Emerging Cardiovascular Risk Factors in Subclinical Hypothyroidism: Lack of Change After Restoration of Euthyroidism

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Subclinical hypothyroidism (SH) is a frequent condition that may be associated with increased cardiovascular risk. There is current interest in determining the effect, if any, of substitutive therapy with L-thyroxine (L-T4) on cardiovascular risk factors in SH and, particularly, on those associated with emerging cardiovacular risk, such as apolipoprotein (apo) B, lipoprotein (Lp) (a), total homocysteine (t-Hcy), and C-reactive protein (CRP). Thus, the aim of this study was to assess the impact of euthyroidism restoration on these emerging risk factors in SH. Forty-two patients diagnosed with SH were consecutively recruited before treatment. These patients were treated with L-T4 for 3 to 6 months with the dose necessary to restore euthyroidism. Lp(a), fasting and postmethionine (n = 28) t-Hcy, and CRP did not change with substitutive therapy, regardless of the respective baseline values, and the decrease in apo B paralleled that of low-density lipoprotein (LDL) cholesterol. Similarly, no treatment effect was observed on homocysteine or CRP in patients with thyrotropin-stimulating hormone (TSH) >10 mIU/L. Monitoring of emerging risk factors did not offer additional arguments for treating patients with SH and, thus, is not justified in their clinical management.

SUBCLINICAL HYPOTHYROIDISM (SH), defined by the presence of increased serum thyrotropin (thyrotropin-stimulating hormone [TSH]) concentration with normal free thyroxine (f-T_4) levels, is an extremely common condition present in 8% of women and 3% of men.[1] This condition was associated with increased cardiovascular mortality 2 decades ago.[2]. More recently, SH has been identified as an independent risk factor for aortic atherosclerosis and myocardial infarction in elderly women[3] and in subjects with TSH levels >10 mIU/L,[4] and variation of thyroid function within the normal range may influence the presence and severity of coronary atherosclerosis,[5] even though the level of evidence is still judged as insufficient.[6-8] In addition to the well-established cardiovascular risk factors, emerging risk factors may play a role in the development of clinical manifestations of atherothrombosis. These factors include, among others, increased blood concentrations of apolipoprotein (apo) B and lipoprotein (Lp) (a), total homocysteine (t-Hcy), and C-reactive protein (CRP). All are thought to increase the risk of different forms of vascular disease, including coronary, peripheral, and cerebrovascular disease. However, their relative and independent contribution to these diseases remains to be established.[9] The effects of L-thyroxine (L-T4) replacement on apo B and Lp(a) concentrations remain controversial,[10-19] whereas very limited information is available on fasting t-Hcy and CRP[20,21] levels and none on postmethionine-loading Hcy levels in patients with SH. Thus, the aim of this study was to assess the impact of correcting SH with L-T4 on the above-mentioned emerging cardiovascular risk factors. This aim is in line with a recent guideline for diagnosis and treatment of subclinical hypothyroidism,[6-8] which rated as insufficient or absent the level of evidence of the benefits of restoration of the TSH levels to reference levels.

SUBJECTS AND METHODS

Forty-two patients (36 women, 6 men; mean age, 51.7 ± 15 years) with newly diagnosed SH were consecutively recruited before treatment in our outpatient Endocrinology Clinic. SH was defined as an elevated TSH concentration (>5 mIU/L) in the presence of normal thyroxine levels in 2 determinations. Underlying thyroid disorders were autoimmune thyroiditis (n = 31), Graves' disease, and toxic multinodular goiter treated with radioiodine or surgery (n = 5) and idiopathic (n = 6). Patients were excluded if a history of nonthyroid illnesses, including recent infection, was present or if they had received vitamins, lipid-lowering drugs, or other medications known to interfere with homocysteine metabolism, lipid profile, or thyroid function. Written informed consent was obtained from all patients.

Study Design

After baseline evaluation and blood sampling, all patients were treated with L-T_4 for 3 to 6 months. Treatment started with 50 μg/d and TSH was measured every 6 to 8 weeks to adjust L-T_4 dose. Mean L-T4 dose required to restore euthyroidism was 90 ± 36 μg/d. All patients were revaluated 6 to 8 weeks after restoration of euthyroidism.

Biochemical Measurements

Blood specimens were collected at inclusion and after restoration of euthyroidism. Serum TSH, f-T_4 and free-T_3 (f-T_3), total cholesterol and triglyceride, and high-density lipoprotein (HDL) cholesterol were determined using commercially available methods. Low-density lipoprotein (LDL) cholesterol was calculated by Friedewald's formula.[22] T-Hcy levels were determined using an automated immunoassay[23] in fasting state in all patients and 6 hours after an oral methionine load (0.1 g /kg/ body weight) in a subgroup of 28 patients. Vitamin B_{12} and red cell folates were measured as previously reported.[24] CRP and Lp(a) were determined using commercial immune turbidimetric methods adapted to the 911 autoanalyzer (Roche Diagnostics, Basel, Switzerland); Apo B was determined in the same autoanalyzer using a commercial method (Roche Diagnostics) standardized against the World Health Organization (WHO)/International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) standard SP-03.

