of patients *vs.* 7% of controls; $P < 0.05$) and were

TABLE 2. Thyroid function, lipoprotein profile, and BMI in SCH patients at baseline and after 6 months of stable euthyroidism or placebo

	Baseline		Post-treatment	
	SCH-L-T_4 (n = 24)	SCH-placebo (n = 25)	SCH-L-T_4 (n = 24)	SCH-placebo (n = 25)
BMI (kg/m^2)	24.2 ± 3.2	22.5 ± 2.5	24.1 ± 3.1	22.8 ± 2.7
TSH (mIU/liter)	6.00 (3.70–15.00)[a]	4.90 (3.65–9.00)	1.52 (0.60–3.20)[d]	4.86 (3.66–6.50)
FT_4 (pmol/liter)	11.6 ± 2.4[b]	12.7 ± 1.7	14.4 ± 2.4	12.9 ± 2.4
FT_3 (pmol/liter)	4.8 ± 0.6	4.8 ± 0.8	5.1 ± 0.6	4.9 ± 0.8
TC (mmol/liter)	5.5 ± 1.2[c]	5.3 ± 1.0	5.0 ± 1.1	5.3 ± 1.1
HDLc (mmol/liter)	1.5 ± 0.3	1.5 ± 0.4	1.4 ± 0.3	1.5 ± 0.3
LDLc (mmol/liter)	3.6 ± 1.1[c]	3.3 ± 0.9	3.1 ± 1.0	3.4 ± 0.9
Triglyceride (mmol/liter)	1.3 ± 0.5	1.4 ± 0.7	1.2 ± 0.6	1.3 ± 0.7
$ApoA_1$ (mg/dl)	161.8 ± 26.3	158.4 ± 24.5	149.0 ± 34.2	161.5 ± 21.5
ApoB (mg/dl)	109.6 ± 28.6	105.3 ± 24.0	101.3 ± 28.0	107.1 ± 27.1
Lp(a) (mg/dl)	25.8 ± 23.1	27.1 ± 26.2	24.5 ± 20.4	25.7 ± 24.6
TC/HDL	3.9 ± 1.4	3.6 ± 1.1	3.6 ± 1.1	3.7 ± 1.0
LDL/HDL	2.6 ± 1.2	2.3 ± 0.9	2.3 ± 0.9	2.4 ± 0.8
LDL/ApoB	1.3 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2

TSH values are expressed as mean and range; the other data are expressed as mean ± SD.
[a] $P < 0.0001$; [b] $P = 0.0003$; [c] $P = 0.003$ *vs.* post-L-T_4 therapy; [d] $P < 0.0001$ *vs.* placebo group.

associated with a positive family history of premature cardiovascular disease and/or diabetes ($P < 0.01$).

After 6 months of stable euthyroidism, L-T_4-treated patients showed a significant decrease in serum TC and LDLc concentrations ($P = 0.003$ for both). LDL/HDL and TC/HDL ratios and ApoB levels decreased slightly and were no longer different from control values. Conversely, Lp(a) levels were unchanged both as a mean and in the six patients with elevated baseline values (55 ± 14 *vs.* 59 ± 13 mg/100 ml) (Tables 1 and 2).

The reduction in serum TC averaged 0.47 ± 0.69 mmol/liter [with a 95% confidence interval (CI) of 0.76–0.16 mmol/liter] or −8.0%; for LDLc, the corresponding values were 0.41 ± 0.59 mmol/liter (95% CI, 0.67–0.15 mmol/liter) or −10.2%. The absolute decrements in serum TC and LDLc levels were directly related to the respective baseline values ($r = 0.43$, $P < 0.05$ and $r = 0.54$, $P < 0.01$, respectively) as well as to the baseline TSH levels ($r = 0.54$, $P < 0.01$ and $r = 0.57$, $P < 0.005$, respectively). A positive relationship between the absolute reductions of both TC and LDLc and the decrease of serum TSH was also observed ($r = 0.59$, $P = 0.002$ and $r = 0.60$, $P = 0.002$, respectively) (Fig. 2). Furthermore, in the subgroup of patients with high TSH value (>6 mIU/liter; n = 9), serum TC reduction averaged 0.85 mmol/liter (95% CI, 1.46–0.25 mmol/liter) or −11.3%; for LDLc, the corresponding values were 0.71 mmol/liter (95% CI, 1.30–0.12 mmol/liter) or −15.6%. By comparison, patients with lower TSH value (≤6 mIU/liter; n = 15) showed a lesser reduction in lipid concentrations: 0.32 mmol/liter (95% CI, 0.59–0.04) or −6.7% for TC ($P < 0.05$), and 0.30 mmol/liter (95% CI, 0.51–0.08) or −8.3% for LDLc ($P = 0.08$), respectively.

