Subclinical Hypothyroidism and Lipid Abnormalities in Older Women Attending a Vascular Disease Prevention Clinic: Effect of Thyroid Replacement Therapy

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The authors evaluated the frequency and type of lipid disorders associated with subclinical hypothyroidism (SH) in older women referred to their university vascular disease prevention clinic. They also assessed the results of thyroid replacement therapy. Fasting serum lipid profiles and thyroid function tests were measured in 333 apparently healthy women (mean age: 71.8 ±7 years). These women were divided into 3 groups: group I: 60–69 years old (n = 132); group II: 70–79 years old (n = 153); group III: 80–89 years old (n = 48). SH was defined as a serum thyrotropin concentration higher than 3.20 mIU/mL with a normal free thyroxine concentration. The prevalence of SH was 7.5%. Thyrotropin was higher than 3.20 mU/mL in 25 women; 7 (5.3%), 14 (9.2%), and 4 (8.3%) in groups I, II, and III, respectively. Low-density lipoprotein cholesterol (LDL-C) concentrations were higher in the women with SH ($p = 0.037$). The mean values of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TC/HDL-C ratio, lipoprotein (a) (Lp[a]), apolipoprotein A-I (apo AI) apolipoprotein B100 (apo B) and apo B/apo A ratio were higher and triglycerides (TG) were lower, compared with those with normal levels of thyrotropin. However, none of these differences reached significance. Restoration of euthyroid status (thyroxine: 50–100 μg/day) in 17 SH women significantly improved TC ($p = 0.017$), LDL-C ($p = 0.014$), TC/HDL-C ($p = 0.05$), LDL-C/HDL-C ($p = 0.03$), apo B ($p = 0.013$), and Lp(a) ($p = 0.0005$) values. SH is relatively common in older women attending a vascular disease prevention clinic. Thyroid hormone replacement therapy significantly improved serum lipids. In particular, the reduction in LDL-C and Lp(a) concentrations may be of clinical benefit.

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Introduction

Thyroid abnormalities increase with age, particularly in women; abnormal results from thyroid function tests (TFTs) are found in approximately 10%–15% of older women.[1] Population-based studies have also shown that the proportion of women over 65 years with abnormal concentrations of serum lipids is high.[2] The thyroid state significantly affects lipid metabolism. Thus, overt hypothyroidism is a cause of dyslipidemia char-

acterized by elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) as a consequence of a decreased uptake of LDL-C by its receptor.[3] Decreased levels of high-density lipoprotein cholesterol (HDL-C) also occur in hypothyroid patients.[4]

Subclinical hypothyroidism (SH) is an asymptomatic state identified by slightly elevated thyrotropin and normal free thyroxine (FT_4) serum concentrations.[5] The increase in thyrotropin serum concentration is modest and usually does not exceed 20 mU/L, with the upper limit of normal in most assays being 5 mU/L or less.[4] The overall prevalence of SH is about 7.5% in women with a particularly high prevalence and up to 16% in women who are older than 60 years of age,[6] whereas in women over 80 years the incidence is lower (6%).[1]

The clinical significance of SH is open to debate. Is SH a biochemical abnormality, or an indicator of risk for atherosclerosis in elderly women?[7] Studies that assessed the lipid profile in SH are limited and show conflicting results. Some reports found that serum TC concentrations were similar to those in normal subjects,[8-12] whereas others report that either an increase in LDL-C or a decrease in HDL-C,[6,8] or both[6] occur. The influence of thyroid function on lipoprotein (a) (Lp[a]) concentrations, and the relationship between HDL-C and thyroid function have not been well documented in SH.[13] Furthermore, a recent study reported a high prevalence of symptomatic peripheral arterial disease in older men and women with SH.[14]

Should SH be treated? This issue is still undecided since neither the contribution of mild thyroid dysfunction to plasma lipid concentrations, nor the response to treatment is well defined.[15]

The aims of this study were to evaluate the prevalence of SH and investigate its impact on lipid metabolism in older women attending a vascular disease prevention clinic. We also assessed the effect of thyroid replacement therapy in patients with SH.

Methods

Subjects

From a total of 395 Greek-origin elderly nonsmoker women, we selected a group of 333 apparently well women aged 60 to 89 years, in keeping with the criteria listed below. These women, mainly from rural parts of the island of Crete, had been referred to our university hospital-based outpatient vascular disease prevention clinic for the assessment of dyslipidemia. These women were divided according to their age into 3 groups: group I: 60–69 years (n = 132); group II: 70–79 years (n = 153); and group III: 80–90 years (n = 48). SH (n = 25) was defined as a raised serum thyrotropin concentration (> 3.20 mIU/mL) with a normal FT_4. Of the 25 women with SH, 22 (88%) agreed to a 6-month trial with thyroxine replacement treatment (50–100 μg/day) to restore the euthyroid state. Of these 22 women, 5 were excluded for the reasons explained below; finally 17 women completed the trial.

