

Update in Lipid Alterations in Subclinical Hypothyroidism

Elizabeth N. Pearce

Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, Massachusetts 02118

Thyroid hormone has multiple effects on the regulation of lipid synthesis, absorption, and metabolism. Studies consistently demonstrate elevated levels of serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, lipoprotein(a), and possibly triglycerides in individuals with overt hypothyroidism, all of which are reversible with levothyroxine therapy. Although it is estimated that 1 to 11% of all patients with dyslipidemia have subclinical hypothyroidism, the effects of subclinical hypothyroidism on serum lipid values are less clear. Apolipoprotein B levels may be increased in patients with subclinical hypothyroidism. Although some studies have demonstrated that total cholesterol and LDL-C levels are elevated in patients with subclinical hypothyroidism, others have not shown any effect of subclinical hypothyroidism on these lipid measurements. Serum triglycerides, lipid subparticle size, and LDL-C oxidizability may be altered in subclinical hypothyroidism, but these studies have also been inconsistent. The preponderance of evidence suggests that HDL-C and lipoprotein(a) levels are not altered in subclinically hypothyroid patients. Smoking and insulin resistance may modify the effects of subclinical hypothyroidism on serum lipid values. Clinical trials to date have not consistently shown a beneficial effect of levothyroxine treatment on serum lipid levels in subclinically hypothyroid patients. (*J Clin Endocrinol Metab* 97: 326–333, 2012)

It has been known for decades that overt hypothyroidism is associated with hyperlipidemia. Subclinical hypothyroidism, defined as an increased serum TSH level in the setting of normal free peripheral thyroid hormone concentrations, is relatively common, occurring in 4–10% of the adult population (1). Although the relationships between subclinical hypothyroidism and serum lipids have been the focus of multiple studies over the last 20 yr, the associations between subclinical hypothyroidism, lipid status, and cardiovascular outcomes remain incompletely understood. This review focuses on several of the most recent and most important clinical studies regarding lipid changes in subclinical hypothyroidism, the impact of thyroid hormone treatment on those changes, and approaches to screening.

Mechanisms for Lipid-Thyroid Interactions

Elevations in total cholesterol and low-density lipoprotein cholesterol (LDL-C) may occur in hypothyroidism due to

several changes in the synthesis, metabolism, and mobilization of lipids. Thyroid hormone induces the hepatic expression of hydroxymethylglutaryl coenzyme A reductase, which results in increased cholesterol synthesis (2). Therefore, in overt hypothyroidism, hepatic cholesterol synthesis is decreased. However, thyroid hormone also increases the expression of cell surface LDL-C receptors expressed in fibroblasts, liver, and other tissues. LDL-C receptor levels are regulated by negative feedback in the presence of high intracellular cholesterol levels. This may be mediated through the sterol regulatory element-binding protein-2 (SREBP-2). The SREBP-2 gene is directly regulated by T_3 (3). The decrease in LDL-C receptors leads to reduced clearance of LDL-C from the serum. Hypothyroidism may also lead to increased intestinal cholesterol absorption due to thyroid hormone actions on Niemann-Pick C1-like 1 protein in the gut (4). The thyroid hormone effects on LDL-C receptor expression and cholesterol absorption

ISSN Print 0021-972X ISSN Online 1945-7197

Printed in U.S.A.

Copyright © 2012 by The Endocrine Society

doi: 10.1210/jc.2011-2532 Received September 9, 2011. Accepted November 28, 2011.

First Published Online December 28, 2011

Abbreviations: ApoB, Apolipoprotein B; CETP, cholesteryl ester transfer protein; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; Lp(a), lipoprotein (a); L-T4, levothyroxine; VLDL, very low-density lipoprotein.

