Effects of Subclinical Hypothyroidism and its Treatment on Serum Lipids

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OBJECTIVE: To determine whether the literature supports an effect of subclinical hypothyroidism on serum lipids and, if so, what are the effects of thyroxine replacement therapy.

DATA SOURCES: Articles were identified on MEDLINE using the MeSH terms hypothyroidism, lipids, or cholesterol.

DATA SYNTHESIS: The majority of studies that determined the prevalence of lipid abnormalities in subclinical hypothyroidism and studies that evaluated the effects of thyroxine replacement on lipids were small, uncontrolled, and varied in inclusion criteria. Six randomized, placebo-controlled trials were identified that evaluated the effect of levothyroxine on lipids in subclinically hypothyroid patients.

CONCLUSIONS: Subclinical hypothyroidism can potentially contribute to a pro-atherogenic lipid profile, with effects being greater at higher thyroid-stimulating hormone levels. Thyroxine replacement reduces total cholesterol and low-density lipoprotein cholesterol, with no effect on triglycerides. Effects on high-density lipoprotein, lipoprotein (a), and apolipoproteins A1 and B require further study. Larger prospective studies are needed to clarify many issues.

KEY WORDS: hypothyroidism, levothyroxine, lipids.

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REQUEST

What are the effects of subclinical hypothyroidism (SCH) and thyroid hormone replacement therapy on serum lipids?

RESPONSE

BACKGROUND

SCH is a condition characterized by normal thyroid hormone levels (total or unbound thyroxine and triiodothyronine) in the presence of elevated thyroid-stimulating hormone (TSH). Even if thyroid hormone levels are "normal," the elevated TSH is indicative of mild thyroid disease or the initial stages of primary hypothyroidism where thyroid gland function deteriorates over time.[1] Common etiologic factors for declining thyroid function include Hashimoto's thyroiditis (identified by the presence of antithyroglobulin antibodies), iodine deficiency, and enzyme defects. SCH commonly progresses to overt hypothyroidism unless an underlying reversible cause is identified and treated (i.e., sick euthyroid syndrome).[1,2] The prevalence of SCH ranges from 1% to 10% in the general population, approaches 20% in the elderly, and is more common in women than men of comparable age.[3-5] Although it is well established that overt hypothyroidism is associated with pro-atherogenic dyslipidemias and an increased risk of cardiovascular disease, it is controversial whether SCH also contributes to dyslipidemias.[2] The role of SCH in dyslipidemias can be examined by answering 3 questions: (1) Is SCH more common in patients with dyslipidemias than in the general population? (2) Do patients with SCH exhibit altered lipid profiles? (3) Does thyroxine replacement therapy in patients with SCH normalize or affect altered lipid profiles? Although several studies suggest an association between SCH and altered lipids, many others have not. The following sections briefly summarize the current literature on SCH and lipids.

Prevalence of Subclinical Hypothyroidism in Dyslipidemic Patients

Numerous studies have reported prevalences of SCH in patients with dyslipidemias (Table 1).[6-15] Most of these

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studies were limited to surveys of relatively small numbers of patients referred to lipid clinics. As a consequence of the overall low prevalence of SCH in the general population, one must be cautious when interpreting the results of these studies, as they are underpowered in terms of sample size for determining the true prevalence of SCH in dyslipidemic patients. An additional consideration is the lack of a gold standard for confirming the diagnosis of SCH. There is no consensus TSH value (or combination of laboratory tests) above which the diagnosis of SCH is confirmed. Thus, high variability in the reporting of prevalence is a consequence of small sample sizes and interstudy differences in the TSH values used for inclusion, as well as differences in age groups and geographic locations of those surveyed. However, despite their limitations, these studies provide the only snapshot of how common SCH appears to be in this select group of patients. The prevalence of SCH in these dyslipidemic populations was 1.4–11.2% (Table 1). Consistent with general population studies, the prevalence of SCH was higher in women for all cited studies. Only 1 study has directly compared the prevalence of SCH in dyslipidemic and nondyslipidemic subjects. Pirich et al.[15] evaluated the prevalence of SCH (TSH >4 mU/L) in 1922 Austrian participants (age 30–48 y) undergoing cholesterol screening. They did not find an increased prevalence of SCH in participants with hypercholesterolemia compared with those with normal cholesterol (1.4% with hypercholesterolemia vs. 0.8% with normal cholesterol; p = NS). Considering that the prevalence of SCH in the general population has been reported to range from 1% to 10%, these studies do not support the notion that SCH is more prevalent in dyslipidemic patients, at least in the age range of 30–70 years.