Measurements

All the participants underwent relevant physical examination and laboratory assessment. All were ambulatory and in good health. Exclusion criteria were recognized thyroid disease or drug therapy known to interfere with thyroid hormone or lipoprotein metabolism (oral contraceptives, β-blockers, amiodarone, glucocorticoids, metoclopramide, lithium). Patients with the following diseases were excluded from the study (n = 62): diabetes, renal failure, malignant disease, paraproteinemia, and liver disease in order to avoid possible secondary hyperlipidemia.

Venous blood samples were taken after fasting overnight for 12 hours. Serum concentrations of TC, HDL-C, and triglycerides (TG) were measured by use of an automated chemistry analyzer (Olympus AU-600) with reagents from the same manufacturer. LDL-C was calculated according to the Friedewald formula.[16] Serum apolipoprotein A-I (apo AI), apolipoprotein B100 (apo B), and Lp(a) were measured by rate nephelometry (lipoprotein [a] [LPA] test, apolipoprotein A-I [APA] test, and apolipoprotein B100 [APB] test, Beckman Instruments Inc, Galway, Ireland). Serum thyrotropin (reference range: 0.15–3.20 mIU/mL), FT_4 (reference range: 9–27 pmol/L), FT_3 (reference range 3–8.5 pmol/L) were measured by Vitros Immunodiagnostic products (Ortho-Clinical Diagnostics, Amersham, UK).

Statistics

Normally distributed values are expressed as mean ± standard deviation (SD), and nonpara-

metric values are expressed as median and range. Within-groups results were assessed by a paired t test or, if the distribution was likely to be non-parametric, by a Wilcoxon signed rank test. The unpaired t test was used for comparisons between groups. All p values are two-tailed and a $p < 0.05$ was accepted as the level of significance. The GraphPad Prism™ Version 2.0 (GraphPad, Software, Inc, San Diego, CA, USA) statistical package was used.

Results

Lipid Profile in the Whole Study Group

More than 50% of participants were above the third report of the National Cholesterol Education Program (NCEP ATP III) reference LDL-C cut-off values 130 mg/dL for patients with 10-year risk </= 20%.[17] Of 333 women, 289 (86.8%) had TC ≥ 200 mg/dL, 286 (85.9%) had LDL-C ≥ 130 mg/dL, 45 (13.5%) had HDL-C ≤ 40 mg/dL, and 147 (44.1%) had TG ≥ 150 mg/dL. Mean TC was 259 ±51 mg/dL, HDL-C was 54 ±14 mg/dL, LDL-C was 177 ±45 mg/dL, TG was 158 ±82 mg/dL, the TC/HDL ratio was 5.2 ±1.7, the LDL/HDL ratio was 3.5 ±1.4, Lp(a) was 22 mg/dL (range 2–219 mg/dL), apo AI was 165 ±27 mg/dL, apo B was 134 ±33 mg/dL, and apo B/apo AI was 0.8 ±0.3.

Analysis of the whole study population (n = 333) by thyrotropin concentrations showed that subjects with the lower concentrations (< 0.15 mIU/L; n = 10) had significantly lower concentrations of TC and LDL-C than those with the higher thyrotropin concentrations (> 3.20 mIU/L; n = 25) (Figure 1). Further analysis by thyrotropin tertiles in the women with normal thyroid function (n = 298) showed a nonsignificant trend toward an increase in LDL-C at higher thyrotropin concentrations (Table I).

Prevalence of SH and Subclinical Hyperthyroidism

From the study population, 25 (7.5%) had thyrotropin concentrations in the range seen in SH; 7 (5.3%) of those were in group I, 14 (9.2%) in group II, and 4 (8.3%) in group III. There were 10 women (3%) with subclinical hyperthyroidism defined as low thyrotropin concentrations (< 0.15 mIU/L) and normal FT_3 and FT_4 concentrations.