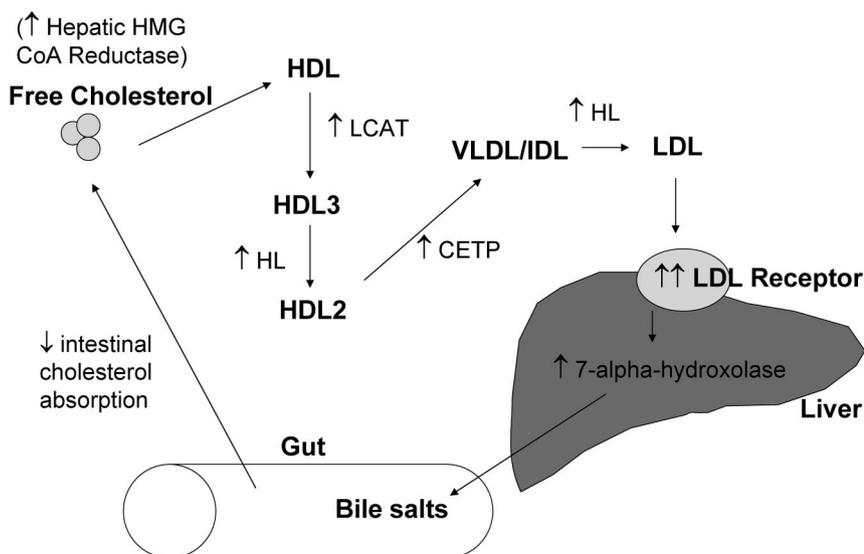


FIG. 1. Effects of thyroid hormone on cholesterol metabolism. Thyroid hormone increases LDL receptor expression, increases CETP concentrations, and increases hepatic lipase (HL) concentrations. Thyroid hormone also increases hepatic cholesterol synthesis by inducing hydroxymethylglutaryl coenzyme A (HMG CoA) reductase and decreases intestinal cholesterol absorption.

outweigh the effects of decreased hepatic cholesterol synthesis, leading to a net accumulation of serum LDL-C in overt hypothyroidism. Although the overall effects of subclinical hypothyroidism on serum lipid levels remain unclear, it is likely that more subtle manifestations of the same alterations that occur in overt hypothyroidism are present in mildly hypothyroid patients.

Cholesteryl ester transfer protein (CETP) transfers cholesterol from high-density lipoprotein cholesterol (HDL-C) to LDL-C and very low density lipoprotein (VLDL). Plasma CETP concentrations are decreased in hypothyroidism and increased in hyperthyroidism, which may lead to alterations in serum HDL-C concentrations (5) (Fig. 1). Thyroid hormone also appears to play a role in the regulation of hepatic lipase, which alters HDL-C subfractions (5). In addition, thyroid hormone stimulates

cholesterol efflux from macrophages to HDL via the ABCA1 transporter (6).

Lipoprotein lipase lowers triglyceride levels through hydrolysis of triglyceride-enriched lipoproteins and facilitates transfer of cholesterol from these lipoproteins to HDL-C. Lipoprotein lipase activity is increased by thyroid hormone. Higher serum triglycerides may be observed in overtly hypothyroid individuals because of their lower lipoprotein lipase activity (7).

Finally, the conversion of cholesterol to bile acids and subsequent fecal excretion is an important mechanism for the removal of cholesterol from the body. Thyroid hormone is known to play a role in the regulation of bile acid synthesis, but this is unlikely to be a primary mechanism for lipid changes in patients with hypothyroidism.

Overt Thyroid Dysfunction and Lipid Levels

Serum total cholesterol and LDL-C levels are increased by approximately 30% in patients with overt hypothyroidism (8) (Table 1), and over 90% of overtly hypothyroid patients have hyperlipidemia (9). Triglyceride levels and VLDL may be normal or increased in overt hypothyroidism (9). Although the effects of overt hypothyroidism on HDL-C have been variable across studies, the preponderance of evidence suggests that HDL-C levels are normal to slightly elevated in overt hypothyroidism, resulting in an unfavorable ratio of LDL-C to HDL-C. All of the lipid abnormalities in overt hypothyroidism are reversible with levothyroxine (L-T4) therapy unless the patient has underlying hyperlipidemia (8). Patients who have higher baseline serum lipid values when overtly hypothyroid will have greater reductions in serum lipid concentrations after the initiation of thyroid hormone treatment.

TABLE 1. Lipid effects of overt and subclinical hypothyroidism

	Overt hypothyroidism	Subclinical hypothyroidism
Total cholesterol	↑ 30%	Unclear: normal to ↑
LDL-C	↑ 30%	Unclear: normal to ↑
HDL-C	Normal to slightly ↑	No change
Triglycerides	Normal to ↑	Unclear: normal to ↑
Lp(a)	↑	No change
ApoB	↑	↑
ApoA-I	↑	No change
Oxidized LDL-C	↑	↑

↑, Increased. [Adapted with permission from E. N. Pearce: Hypothyroidism and dyslipidemia: modern concepts and approaches. *Curr Cardiol Rep* 6:451–456, 2004 (58), with permission. © Springer.]