Table 1. Prevalence of Subclinical Hypothyroidism in Patients with Dyslipidemias

Reference	n	Age (y)	Country	TSH criteria for SCH (mU/L)	Prevalence (%)
Series et al. (1988)[6]	2250	25–59	UK	>5.0	8.6
Ball et al. (1991)[7]	272	37–69	UK	>6.0	3.7
Glueck et al. (1991)[8]	395	39 ± 14	US	>5.0	2.5
O'Kane et al. (1991)[9]	220	31–72	Northern Ireland	>5.0	4.6
Florkowski et al. (1992)[10]	200		UK		4.0
Ruckert et al. (1993)*	1210		France		11.2
Diekman et al. (1995)[12]	1509	57 ± 12	Netherlands	>5.0	1.9
Tsimihodimos et al. (1999)[13]	248		Greece	>5.2	4.4
Bindels et al. (1999)[14]	1191	40–60	Netherlands	>4.0	5.6
Pirich et al. (2000)[15]	1922	30–48	Austria	>4.0	1.4

SCH = subclinical hypothyroidism; TSH = thyroid-stimulating hormone.
*Results of the Ruckert study are presented by Kahaly GJ.[11]

Lipids in Patients with Subclinical Hypothyroidism

Many studies have also attempted to determine whether SCH is associated with causing or contributing to the development of dyslipidemias and, if so, which lipid parameters are affected. Most studies were small (6–69 subjects), case–control or cohort studies comparing mean lipid parameters in patients with SCH with mean lipid parameters in euthyroid control subjects. The majority of study participants were women. Studies that evaluated the effect of SCH on serum lipid parameters are summarized in Table 2.[16-25]

Several studies were able to demonstrate an elevation of either total cholesterol (TC) and/or low-density lipoprotein (LDL) cholesterol in subjects with SCH.[16-20] However, just as many studies found no difference in TC and LDL levels between SCH patients and euthyroid controls.[21-25] The discrepancy in results may be explained by a sharp divergence in the patient populations studied. The vast majority of subjects participating in the studies that showed no difference had TSH values <10 mU/L (mean TSH range 4.7–11.5), including many with TSH values <5 mU/L. These TSH values are indicative of milder SCH and less advanced thyroid disease. This includes the largest study conducted to date, by Vierhapper et al.,[25] in which 1055 patients with SCH were compared with 4886 patients with normal thyroid function. Mean TSH was 4.7 mU/L in the SCH group, a level not meeting criteria for SCH in some studies. Not surprisingly, this study failed to show a significant difference in TC, LDL, high-density lipoprotein (HDL) cholesterol, or triglycerides between groups.

In contrast, positive studies[16-20] included patients with SCH exhibiting much higher TSH levels (>10 mU/L), with many subjects having TSH levels >20–40 mU/L. This suggests that appreciable changes in TC and LDL may only be evident in SCH patients with more advanced thyroid disease. It is important to note that absolute values of TC and LDL tended to be higher in patients with SCH than in controls, even in the studies that failed to demonstrate a significant difference. These studies were likely underpowered to demonstrate the small differences in lipids of milder SCH.