In the placebo group, no significant changes in any of the lipoprotein levels were seen. A comparison of the mean treatment effects between placebo- and L-T_4-treated patients did not reach the statistical significance in any of the lipid parameters (Table 2).

Discussion

A relationship between dyslipidemia and atherosclerosis is well established in overt hypothyroidism (24). Early clinical and autopsy studies have suggested an association between subclinical hypothyroidism and coronary heart disease (25–27). Furthermore, in a recent population-based survey, subclinical hypothyroidism emerged as an independent risk factor for aortic atherosclerosis and myocardial infarction (14). However, the association of SCH with changes in serum lipid levels and the effect of L-T_4 replacement on these changes are still open questions, despite the fact that several clinical trials have addressed the issue. In some large epidemiological studies, no association could be detected between SCH and serum TC or LDLc levels (1, 28). Tzotzas *et al.* (23) recently reported that none of the commonly measured lipoproteins differed between SCH patients and controls, nor did the lipoprotein profile change significantly in SCH patients upon achieving euthyroidism. In contrast, Caron *et al.* (29) reported lower HDLc levels in SCH patients than in a control group and demonstrated a significant increase in ApoA and HDLc levels after L-T_4 therapy, with normalization of the TC/HDLc ratio. Arem and Patsch (30), on the other hand, reported a reduction in LDLc, ApoB, and the TC/HDL ratio after L-T_4 replacement in a group of SCH patients with a mean TSH level of 16.6 mIU/liter. Recently, a double-blind, placebo-controlled trial (31) demonstrated the effectiveness of L-T_4 replacement therapy in both reducing LDL cholesterol levels and improving clinical symptoms of hypothyroidism in SCH patients. Moreover, LDLc decrease was more pronounced in SCH patients with high TSH values (>12 mIU/liter) or elevated pretreatment LDLc levels (>4.0 mmol/liter). These rather disparate results may depend on differences in patient selection (*e.g.* cause and duration of thyroid dysfunction, range of TSH values, smoking status) as well as time of evaluation after restoration of euthyroidism.

All of our patients had autoimmune thyroiditis with stable subclinical hypothyroidism of at least 6-month duration, and the control subjects were matched to the patients by sex, age, and BMI. In the comparison, this group of patients had significantly raised TC, LDLc, and ApoB levels, and 6 months of stable euthyroidism led to a significant reduction of TC and LDLc along with a slight decrease of ApoB levels. Both