Observational Studies of Lipids in Subclinical Hypothyroidism

The results of observational studies of serum lipid levels in patients with subclinical hypothyroidism have been inconsistent (Table 2). In a cross-sectional study of 7000 thyroid clinic outpatients, total cholesterol and LDL-C were clearly elevated in overtly hypothyroid patients, but there were no significant differences in serum total cho-

TABLE 2. Observational studies of serum lipids in subclinical hypothyroidism

First author, year (Ref.)	No. of patients		Mean total cholesterol (mg/dl)		Mean LDL-C (mg/dl)		Mean HDL-C (mg/dl)		Mean triglycerides (mg/dl)	
	Euthyroid	SCH	Euthyroid	SCH	Euthyroid	SCH	Euthyroid	SCH	Euthyroid	SCH
Canaris, 2000 (13)	22,842	2,336	216	224 ^a	140	146 ^a	51	53	147	156
Vierhapper, 2000 (10)	4,866	1,055	217	219	134	137	57	56	123	125
Hueston, 2004 (11)	8,013	215	217	226 ^a	136	140	51	51	158	178 ^a
Walsh, 2005 (14)	1,906	119	224	243 ^a	135 (n = 580)	158 ^a (n = 30)	58 (n = 580)	58 (n = 30)	54	62
Bell, 2007 (15)	1,271	80	213	221	134	139	55	58	46	48
Lai, 2011 (16)	1,283	102					51	49 ^a	58	67 ^a

SCH, Subclinical hypothyroidism.

^a Significantly different from the euthyroid group.

lesterol, LDL-C, HDL-C, or triglyceride levels between subclinically hypothyroid patients and the euthyroid control group (10). Among 8586 adults over age 40 from the National Health and Nutrition Examination Survey III database, after adjustment for age, race, sex, and the use of lipid-lowering drugs, subclinical hypothyroidism (defined as a serum TSH of 6.7 to 14.99 mIU/liter) was not associated with alterations in total cholesterol, LDL-C, triglycerides, or HDL-C (11).

By contrast, among a population-based sample of 2799 elderly black and Caucasian subjects, serum TSH values above 5.5 mIU/liter were associated with an average 9 mg/dl elevation in total cholesterol (12). Among 25,862 participants in a statewide health fair in Colorado, fasting total cholesterol, triglyceride, and LDL-C levels were significantly greater in individuals with diminished thyroid function, with higher levels in subclinically hypothyroid subjects than in euthyroid subjects (13). In a community-based sample of 2108 Australian participants, serum TSH was positively correlated with total cholesterol, triglycerides, and LDL-C, although these relationships were no longer observed after adjustment for age and sex. No associations were observed between serum TSH and HDL-C (14). Among a community-based sample of 1432 Australian women, total cholesterol and triglycerides were positively correlated with serum TSH, although total cholesterol, LDL-C, triglycerides, and HDL-C did not differ between subclinically hypothyroid and euthyroid women (15). Finally, among 1534 Chinese adults, individuals with subclinical hypothyroidism had higher triglycerides and lower HDL-C than euthyroid individuals (16).

Observational Studies of Lipids within the Normal TSH Range

The largest cross-sectional population studies suggest that there may be associations between thyroid function and

serum lipid levels even within the normal TSH range. Among a cohort of 2771 euthyroid Hispanic individuals, after adjustment for age, gender, and body mass index, free T₄ was positively associated with serum HDL-C, and serum TSH was positively associated with total cholesterol and triglycerides (17). Among 30,656 euthyroid individuals in the HUNT Study (serum TSH, 0.2–4.5 mIU/liter), there were significant positive associations between serum TSH and total cholesterol, LDL-C, and triglycerides and an inverse relationship between serum TSH and HDL-C (18). By contrast, in a smaller cohort of 1240 euthyroid subjects, there were no significant correlations between serum TSH and serum total cholesterol, LDL-C, HDL-C, or triglycerides (19).