This hypothesis is supported in the study by Staub et al.,[23] which stratified patients based on TSH and found that elevated LDL concentrations (>175 mg/dL or 2 standard deviations above the mean in controls) were more frequent in patients with TSH >12 mU/L (42.9% SCH vs. 11.4% euthyroid controls; $p < 0.05$). In addition, a common finding of both positive

and negative studies was a positive correlation between increasing LDL and increasing TSH,[16] and an inverse relationship between LDL and unbound thyroid hormone levels.[17,19,25] Taken together, SCH does appear to affect serum lipids, as elevations in TSH above the normal range correlate with increasing LDL and possibly TC levels. The change in TC and LDL may not be appreciable in milder SCH (TSH <10 mU/L), but appears more relevant as thyroid disease advances (TSH >10 mU/L). One study estimated that for an increase in serum TSH of 1 mU/L, TC rose 3.5 mg/dL in women and 6.2 mg/dL in men.[14]

The effect of SCH on other lipid parameters is not as clear. SCH appears to have little effect on serum triglycerides. SCH has also been reported to be associated with decreased levels of HDL in some studies,[18-20] and normal in others.[16,17,22-25] Concentrations of lipoprotein (a) and apolipoproteins A1 and B have only been included in a few studies, with inconclusive results.[18,21,23,24] As most studies have focused on TC and LDL, the effect of SCH on these other lipid parameters requires confirmation in larger studies.

Effect of Treatment of Subclinical Hypothyroidism on Lipids

The evaluation of the effects of thyroxine replacement on serum lipids in patients with SCH is difficult due to variable study designs, small sample sizes, and, consequently, mixed results. Most studies are uncontrolled and longitudinal in design. Only 6 randomized, placebo-controlled studies, with a combined total of 245 patients with SCH (93% women), were identified.[26-31] These studies used various levothyroxine replacement doses ranging from 50 to 150 µg, with most studies treating to euthyroidism,[26-31] while 1 administered 150 µg to all study subjects regardless of TSH.[31] The results of the randomized studies are summarized in Table 3.[26-31]

Two of the 6 randomized studies support a favorable effect of thyroxine replacement therapy on serum lipids in patients with SCH.[26,27] The majority of patients in these 2 studies had a previous history of thyroid disease. Caraccio et al.[26] conducted a randomized, placebo-controlled clinical trial in 49 men and premenopausal women. At baseline, patients with SCH exhibited significantly higher mean TC (208.8 ± 23.2 vs. 181.7 ± 23.2 mg/dL; $p < 0.01$), LDL (131.5 ± 38.7 vs. 112.1 ± 19.3 mg/dL; $p = 0.01$), and apolipoprotein B (107.4 ± 26.1 vs. 88.0 ± 19.7 mg/dL; $p = 0.001$) levels than did controls, whereas other lipid parameters did not differ. Levothyroxine therapy for 6 months resulted in significantly greater reductions compared with placebo in TC (–8% levothyroxine vs. 0% placebo; $p = 0.003$) and LDL (–10.2% levothyroxine vs. 3% placebo; $p = 0.003$). No changes in other lipid parameters were observed. Patients with higher baseline TSH (>6 mU/L; n = 9 vs. <6 mU/L; n = 15) had greater reductions in TC (–11.3% vs. –6.7%; $p < 0.05$) and LDL (–15.6% vs. –8.3%; $p = 0.08$).

Similarly, a second prospective, placebo-controlled, double-blind study by Meier et al.[27] was conducted in 66 women with SCH. Mean baseline concentrations of TC (243.6 ± 7.7 vs. 235.9 ± 7.7 mg/dL) and LDL (154.7 ± 7.7 vs. 146.9 ± 7.7 mg/dL) were comparable between treated and untreated groups. Levothyroxine-treated women exhibited greater reductions in TC (–9.3 mg/dL; $p = 0.015$) and LDL (–12.8 mg/dL; $p = 0.004$) compared with control subjects, especially in patients with greater baseline elevations of TSH. Patients with baseline TSH levels >12 mU/L (n = 13) had significantly greater decreases in TC (–11.2 ± 5.4 vs. –7.7 ± 4.6 mg/dL; $p = 0.06$) and LDL (–14.3 ± 5.8 vs. –12.0 ± 5.8 mg/dL; $p = 0.03$) than did those with milder SCH. Likewise, patients with higher pretreatment lipid values had significantly greater reductions in TC ($p = 0.01$), LDL ($p < 0.0001$), and apolipoprotein B-100 levels ($p = 0.02$). Insignificant changes were seen for HDL, triglyceride, apolipoprotein A1, and lipoprotein (a) levels.