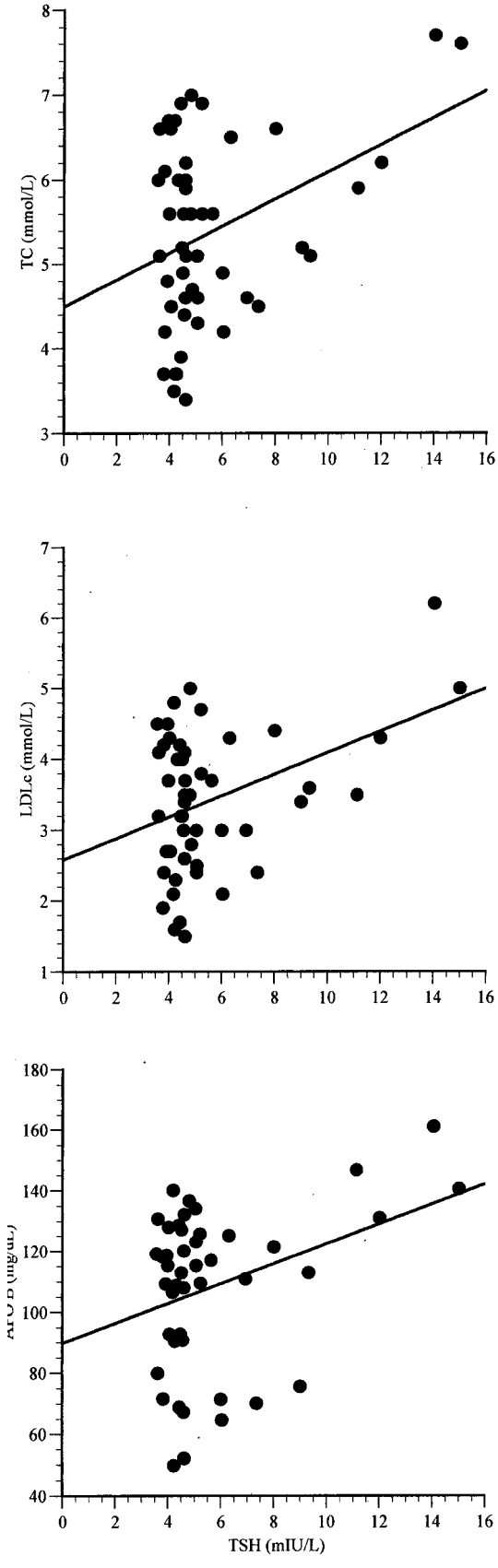

FIG. 1. Relationship between serum TSH and serum TC, LDLc, and ApoB levels in the study subjects at baseline.

TC/HDL and LDL/HDL ratios showed a slight, although not statistically significant, decrease, probably due to a concomitant marginal reduction in serum HDLc levels. Moreover, the tendency toward a pretreatment higher serum TSH level and worse lipid profile in the L-T4-treated than the placebo group may explain the lack of significant differences in TC and LDLc levels between the two groups at follow-up.

The decrements in TC and LDLc observed in the current study are almost twice as large as the mean decrements in 13 recently analyzed trials of L-T_4 therapy in SCH (22). This quantitative difference, and, more in general, the high variability of the reported therapeutic effects of L-T_4, are likely to result from three main factors: 1) suboptimal treatment of SCH; 2) different duration of restored euthyroidism; and 3) degree of initial dyslipidemia. In line with the latter explanation, we and others (17, 31) find that the changes in TC and LDLc with L-T_4 treatment are more pronounced in those patients that have the highest baseline cholesterol values. Furthermore, baseline TSH levels were directly related to baseline TC and LDLc levels and predicted the extent of their reduction after active treatment; in fact, the observed changes in TC and LDLc were significantly associated with the corresponding changes in TSH levels. Finally, according to a recent double-blind, placebo-controlled study (31), we found a better improvement in TC and LDLc levels in the subgroup of SCH patients with high TSH levels (>6 mIU/liter). Overall, these data suggest that the increase in serum total and LDLc values in SCH is, to an extent, related to the increase in TSH levels and that minimal treatment-induced changes in the latter have a measurable effect on TC and LDLc.

It should be emphasized that the observed decrease in LDLc levels induced by L-T_4 replacement therapy, although modest, is significant in terms of risk reduction for coronary heart disease (32). Although comparable data are not available for premenopausal women (*i.e.* the majority of our study population), the Helsinki Heart Study has shown that, in men a decrease of only 7% in LDLc levels is associated with a 15% reduction in the incidence of coronary heart disease (33). Thus, LDLc levels higher than 3.4 mmol/liter are generally considered to be the cut-off for treatment due to the increased risk of coronary heart disease (34). With regard to this, it should also be recalled that SCH is associated with reversible abnormalities of diastolic and systolic cardiac function (10, 11); moreover, preliminary data suggest the presence of endothelial dysfunction in SCH (35, 36).

Because of the evidence linking raised Lp(a) concentrations with the development of atherosclerosis (37), attention has focused on serum Lp(a) levels in thyroid diseases. This lipoprotein is synthesized mainly in the liver and consists of a LDL particle bound to an apoprotein that is structurally similar to plasminogen. The relationship between overt hypothyroidism and Lp(a) levels and the effect of L-T_4 therapy are still controversial (38). Fewer studies have investigated Lp(a) in SCH with inconsistent results. In some reports, raised Lp(a) levels were found in SCH patients with TSH values above 12 mIU/liter (16, 39); Tzotzas *et al.* (23), however, detected increased Lp(a) levels only in a subgroup of 13 postmenopausal SCH women, regardless of their serum TSH level. In the present series, raised Lp(a) levels were found in 25% of SCH patients *vs.* 7% of controls but remained