Observational Studies of Other Lipid Alterations in Subclinical Hypothyroidism

Concentrations of apolipoprotein B (ApoB), a major constituent of LDL-C and VLDL, are significantly higher in subclinical hypothyroidism (20) and have been shown to decrease after L-T₄ treatment (21, 22). Lipoprotein(a) [Lp(a)] is a form of LDL-C in which Lp(a) and ApoB are covalently bound by a disulfide bridge; it may be particularly atherogenic and thrombogenic. Lp(a) levels are increased in patients with overt hypothyroidism and decrease after L-T₄ treatment (23). However, most studies to date have not found significantly elevated Lp(a) levels in patients with subclinical hypothyroidism and have not demonstrated any effect of L-T₄ treatment on serum Lp(a) concentrations (23–26).

Although there is no consistent effect of subclinical hypothyroidism on overall HDL-C serum concentrations, thyroid hormone does appear to play a role in determining the size and density of HDL-C particles. HDL-C particles can be categorized by size into the smaller HDL₂ (primarily incorporating the protein ApoA-I) and larger HDL₃

(incorporating both ApoA-II and ApoA-I) subfractions. HDL-C that incorporates more ApoA-I conveys more cardiovascular protection. ApoA-I concentrations are increased in overt hypothyroidism, whereas ApoA-II levels are unchanged (27). This beneficial change in HDL-C subfractions may help to moderate the atherogenic LDL-C changes seen in overt hypothyroidism. However, ApoA-I levels were not altered by L-T4 therapy in one study of subclinically hypothyroid individuals (22).

Remnant lipoproteins, such as chylomicron remnants and VLDL remnants, are triglyceride-rich lipoproteins present in serum in the postprandial state. These lipoproteins are taken up by macrophages in the arterial wall and are therefore atherogenic. T₄ increases the clearance of chylomicron remnants from the serum (28). Therefore, hypothyroidism is associated with elevated serum concentrations of remnant lipoproteins (26, 29). Investigators have demonstrated a 7-fold increase in the risk for postprandial lipidemia (defined as an increase of 80% or more in serum triglycerides 4–6 h after eating) in both overt and subclinical hypothyroidism compared with euthyroid controls (30). This effect is reversible with L-T4 treatment (31).

Qualitative as well as quantitative changes in serum lipids may result from hypothyroidism and may add to cardiovascular risk. It has been demonstrated, for example, that oxidizability of LDL-C is increased in overt hypothyroidism in some (32, 33), but not all (34), studies. In one study, levels of oxidized LDL-C were higher in patients with subclinical hypothyroidism than in euthyroid controls (35). The significance of these findings is not entirely clear, but oxidative modifications of LDL-C may play a role in the initiation of atherosclerosis.

Lipid subparticle size may also be altered in overt and subclinical hypothyroidism. Among 1794 women in the Framingham Offspring Study cohort, we found that large low-density lipoprotein (LDL) subparticle concentrations, but not the more atherogenic small LDL-C, was greater with increasing serum TSH levels (36). Ozcan *et al.* (37) noted lower small, dense LDL concentrations despite overall elevations in serum LDL-C concentrations in 84 subclinically hypothyroid patients compared with euthyroid controls. However, in a cross-sectional Korean study, there were no differences in LDL particle size among 46 subclinically hypothyroid patients, 57 subclinically hypothyroid patients, and age- and sex-matched euthyroid controls (38).

Potential Mediators of the Effects of Subclinical Hypothyroidism on Serum Lipids

There are multiple potential reasons for the disparate results of observational studies of lipid levels in subclinically

hypothyroid patients. These include differences in patient ages, ethnicity, gender, and degree and duration of hypothyroidism across studies. In addition, most observational studies have not adjusted for differences in insulin resistance and smoking behavior, which have been identified as potential modifiers of the relationship between thyroid status and serum lipids. The LDL-C elevation in hypothyroid patients is enhanced in patients with insulin resistance (39, 40). Serum LDL-C and total cholesterol concentrations are approximately 25% higher in hypothyroid smokers compared with hypothyroid nonsmokers (41).