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Table 1. Characteristics of Patients at Baseline and After Restoration of Euthyroidism

Variable	Baseline	Posttreatment	*P* Value
BMI (kg/m^2)	28.6 ± 5.2	28.5 ± 5.1	NS
TSH (mIU/L)	10.4 ± 6.0	2.37 ± 1.6	<.001
f-T_4 (pmol/L)	12.87 ± 1.8	17.6 ± 3.9	<.001
f-T_3 (pmol/L)	5.55 ± 0.6	5.8 ± 0.8	<.05
Creatinine (μmol/L)	83.4 ± 11.5	82.2 ± 10.6	NS
Vitamin B_{12} (pmol/L)	409.2 ± 141.6	406.9 ± 138	NS
Red cell folate (nmol/L)	1,072 ± 265	947 ± 261	NS
Total cholesterol (mmol/L)	5.7 ± 1.0	5.5 ± 1.0	<.05
LDL cholesterol (mmol/L)	3.8 ± 0.8	3.5 ± 0.9	<.01
HDL cholesterol (mmol/L)	1.50 ± 0.4	1.42 ± 0.4	NS
Triglycerides (mmol/L)	1.05 ± 0.5	1.08 ± 0.7	NS

Abbreviation: NS, not significant.

Statistical Analyses

All data are expressed as means ± SD. Paired Student's *t* test and Wilcoxon signed rank test were applied, as appropriate, for comparisons before and after L-T_4 treatment. Significance was defined as $P < .05$. Analysis was performed using the SPSS 10.0 statistical package for Windows (SPSS, Chicago, IL).

RESULTS

The main clinical and biochemical characteristics of patients before and after L-T_4 therapy are summarized in Table 1. By definition, all patients presented with increased TSH levels (>5 mIU/L;, range, 5.3 to 29.14 mIU/L) and f-T_4 and f-T_3 within reference range (9.2 to 23 pmol/L and 4 to 8 pmol/L, respectively) at baseline. No patients had vitamin B_{12} and/or folate deficiency,[24] and plasma creatinine concentrations were within the respective age and sex reference range. After L-T_4 therapy, serum TSH levels decreased to normal range in all patients, whereas f-T_4 and f-T_3 increased significantly, although remaining within normal range. No significant changes were observed in body mass index (BMI), folate, vitamin B_{12}, and creatinine levels. Restoration of euthyroidism was associated with a 4% and 6.5% decrease in total and LDL cholesterol, respectively. In the subgroup of patients with TSH levels >10 mIU/L (n = 16, mean TSH concentration 16.31 ± 6.58; range, 10.5 to 29.4mIU/L), the percent reduction was 6.9% for total and 10.4% for LDL cholesterol, whereas no significant changes were observed in patients with initial TSH levels between 5 and 10 mU/L. Treatment did not change triglyceride and HDL cholesterol levels.

The effects of L-T_4 treatment on emerging cardiovascular risk factors are shown in Table 2. Apo B levels decreased significantly in the whole group (5.6%) and in the subgroup of patients with initial TSH levels >10 mIU/L (7.0%), but not in those with TSH ≤10 mIU/L (4.7%). Lp(a) concentrations remained unchanged both in the whole group and in patients with TSH levels >10 mIU/L.

The percentage of patients with pretreatment t-Hcy >10 μmol/L was 40.5%. Although this percentage decreased to 35.7% after treatment, mean fasting (9.5 ± 2.9 *v* 9.4 ± 3.6 μmol/L) and postmethionine t-Hcy (32.1 ± 7.9 *v* 32.2 ± 7.6 μmol/L) remained unchanged (Table 2). In the subgroups of patients with baseline TSH levels >10 mIU/L and those with t-Hcy concentrations >10 μmol/L, t-Hcy levels also remained unchanged.

Table 2. Analyses of Emerging Cardiovascular Risk Factors Before and After Levothyroxine Replacement

Variable	Baseline	Posttreatment	*P* Value
Apolipoprotein B (g/L)			
All patients	1.10 ± 0.25	1.04 ± 0.24	<.01
Baseline TSH (>10 mIU/L)	1.21 ± 0.27	1.12 ± 0.23	<.001
Lipoprotein (a) (mg/L)			
All patients	349 ± 309	312 ± 290	NS
Baseline TSH (>10 mIU/L)	341 ± 273	326 ± 234	NS
Fasting t-Hcy (μmol/L)			
All patients	9.5 ± 2.93	9.4 ± 3.7	NS
Baseline TSH (>10mIU/L)	9.6 ± 2.88	9.1 ± 3.5	NS
Baseline t-Hcy (>10 μmol/L)	12.2 ± 2.7	11.4 ± 3.7	NS
Postmethionine t-Hcy (μmol/L) (n = 28)			
All patients	32.0 ± 7.9	32.2 ± 7.6	NS
Baseline TSH (>10 mIU/L)	32.6 ± 7.3	34.1 ± 8.6	NS
C-reactive protein (mg/L)			
All patients	3.38 ± 3.58	3.46 ± 4.26	NS
Baseline TSH (>10 mIU/L)	2.94 ± 3.84	3.67 ± 4.14	NS
Baseline CRP (>3 mg/L)	6.8 ± 3.95	6.42 ± 5.68	NS

Abbreviation: NS, not significant.