The majority of nonrandomized, uncontrolled studies have also demonstrated a reduction in TC with levothyrox-

Table 2. Serum Lipid Concentrations in Patients with Subclinical Hypothyroidism

Reference	n	Mean TSH (mU/L)	Mean TC (mg/dL)			Mean LDL (mg/dL)		
			Controls	SCH	p Value	Controls	SCH	p Value
Miura et al. (1994)[16]	34	20.1 ± 19.3	215	231	NS	128	153	<0.02
Valdemarsson et al. (1983)[17]	12	61.3 ± 8.9				131	176	<0.001
Kung et al. (1995)[18]	32	14.2 ± 8.9	206	232	<0.005	133	152	<0.005
Althaus et al. (1988)[19]	52	8.6 ± 1.0	211	229	NS	141	162	<0.01
Lam et al. (1986)[20]	6	46.6 ± 23.0	140	200	<0.05			
Geul et al. (1993)[21]	31	>4.2	274	281	NS			
Parle et al. (1992)[22]	57	10.9 ± 6.8	241	252	NS	161	166	NS
Staub et al. (1992)[23]	35	3.0 ± 0.3	243	224	NS	141	129	NS
	14	8.6 ± 0.5	243	220	NS	141	133	NS
	20	22.7 ± 1.8	243	255	NS	141	163	NS
Tzotzas et al. (2000)[24]	23	11.5 ± 3.4	225	241	NS	148	63	NS
Vierhapper et al. (2000)[25]	1055	4.7 ± 2.0	217	219	NS	134	137	NS

LDL = low-density lipoprotein cholesterol; SCH = subclinical hypothyroidism; TC = total cholesterol; TSH = thyroid-stimulating hormone.

ine replacement therapy in patients with SCH.[12,24,32] In concordance with the 2 randomized trials, noncontrolled studies demonstrating a decline in TC and/or LDL included more patients with higher baseline TSH values (TSH >10 mU/L).[12,13,16] A pooled analysis by Tanis et al.[32] that combined results from 13 studies conducted prior to 1995 concluded that restoration of euthyroidism with levothyroxine reduced TC by an average of 15.5 mg/dL when considering all patients with SCH independently of baseline parameters. A second, more recent review by Danese et al.[33] also pooled results from 13 studies to evaluate the expected change in lipids after levothyroxine therapy in patients with SCH. This analysis found an overall 7.7 mg/dL decrease in TC and a 10.1 mg/dL decrease in LDL. In these nonrandomized studies, no other lipid parameters were favorably altered; however, 1 study[16] noted a decrease in HDL from a mean of 58 ± 15.1 mg/dL to 54.5 ± 14.3 mg/dL after thyroxine treatment ($p < 0.02$).

Conversely, 4 of the 6 randomized trials (n = 112) did not discern any beneficial effects in treating SCH.[28-31] In comparison with the 2 positive studies, only 1 study evaluated comparable lipid parameters, whereas the other 3 studies evaluated only select lipid parameters. All 4 negative trials included smaller numbers of patients and may have been underpowered to demonstrate statistically significant differences. Baseline TC in these studies was comparable to that in the positive studies (baseline TC 220.4–263.0 mg/dL). The study by Kong et al.[28] excluded patients with a previous history of thyroid disease and used a narrow TSH window for inclusion (5–10 mU/L). Only the study by Nystrom et al.[31] excluded patients with coronary artery disease. Due to the inconsistent inclusion and exclusion criteria used in the various randomized studies, it is unclear whether differences in the outcomes between the positive and negative studies are attributable to differences in patient characteristics. Although the majority of nonrandomized studies support an effect of thyroxine therapy on lipids in SCH patients, 2 small case-series failed to find a significant effect.[12,24] These negative studies included patients with smaller elevations in TSH. As discussed in the previous section, significant elevations of lipids may only be apparent in more advanced SCH, and thus appreciable reductions may also only be detectable for patients with higher TSH levels. In addition, despite not achieving statistical significance in these negative studies, the changes in lipid parameters trended in a favorable direction with levothyroxine therapy.