Effects of L-T4 Therapy on Serum Lipids in Subclinical Hypothyroidism

Multiple interventional studies have evaluated the effects of L-T4 treatment on lipid profiles in patients with subclinical hypothyroidism, with mixed results (Table 3). Tzotzas *et al.* (23) found that baseline lipid profiles in a group of 24 patients with subclinical hypothyroidism did not differ from euthyroid controls, and that L-T4 treatment did not cause any significant change in serum lipid levels. Similarly, Kong *et al.* (42) randomized 40 patients with subclinical hypothyroidism to L-T4 treatment *vs.* placebo and found no significant differences in lipid measurements between the two groups after 6 months. However, the hypothyroid patients may not have been adequately treated because serum TSH averaged 3.4 mIU/liter in the treatment group at 6 months. Caraccio *et al.* (24) randomly assigned 49 patients with subclinical hypothyroidism to treatment with L-T4 or placebo and found that serum total cholesterol and LDL-C values were significantly higher in the 49 subclinically hypothyroid patients at baseline than in 33 euthyroid controls. After 6 months of adequate L-T4 therapy, the treated patients had significant decreases in serum total cholesterol and LDL-C values, although HDL-C and triglyceride levels did not change. In a double-blinded study, Meier *et al.* (25) randomly assigned 66 subclinically hypothyroid women to L-T4 treatment or placebo. After treatment, they found reductions from baseline total cholesterol and LDL-C concentrations in the L-T4 group, with more marked reductions seen in patients with initial LDL-C levels above 155 mg/dl or serum TSH levels above 12 mIU/liter. However, LDL-C changes did not differ significantly between the L-T4 and placebo groups, and there were no significant differences in HDL-C or triglyceride levels in the L-T4 group compared with the controls.

A subgroup of 64 subclinically hypothyroid participants from the Fifth Tromsø study were randomized to treatment with L-T4 *vs.* placebo (43); the treated patients

TABLE 3. Effects of L-T4 therapy on serum lipids in subclinical hypothyroidism

First author, year (Ref.)	Tzotzas, 2000 (23)	Meier, 2001 (25)	Kong, 2002 (42)	Caraccio, 2002 (24)	Iqbal, 2006 (43)	Razvi, 2007 (45)	Duman, 2007 (46)	Adrees, 2009 (44)
Study design	23 SCH patients treated with L-T4 vs. 38 euthyroid controls tested only at baseline	63 SCH women randomized to L-T4 vs. placebo	40 SCH women randomized to L-T4 vs. placebo	49 SCH patients randomized to L-T4 vs. placebo	64 SCH patients randomized to L-T4 vs. placebo	100 SCH patients L-T4 vs. placebo (crossover)	19 SCH patients randomized to no treatment; 20 to L-T4	56 SCH women treated with L-T4 vs. 56 euthyroid women tested at baseline only
TSH (mIU/liter)								
L-T4 group baseline	11.5	12.8	8.0	6.0 ^b	5.8	5.3	10.9	13.2 ^b
L-T4 group posttreatment	2.1 ^a	3.1 ^{a,b}	3.4 ^{a,b}	1.5 ^{a,b}	1.5 ^{a,b}	0.5 ^{a,b}	2.0 ^{a,b}	1.6 ^a
Controls baseline	2.2	10.7	7.3	4.9	5.4	5.3	11.0	1.9
Controls posttreatment		9.9	5.6	4.9	5.4	5.2	10.9	
Total cholesterol (mg/dl)								
L-T4 group baseline	241	243	216	212	228	232	204	219 ^b
L-T4 group posttreatment	230	236 ^a	220	193 ^a	224	220 ^b	202	207 ^a
Controls baseline	226	236	205	205	220	232	206	195
Controls posttreatment		232	217	205	224	232	202	
LDL-C (mg/dl)								
L-T4 group baseline	163	154	127	139	143	139	126	130 ^b
L-T4 group posttreatment	151	143 ^a	135	120 ^a	139	131 ^b	130	120 ^a
Controls baseline	148	147	127	127	139	139	124	112
Controls posttreatment		143	139	131	139	143	128	
HDL-C (mg/dl)								
L-T4 group baseline	59	66	39	58	58	66	52	62
L-T4 group posttreatment	56	66	40	58	58	62 ^b	53	61
Controls baseline	57	62	54	54	58	66	50	64
Controls posttreatment		62	57	58	58	66	53	
Triglycerides (mg/dl)								
L-T4 group baseline	120	50	159	50	58	46	138	54 ^b
L-T4 group posttreatment	116	50	168	46	58	50	93	54
Controls baseline	95	58	115	54	62	46	132	39
Controls posttreatment		58	115	50	62	50	128	

SCH, Subclinical hypothyroidism.