The percentage of patients with CRP >3 mg/L was 34.4%. No treatment effect was observed on CRP levels either in the whole group of patients or in the subgroups with baseline TSH levels >10 mIU/L and those with initial CRP concentration >3 mg/L.

DISCUSSION

Patients with SH are more likely to develop cardiovascular disease, and emerging cardiovascular risk factors might help to explain this association.[3-5] A major finding of this study is that in patients with SH, restoration of euthyroidism did not modify Lp(a), fasting or postmethionine t-Hcy and CRP levels, regardless of their respective baseline values and pretreatment TSH levels. Furthermore, we confirm the beneficial effect of L-T_4 treatment on total and LDL cholesterol and apo B concentrations only in patients with TSH levels >10 mU/L. However, apo B determination does not appear to be of a major value in the decision to treat SH, given the parallel change in LDL cholesterol.

Most, but not all, studies found an association between SH and lipid profile. Our findings are largely in line with the results of intervention studies that show that L-T_4 replacement significantly reduces serum total and LDL cholesterol, but does not influence triglyceride and HDL cholesterol, and that lipid improvement is related to baseline TSH concentration.[10-12,16,18,19] Only limited data exist on the effects of L-T_4 therapy on apo B levels[11,12,16-18] and remain controversial. The present study supports a significant reduction in apo B levels following L-T_4 treatment if the initial TSH level is >10 mIU/L,[11,16,18] but is inconsistent with the results of Caraccio et al,[12] who found that although apo B was increased in SH, it did not decrease significantly after L-T_4 replacement. Further, Tzotzas et al[17] did not find increased apo B in these patients or change after treatment. However, bearing in mind that the decrease in apo B levels paralleled that of LDL cholesterol and that all studied patients had triglyceride levels ≤200 mg/dL and the majority <150 mg/dL, alterations in LDL cholesterol/apo B are unlikely.[25] Thus, our findings did not justify apo B determinations to make the decision to treat SH. Although increased Lp(a) has been reported[12,13,26] in subclinical hypothyroidism only, Milionis et al[13] and Yildirimkaya et al[18] showed a significant decrease in Lp(a) levels after restoration of euthyroidism.

Plasma t-Hcy concentrations appear to be an independent risk factor for coronary artery disease, and thyroid status is a determinant of plasma t-Hcy concentration.[9,27,28] Patients with clinical hypothyroidism have elevated plasma t-Hcy levels, and these levels decrease once the euthyroidism is restored,[29-32] which suggests that t-Hcy could explain, at least in part, the increased risk for cardiovascular disease in these patients. Information is limited on the effect of SH on plasma t-Hcy, but their concentrations appear to be normal.[4,33] Consistent with these findings, in the 2 previous studies that examined the effect of L-T_4 replacement on t-Hcy[20,21] and in our study, restoration of euthyroidism in patients with SH did not decrease t-Hcy, regardless of their baseline TSH or t-Hcy levels. T-Hcy response to L-T_4 treatment in patients with clinical hypothyroidism is mainly explained by concurrent changes in renal function.[30,31]

Thus, because the main determinants of t-Hcy concentrations, such as vitamin concentrations and renal function remained unchanged in the present and previous studies, the lack of change in t-Hcy levels after euthyroidism restoration in patients with SH is not surprising.[20,21] Fasting t-Hcy may fail to identify a fraction of subjects with high postmethionine t-Hcy levels.[34,35] Our study is the first to analyze postmethionine t-Hcy levels in SH and in accord with the only study conducted in patients with clinical hypothyroidism,[32] L-T_4 treatment was also unable to lower postmethionine load t-Hcy levels, which emphasizes the lack of relationship between homocysteine and treatment of SH.

Finally, only 1 previous study[21] investigated CRP concentrations in patients with overt or SH and found increased plasma levels of this protein. However, CRP levels did not correlate with the extent of hypothyrodism and were unaffected after L-T_4 treatment. Accordingly, we found no influence of euthyroidism restoration on CRP levels in any patients or in those with CRP values (>3 mg/L) considered to have an increased cardiovascular risk.[36]

In conclusion, based on the present and most previous studies, in terms of classical lipid and emerging lipid and nonlipid cardiovascular risk factors, a lack of evidence exist on the benefit of euthyroidism restoration in patients with TSH levels between 5 and 10 mU/L. Furthermore, measurement of emerging risk factors did not offer additional arguments for treating patients with TSH levels >10 mU/L. Thus, at present, the clinical use of these emerging cardiovascular risk factors in the clinical management of SH appears unwarranted.

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