In summary, studies suggest that levothyroxine replacement therapy in SCH induces favorable changes in lipid profiles (reductions in LDL, TC, and to a lesser extent, apolipoprotein B), especially in patients with higher baseline TSH levels (>10–12 mU/L). This suggests that replacement therapy may be warranted in SCH patients with more advanced thyroid disease (borderline overt hypothyroidism). The effect of treatment on HDL levels is questionable, as most studies suggest no change, but a decline was reported in 1 study. Other lipid parameters, such as triglycerides, apolipoprotein A1, and lipoprotein(a) do not appear to be affected with treatment.

Summary

Studies evaluating the relationship between SCH and lipids and those investigating the role of levothyroxine replacement therapy in SCH have been limited by small sample sizes and highly variable inclusion criteria. Despite the limitations, the literature overall suggests that SCH may cause or contribute to pro-atherogenic lipid levels, as most evidence supports a relationship between increasing TSH and elevated TC/LDL, despite many small studies failing to demonstrate statistically significant elevations in lipids in patients with SCH. However, the effect on other lipid parameters is equivocal due to a paucity of studies. Treatment of SCH with thyroxine therapy may resolve or minimize changes in TC and LDL, with the effect being more pronounced in patients with more advanced thyroid disease, as indicated by TSH levels >10 mU/L. Larger

Table 3. Randomized, Controlled Trials Evaluating Levothyroxine Therapy in Patients with SCH

Reference	n (M/W)	Age Range (y)	Country	Pre/Post Mean TSH in Treatment Group (mU/L)	Pre/Post Mean TC and LDL with Treatment (p Value)
Caraccio et al. (2002)[26]	49 (7/42)	18–50	Italy	6.00/1.52	TC 213/193 (0.003); LDL 139/120 (0.003)
Meier et al. (2001)[27]	66 (0/66)	58.5 ± 1.3	Switzerland	12.8/3.1	TC 244/236 (0.015); LDL 155/143 (0.004)
Kong et al. (2002)[28]	40 (0/40)	53 ± 3	UK	8.0/3.4	TC 216/212 (0.4); LDL 127/119 (0.8)
Cooper et al. (1984)[29]	33 (1/32)	44–78	US	10.8/2.6	TC 254/245 (NS); LDL not reported
Jaeschke et al. (1996)[30]	37 (9/28)	68 ± 9.4	Canada	12.31/4.61	TC 220/217 (0.15); LDL 141/136 (0.42)
Nystrom et al. (1988)[31]	20 (0/20)	51–73	Sweden	7.7/1.9	TC 263/255 (NS); LDL not reported

LDL = low-density lipoprotein cholesterol; NS = no significant change in pretreatment vs. posttreatment levels in treatment group (actual p value not reported); TC = total cholesterol; TSH = thyroid-stimulating hormone.

studies are needed to confirm the effects of levothyroxine replacement on serum lipids and to determine a threshold for treating lipids with thyroxine in SCH patients. Lastly, more research must be conducted to answer further questions such as whether these alterations in lipids are clinically relevant, at what stage of SCH does it become important, and the significance of SCH on the effect of antihyperlipidemic agents. Until some of these controversies are resolved, it would be prudent to evaluate all patients with dyslipidemias for underlying thyroid disorders and consider levothyroxine replacement therapy in those with repeated TSH levels >10 mU/L, patients whose TSH continues to increase over time, patients with elevated TSH who test positive for the presence of antithyroglobulin antibodies, patients with a history of radioactive iodine ablation, or patients whose lipids appear refractory to standard doses of lipid-lowering therapies. As more information is collected regarding the pathologic consequences of SCH, the risk-to-benefit ratio of treating or not treating SCH patients must be weighed accordingly.