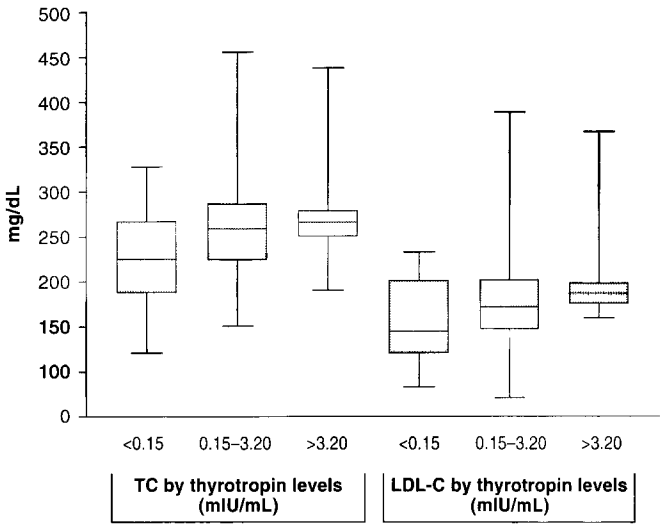

Figure 1. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels among older women with low (n = 10), normal (n = 298), and high (n = 25) levels of thyrotropin. Low thyrotropin levels were associated with significantly lower levels of TC (224 ±65 vs 276 ±48 mg/dL, p = 0.015) and LDL-C (156 ±51 vs 196 ±42 mg/dL, p = 0.037) compared with the high thyrotropin group (gray area represents 25–75% of values, thin vertical rule designates the range, and the horizontal divider the median values).

Lipid Profiles in the SH Group

Table II shows the lipid profiles of the SH women (n = 25) in comparison with women with normal thyrotropin concentrations (n = 298).

Effects of Treatment with Thyroxine on the Lipid Profile

Of 25 women with SH, 22 (88%) agreed to follow a thyroid hormone replacement trial with thyroxine (50–100 μg/day). The aim was the restoration of euthyroidism; 17 women completed the trial. One woman was lost to follow-up, 2 women were excluded because of a very low compliance with treatment, and 2 women because during the trial 1 started on statin therapy and the other on tamoxifen, which can cause hypertriglyceridemia in susceptible patients.[18]

Table I. Low-density lipoprotein cholesterol (LDL-C) levels by thyrotropin tertiles among euthyroid older women. A nonsignificant trend toward an increase in LDL-C was observed.

Thyrotropin	Low Normal (n = 99)	Middle (n = 99)	High Normal (n = 100)	p
LDL-C, mg/dL	170 ±41	176 ±46	181 ±48	NS

LDL-C = low-density lipoprotein cholesterol.

Table II. Mean (± standard deviation) of age, thyrotropin, and lipid parameters in elderly women with subclinical hypothyroidism and dyslipidemia.

	Controls (n = 298)	Subclinical Hypothyroidism (n = 25)	Difference (%)	p
Age, years	71.9 ±7.0	72.6 ±7.8		NS
TC, mg/dL	259 ±50	276 ±48	+6.6	NS
HDL-C, mg/dL	53 ±14	56 ±16	+5.7	NS
LDL-C, mg/dL	176 ±45	196 ±42	+11.4	0.038
TG, mg/dL	161 ±83	149 ±73	-7.4	NS
TC/HDL-C	5.2 ±1.7	5.4 ±2.2	+3.8	NS
LDL-C/HDL-C	3.5 ±1.4	3.8 ±1.7	+8.6	NS
Thyrotropin, mIU/mL	1.07 ±0.61	7.13 ±5.83		<0.0001
Lp(a), mg/dL	22 (2–160)	22 (2–146)	0	NS
apo AI, mg/dL	165 ±27	170 ±30	+3.0	NS
apo B, mg/dL	134 ±33	138 ±32	+2.9	NS
apo B/apo AI	0.8 ±0.3	0.9 ±0.3	+12.5	NS
Fibrinogen, mg/dL	292 ±95	284 ±67	-2.7	NS

TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, Lp(a) = lipoprotein (a), apo AI = apolipoprotein A-I, apo B = apolipoprotein B100.

The normalization of thyrotropin (median = 2.25; range = 0.11–3.00 mIU/L) in these women was associated with a significant reduction in TC (–23 mg/dL [–8.4%], p = 0.017); LDL-C (–18 mg/dL [–9.6%], p = 0.014); TC/HDL ratio (–0.4 [–8.2%], p = 0.05); LDL/HDL ratio (–0.2 [–6.1%], p = 0.03), Lp(a) (–7.9 mg/dL [–23.5%], p = 0.0005); apo AI (–37 mg/dL [–21.4%], p < 0.0001); apo B (–14 mg/dL [–10.7%], p = 0.013) (Table III). Additionally,

Table III. Mean (± standard deviation), percentage of changes in thyrotropin and lipid parameters in patients with subclinical hypothyroidism before and after treatment.