^a Significantly different from baseline.^b Significantly different from placebo/control.

had a significant decrease in ApoB levels at the end of the study compared with baseline, but no differences in serum lipid changes were noted overall between the treatment and placebo groups. In another study, serum lipid levels were measured in 56 women with subclinical hypothyroidism before and after 18 months of L-T4 treatment and compared with values in 56 age-matched euthyroid women

(44). Total cholesterol, triglycerides, LDL-C, and Lp(a) were all greater at baseline in the subclinically hypothyroidism women than in the controls, and values decreased to control levels after the L-T4 treatment. Razvi *et al.* enrolled 100 patients with subclinical hypothyroidism in a randomized, blinded, crossover L-T4 trial of 12-wk L-T4 vs. placebo (45). The L-T4 treatment significantly decreased total cholesterol

and LDL-C levels; there were no significant effects on HDL-C, triglycerides, ApoB, or ApoA1 levels.

Finally, 59 patients with subclinical hypothyroidism were randomized to no treatment *vs.* treatment with simvastatin *vs.* treatment with L-T4 (46). The simvastatin-treated, but not the L-T4-treated patients had significant reductions in LDL-C, total cholesterol, and triglycerides. Endothelium-dependent vasodilatation also improved only in the simvastatin group.

A recent Cochrane review of thyroid hormone replacement in subclinical hypothyroidism concluded that although there was a trend toward favorable effects of treatment on total cholesterol, there was no significant evidence of a treatment effect on cholesterol levels, HDL-C, LDL-C, triglycerides, ApoA, ApoB, or Lp(a) (47).

Cardiovascular Risk in Subclinical Hypothyroidism

Increased serum lipid levels are one of many cardiovascular risk factors that have been associated with subclinical hypothyroidism. Others include diastolic hypertension, impaired endothelial function, increased arterial stiffness, and possibly altered coagulation parameters and elevated C-reactive protein levels (1). Both systolic and diastolic cardiac function are likely impaired in subclinically hypothyroid patients. Results of prospective cohort studies examining the relationship of baseline subclinical hypothyroidism to risk for coronary disease and all-cause and cardiovascular mortality have been inconsistent (1), although recent meta-analyses have suggested that subclinical hypothyroidism may be associated with modestly increased cardiovascular risk (48), especially among younger individuals (49). It is important to note that whereas interventional studies have addressed the effects of L-T4 therapy on serum lipids and other surrogate endpoints, no clinical trial to date has examined the effect of L-T4 therapy on cardiovascular events or cardiovascular mortality in subclinically hypothyroid patients.

Recommendations for Screening and Therapy

Hyperlipidemia and subclinical hypothyroidism are both relatively common in the general population. Estimates of the prevalence of subclinical hypothyroidism among patients with dyslipidemia range from 1.4 to 11.2% (50). In one meta-analysis, subclinical hypothyroidism was determined to be two to three times more common in patients with elevated total cholesterol levels than in patients with normal fasting serum lipids (51). The American Thyroid

Association has recommended that all adults should be screened for thyroid dysfunction starting at age 35 (52), although guidelines from other organizations including the American Academy of Physicians do not advocate general population screening for subclinical thyroid disease (1). Evaluation for hypothyroidism is recommended as part of the initial workup in all patients with hyperlipidemia (53).

Whether or not to treat patients with subclinical hypothyroidism remains controversial. There is general consensus that individuals with serum TSH values greater than 10 mIU/liter should receive L-T4 treatment, but published opinions regarding less severe subclinical hypothyroidism vary (54, 55). A new joint American Thyroid Association and American Association of Clinical Endocrinologists guideline for the treatment of hypothyroidism is currently in preparation. Clinical trials to date have not consistently shown a lipid-lowering benefit of L-T4 therapy alone in subclinically hypothyroid patients. Therefore, in patients diagnosed with both subclinical hypothyroidism and clinically significant hyperlipidemia, therapeutic lifestyle changes should be instituted immediately and lipid-lowering medications added as appropriate, regardless of whether or not L-T4 therapy is instituted.