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EXTRACTO

OBJETIVO: Determinar si en la literatura biomédica se documenta que el hipotiroidismo subclínico afecta las concentraciones séricas de lípidos.

De ser así, se desea evaluar el efecto de la terapia de reemplazo hormonal con tiroxina en las concentraciones séricas de lípidos.

FUENTES DE INFORMACIÓN: Se identificaron artículos a través del sistema de datos de MEDLINE utilizando los términos MESH de hipotiroidismo, lípidos, o colesterol.

SÍNTESIS DE DATOS: El hipotiroidismo subclínico es una condición que se caracteriza por unas concentraciones normales de las hormonas tiroidea en presencia de unos niveles elevados de la hormona estimulante de la tiroide (TSH, por sus siglas en inglés). La mayoría de las publicaciones que evaluaban la prevalencia de anormalidades en lípidos en pacientes con hipotiroidismo subclínico o la prevalencia de hipotiroidismo subclínico en pacientes con anormalidades en lípidos eran estudios con pocos pacientes, no controlados, y que tenían diferentes criterios de inclusión. Se encontraron limitaciones similares en los estudios que evaluaban el efecto del reemplazo de tiroxina en las concentraciones séricas de lípidos. Se identificaron 6 estudios aleatorios, controlados con placebo que evaluaron el efecto de levotiroxina en las concentraciones séricas de lípidos en pacientes con hipotiroidismo subclínico.

RESUMEN: El hipotiroidismo subclínico puede potencialmente contribuir al desarrollo de un perfil lipídico pro-aterogénico. Este efecto se hizo más pronunciado cuanto mayor eran los niveles de TSH. El reemplazo de tiroxina redujo las concentraciones totales de colesterol y del colesterol de lipoproteina de baja densidad, pero no tuvo efecto en las concentraciones de triglicéridos. El efecto de reemplazo hormonal en las concentraciones de la lipoproteina de alta densidad, lipoproteina (a), y las apolipoproteina A_1 y B no se ha establecido y necesita estudiarse. Se requieren estudios prospectivos con un mayor número de personas para aclarar el efecto del hipotiroidismo subclínico y del reemplazo de tiroxina en las concentraciones séricas de lípidos.

Mirza D Martínez

RÉSUMÉ

OBJECTIF: Déterminer si la littérature est en faveur d'un effet de l'hypothyroïdie infraclinique sur les lipides sériques, et si oui, quels seraient les effets du traitement substitutif par la thyroxine.

REVUE DE LITTÉRATURE: Articles repérés par une recherche sur MEDLINE (mots-clés: hypothyroïdie, lipides, cholestérol).

RÉSUMÉ: La majorité des études qui ont évalué la prévalence des anomalies lipidiques dans l'hypothyroïdie infraclinique et, inversement, des études qui ont évalué les effets du traitement substitutif par la thyroxine sur les lipides, sont de faible taille, non contrôlées, et avec des critères d'inclusion variables. Il a été identifié six études à recrutement aléatoire, contrôlées par placebo, qui ont évalué l'effet de la L-thyroxine sur les lipides de patients atteints d'hypothyroïdie infraclinique.

CONCLUSIONS: La littérature suggère que l'hypothyroïdie infraclinique est susceptible de contribuer à un profil lipidique athérogène, et ce d'autant plus que les niveaux de TSH sont élevés. La littérature suggère que le traitement substitutif par la thyroxine diminue le cholestérol total et le cholestérol des lipoprotéines de basse densité, sans effet sur les triglycérides. Les effets sur les lipoprotéines de haute densité, la lipoprotéine (a), et les lipoprotéines A_1 et B nécessitent d'autres études. Ces pistes devront être clarifiées par des études prospectives de plus grands effectifs.

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