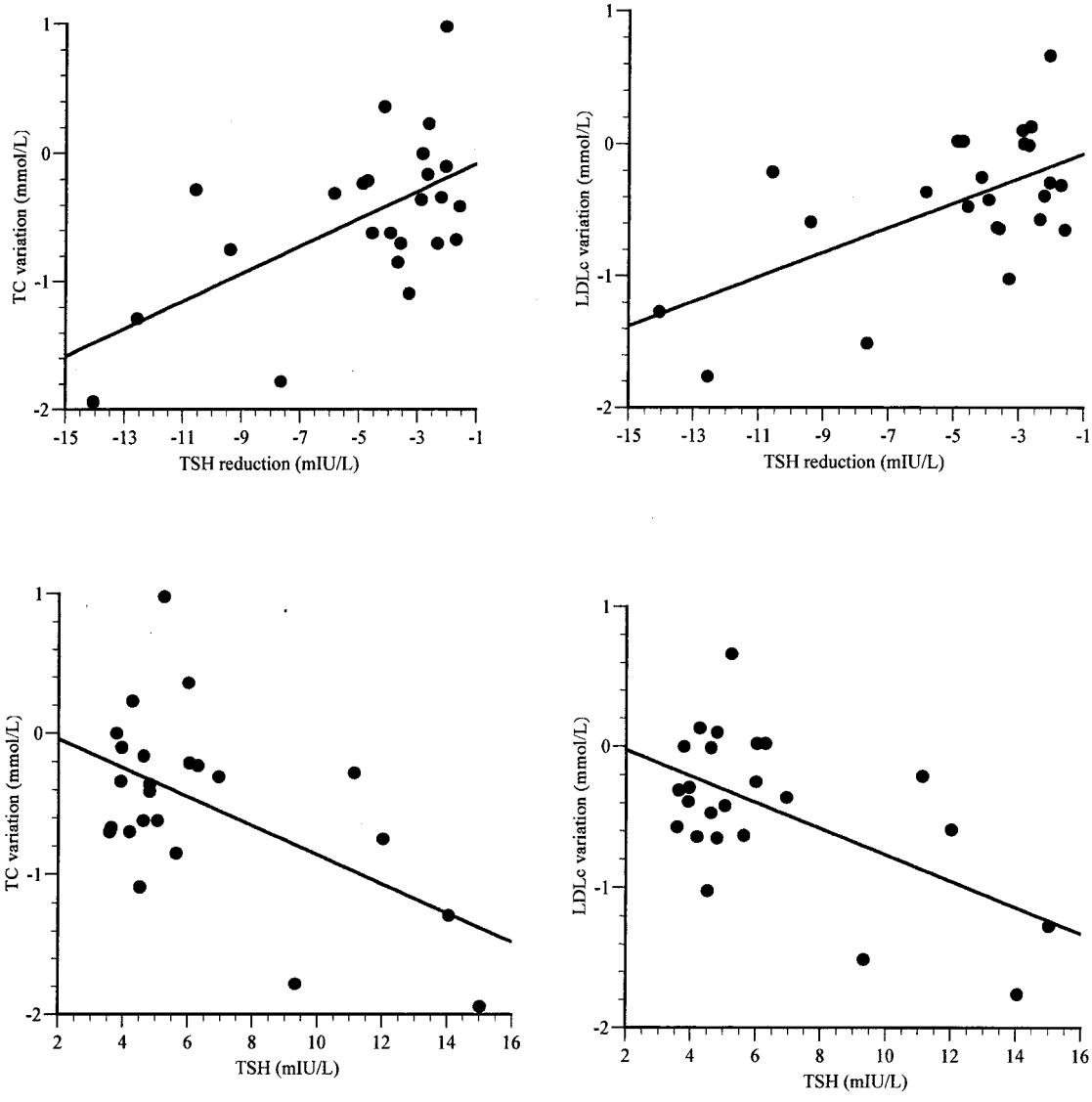

FIG. 2. Relationship between baseline values (*bottom panels*) and treatment-induced changes in TSH (*top panels*) and treatment-induced changes in TC and LDLc concentrations in subclinical hypothyroid patients after 6 months of stable euthyroidism.

unchanged 6 months after restoring euthyroidism by L-T_4 replacement. Furthermore, we found a significant association between elevated Lp(a) levels and a positive family history for coronary heart disease and/or diabetes mellitus. Although the possible role of thyroid autoimmunity *per se* in the Lp(a) metabolism should be not overlooked (40), these results suggest that altered Lp(a) concentrations reflect a genetic influence (41) rather than a reduced thyroid hormone action, and are therefore unaffected by L-T_4 treatment. Obviously, inherently elevated Lp(a) levels may conspire with the raised LDLc of untreated SCH to enhance cardiovascular risk.

In conclusion, only serum LDLc levels are increased specifically and reversibly in association with SCH; the increase is to an extent related to the increase in TSH levels and may translate into a sizeable cardiovascular risk. Altered Lp(a) values, which express genetic influence rather than reduced thyroid hormone action, may conspire with the raised LDLc of untreated SCH patients to enhance such risk.

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