	Pretreatment (n = 17)	Post-treatment (n = 17)	Change %	p
TC, mg/dL	274 ±24	251 ±25	−8.4	0.017
HDL-C, mg/dL	59 ±16	57 ±12	−3.4	NS
LDL-C, mg/dL	187 ±14	169 ±22	−9.6	0.014
TG, mg/dL	137 ±59	120 ±43	−12.4	NS
TC/HDL-C	4.9 ±1.1	4.5 ±1.0	−8.2	0.05
LDL-C/HDL-C	3.3 ±0.9	3.1 ±0.8	−6.1	0.03
Thyrotropin, mIU/mL	7.64 ±6.62	1.86 ±1.01	−75.7	0.003
Lp(a), mg/dL	34 (5 to 146)	26 (2 to 128)	−23.5	0.0005
Apo AI, mg/dL	173 ±32	136 ±14	−21.4	<0.0001
Apo B, mg/dL	131 ±19	117 ±23	−10.7	0.013
Apo B/apo AI	0.8 ±0.2	0.9 ±0.2	+12.5	NS

TC = total cholesterol, HDL-C = high density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides, Lp(a) = lipoprotein (a), apo AI = apolipoprotein A-I, apo B = apolipoprotein B100.

Table III shows a small nonsignificant decrease in TG (−12.4%), and HDL-C (−3.4%) and an increase in apo B/apo AI ratio (+12.5%).

As mentioned above (Table III), Lp(a) levels did not differ significantly between the group with normal thyrotropin (22 mg/dL; range 2 to 160) and the SH group (22 mg/dL; range 2 to 146). After treatment with thyroxine there was a significant decrease in mean Lp(a) levels (from 34 mg/dL, range 5–146 mg/dL to 26 mg/dL, range 2–128 mg/dL, $p = 0.0005$). Figure 2 shows the comparison of treatment in the 2 groups of SH women with respect to Lp(a) levels. In the group with an initial Lp(a) >30 mg/dL, the median reduction was 21.9%, from 67 mg/dL (range: 38 to 146), to 50 mg/dL (range: 24 to 128), ($p = 0.031$). In contrast, the median in the group with initial Lp(a) levels <30 mg/dL was reduced by 49.3%, from 13 mg/dL (range: 5 to 26), to 7 mg/dL (range: 2 to 23), ($p = 0.003$).

Discussion

In the present study the prevalence of SH in older women was 7.5%. This is higher than the prevalence observed in a population-based sample of older women,[13] and nearly twice that seen in another outpatient-based study.[19] Regarding the groups I, II, III, SH occurred in 5.3%, 9.2%, and 8.3%, respectively. These values are slightly different from the prevalence rate in population-based studies.[1,20,21]

Thyrotropin normalization occurred in those subjects receiving thyroxine therapy for 24 weeks. The posttreatment mean TC was reduced by 8.4% (23 mg/dL), a value similar to that reported in a recent meta-analysis.[13] Because there is a relation between TC levels and death from coronary heart disease (CHD) in older persons,[22] this reduction may significantly reduce the long-term risk of CHD.[23] The average reduction in TC was 7.4% in women with initial thyrotropin levels <10

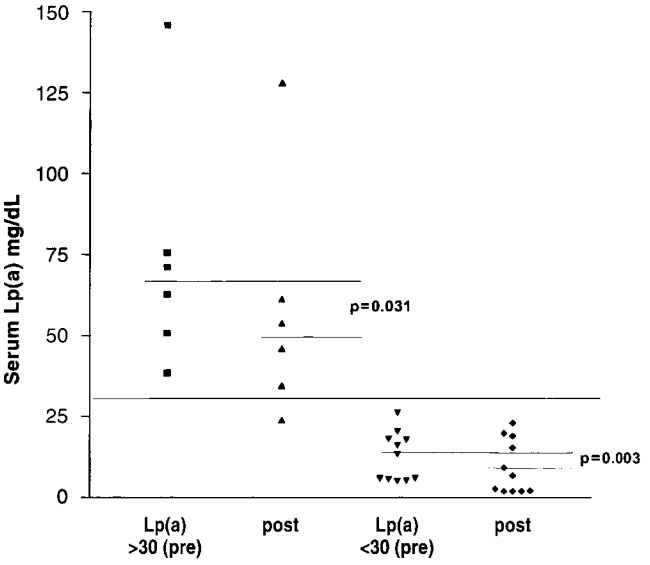

Figure 2. Comparison of 24-week treatment with thyroxine in the 17 SH women with respect to Lp(a) levels (the horizontal bars denote median values). The percentage decrease in the patients with Lp(a) levels > 30mg/dL was 21.9% (p=0.031). The corresponding decrease in the patients with Lp(a) levels < 30 mg/dL was 49.3% (p = 0.003).