Thyroid Hormone Analogs for the Treatment of Hyperlipidemia

In the 1970s, dextrothyroxine was studied as an antihyperlipidemia agent in the Coronary Drug Project, but its use was associated with increased mortality in patients with underlying cardiac disease (56). More recently, it has been recognized that it is predominantly β -isoforms of the thyroid hormone receptor that are responsible for the regulation of serum cholesterol levels, whereas α -receptor isoforms mediate effects on bone and on heart rate. A number of β -isoform-specific thyroid hormone analogs are currently in development, with the goal of targeting thyroid hormone therapy to relevant tissues while avoiding the adverse effects of systemic thyrotoxicosis (57). Such analogs may eventually be useful for treating hyperlipidemia in euthyroid patients.

Conclusions

Thyroid hormone has multiple effects on lipid synthesis and metabolism. The net effect in patients with overt hypothyroidism is an increase in serum total cholesterol, LDL-C, ApoB, and Lp(a) levels, and possibly triglyceride levels. Treatment with L-T4 reverses these changes. The effects of subclinical hypothyroidism on serum lipid values are less clear. ApoB levels may be elevated in patients with

subclinical hypothyroidism. Although some studies have demonstrated that total cholesterol and LDL-C levels are elevated in patients with subclinical hypothyroidism, others have not shown any effect of subclinical hypothyroidism on these lipid measurements. Serum triglycerides, lipid subparticle size, and LDL-C oxidizability may be altered in subclinical hypothyroidism, but these studies have also been inconsistent. The preponderance of evidence suggests that HDL-C and Lp(a) levels are not altered in subclinically hypothyroid patients. Smoking and insulin resistance may modify the effects of subclinical hypothyroidism on serum lipid values. Clinical trials to date have not consistently shown a significant beneficial effect of L-T4 therapy on lipids in patients with subclinical hypothyroidism, possibly because these lipid changes are relatively subtle, and studies conducted to date do not have sufficient power to detect small differences between treatment and control groups. Given current evidence, specific lipid-lowering treatment should be instituted in hyperlipidemic patients with subclinical hypothyroidism, regardless of whether or not they are treated with L-T4.

Acknowledgments

Address all correspondence and requests for reprints to: Elizabeth N. Pearce, M.D., M.Sc., Boston University School of Medicine, 88 East Newton Street, Evans 201, Boston, Massachusetts 02118. E-mail: elizabeth.pearce@bmc.org.

Disclosure Summary: E.P. has received lecture fees from Merck Serono.