mIU/mL (n = 14; p = 0.021) and 9.9% in those with thyrotropin levels > 10 mIU/mL (n = 3; p = NS). The corresponding reduction in LDL-C levels was 8.9% (p = 0.0067) and 12.4% (p = NS). These effects are due to modulation of LDL receptor activity.[24,25] The magnitude of this reduction in TC has been calculated to reduce the 10-year risk of CHD in a 60-year-old woman with no other risk factors from 10% to 9%.[26] Of the 17 SH women, 10 (58.8%) reached borderline high TC levels (200–239 mg/dL),[17] while in 2 women the TC remained unchanged. At the end of the study only 1 woman was below the NCEP ATP III reference LDL-C target value (<130 mg/dL) for patients with 10-year risk </= 20%.[17] Lp(a), according to the recently published AHA/ACC scientific statement, is recognized as a conditional risk factor for CHD.[27] Nevertheless, in the presence of other risk factors, high levels of Lp(a) could contribute to cardiovascular risk.[28] In previous studies Lp(a) levels were elevated in SH.[29,30] In our study we found similar Lp(a) levels between the women with normal thyrotropin and those with SH. Thyroxine replacement therapy resulted in a significant reduction in Lp(a) levels. The precise mechanism involved is unknown. An earlier study suggested that thyroid hormones exert a direct effect on apo(a) synthesis.[31] In another study, the treatment of hyperthyroid patients caused an increase in both LDL and Lp(a) plasma concentrations.[32] The LDL receptor status and Lp(a) synthesis may influence the circulating levels of Lp(a).[31] However, statins significantly modify LDL receptor activity but have no equal effect on the plasma concentration of Lp(a).[33] In vivo studies in hypothyroid animals report a reduction of plasma apo B-100 concentrations[34] and significant suppression of hepatic apo B synthesis after the administration of pharmacologic doses of 3,5,3-triiodo-L-thyronine.[35] Because the Lp(a) plasma concentration is influenced more by the synthetic rate than by its catabolism,[32] and given that Lp(a) is metabolized by an LDL-C-receptor-independent pathway,[31] a reduction in apo B synthesis might be the most important mechanism by which thyroxine therapy affects Lp(a) levels.[32]

The favorable effect of the treatment (in our study) seems to be more apparent on large-size apo(a) isoforms because there is a strong inverse association between the concentration of Lp(a) and the size of the apo(a) isoforms.[36,37] Thus, the reduction in subjects with Lp(a) levels < 30 mg/dL was proportionally higher than the corresponding reduction seen in subjects with Lp(a) levels > 30 mg/dL (49.3% vs 21.9%).

For patients with elevated Lp(a) levels, the primary treatment goal is LDL-C reduction.[38] If the LDL-C concentration cannot be reduced to the goal level, treatment may be initiated with drugs that could exert Lp(a)-lowering effects like nicotinic acid,[39] bezafibrate,[40] ciprofibrate,[41] and, in particular in postmenopausal women, estrogen replacement therapy.[42]

Our study demonstrates that HDL-C and TG levels are not significantly affected by thyroxine. In fact, there was a nonsignificant trend toward a decrease in HDL-C possibly due to an increase in hepatic lipase activity.[43] Finally, a significant negative effect of treatment on apo AI levels may be explained by the suppressive effect of thyroid hormone on apo AI gene activity.[44] However, results from recent studies show dual effects (stimulation and suppression) of thyroid hormone on apo AI gene activity.[44]

Thyroid dysfunction is associated with alterations in cardiovascular and renal function.[45]

Increased levels of serum creatinine have been found in hypothyroidism.[46] In turn, there is evidence that impaired renal function per se predicts vascular risk.[47] SH does not seem to induce changes in renal function,[45] but it is associated with cardiac dysfunction and an enhanced risk for atherosclerosis.[48]

In addition to SH, there was a 3% prevalence of subclinical hyperthyroidism. This is broadly in the range reported in the literature.[6] These women are also at increased risk, since in older persons a low thyrotropin concentration is associated with a threefold greater relative risk of atrial fibrillation.[49] This effect is clinically relevant because atrial fibrillation is a risk factor for stroke, congestive heart failure, and arterial thromboembolism.[4]

Conclusion

Our results show that SH is a relatively common condition in older women attending an outpatient vascular disease prevention clinic. Thyroid hormone replacement therapy exerted significant changes in serum lipids. The reduction in LDL-C and Lp(a) levels might provide a therapeutic advantage.

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