References

- Biondi B, Cooper DS 2008 The clinical significance of subclinical thyroid dysfunction. *Endocr Rev* 29:76–131
- Choi JW, Choi HS 2000 The regulatory effects of thyroid hormone on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Endocr Res* 26:1–21
- Shin DJ, Osborne TF 2003 Thyroid regulation and cholesterol metabolism are connected through sterol regulatory element-binding protein-2 (SREBP-2). *J Biol Chem* 278:34114–34118
- Gälman C, Bonde Y, Matasconi M, Angelin B, Rudling M 2008 Dramatically increased intestinal absorption of cholesterol following hypophysectomy is normalized by thyroid hormone. *Gastroenterology* 134:1127–1136
- Tan KC, Shiu SW, Kung AW 1998 Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism. *J Clin Endocrinol Metab* 83:140–143
- Boone LR, Lagor WR, Moya Mde L, Niesen MI, Rothblat GH, Ness GC 2011 Thyroid hormone enhances the ability of serum to accept cellular cholesterol via the ABCA1 transporter. *Atherosclerosis* 218:77–82
- Lam KS, Chan MK, Yeung RT 1986 High-density lipoprotein cholesterol, hepatic lipase and lipoprotein lipase activities in thyroid dysfunction—effects of treatment. *Q J Med* 59:513–521
- Kuusi T, Taskinen MR, Nikkilä EA 1988 Lipoproteins, lipolytic enzymes and hormonal status in hypothyroid women at different levels of substitution. *J Clin Endocrinol Metab* 66:51–56
- O'Brien T, Dinneen SF, O'Brien PC, Palumbo PJ 1993 Hyperlipidemia in patients with primary and secondary hypothyroidism. *Mayo Clin Proc* 68:860–866
- Vierhapper H, Nardi A, Grösser P, Raber W, Gessl A 2000 Low-density lipoprotein cholesterol in subclinical hypothyroidism. *Thyroid* 10:981–984
- Hueston WJ, Pearson WS 2004 Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med* 2:351–355
- Kanaya AM, Harris F, Volpato S, Pérez-Stable EJ, Harris T, Bauer DC 2002 Association between thyroid dysfunction and total cholesterol level in an older biracial population. The Health, Aging, and Body Composition Study. *Arch Intern Med* 162:773–779
- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC 2000 The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med* 160:526–534
- Walsh JP, Bremner AP, Bulsara MK, O'Leary P, Leedman PJ, Feddema P, Michelangeli V 2005 Thyroid dysfunction and serum lipids: a community-based study. *Clin Endocrinol (Oxf)* 63:670–675
- Bell RJ, Rivera-Woll L, Davison SL, Topliss DJ, Donath S, Davis SR 2007 Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease—a community-based study. *Clin Endocrinol (Oxf)* 66:548–556
- Lai Y, Wang J, Jiang F, Wang B, Chen Y, Li M, Liu H, Li C, Xue H, Li N, Yu J, Shi L, Bai X, Hou X, Zhu L, Lu L, Wang S, Xing Q, Teng X, Teng W, Shan Z 2011 The relationship between serum thyrotropin and components of metabolic syndrome. *Endocr J* 58:23–30
- Garduño-García Jde J, Alvirde-García U, López-Carrasco G, Padilla Mendoza ME, Mehta R, Arellano-Campos O, Choza R, Sauque L, Garay-Sevilla ME, Malacara JM, Gomez-Perez FJ, Aguilar-Salinas CA 2010 TSH and free thyroxine concentrations are associated with differing metabolic markers in euthyroid subjects. *Eur J Endocrinol* 163:273–278
- Asvold BO, Vatten LJ, Nilsen TI, Bjørø T 2007 The association between TSH within the reference range and serum lipid concentrations in a population-based study. The HUNT Study. *Eur J Endocrinol* 156:181–186
- Lu L, Wang B, Shan Z, Jiang F, Teng X, Chen Y, Lai Y, Wang J, Xue H, Wang S, Li C, Liu H, Li N, Yu J, Shi L, Hou X, Xing Q, Bai X, Teng W 2011 The correlation between thyrotropin and dyslipidemia in a population-based study. *J Korean Med Sci* 26:243–249
- Monzani F, Caraccio N, Kozàková M, Dardano A, Vittone F, Viridis A, Taddei S, Palombo C, Ferrannini E 2004 Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 89:2099–2106
- Pérez A, Cubero JM, Sucunza N, Ortega E, Arcelús R, Rodríguez-Espinosa J, Ordoñez-Llanos J, Blanco-Vaca F 2004 Emerging cardiovascular risk factors in subclinical hypothyroidism: lack of change after restoration of euthyroidism. *Metabolism* 53:1512–1515
- Ito M, Arishima T, Kudo T, Nishihara E, Ohye H, Kubota S, Fukata S, Amino N, Kuma K, Sasaki I, Hiraiwa T, Hanafusa T, Takamatsu J, Miyauchi A 2007 Effect of levo-thyroxine replacement on non-high-density lipoprotein cholesterol in hypothyroid patients. *J Clin Endocrinol Metab* 92:608–611
- Tzotzas T, Krassas GE, Konstantinidis T, Bougoulia M 2000 Changes in lipoprotein(a) levels in overt and subclinical hypothyroidism before and during treatment. *Thyroid* 10:803–808
- Caraccio N, Ferrannini E, Monzani F 2002 Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab* 87:1533–1538
- Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R, Müller B 2001 TSH-controlled L-thyroxine therapy reduced cholesterol levels and clinical symptoms in

- subclinical hypothyroidism: a double blind, placebo-controlled trial. *J Clin Endocrinol Metab* 86:4860–4866
26. Ito M, Takamatsu J, Sasaki I, Hiraiwa T, Fukao A, Murakami Y, Isotani H, Miyauchi A, Kuma K, Hanafusa T 2004 Disturbed metabolism of remnant lipoproteins in patients with subclinical hypothyroidism. *Am J Med* 117:696–699
 27. O'Brien T, Katz K, Hodge D, Nguyen TT, Kottke BA, Hay ID 1997 The effect of the treatment of hypothyroidism and hyperthyroidism on plasma lipids and apolipoproteins AI, AII, and E. *Clin Endocrinol (Oxf)* 46:17–20
 28. Weintraub M, Grosskopf I, Trostanesky Y, Charach G, Rubinstein A, Stern N 1999 Thyroxine replacement therapy enhances clearance of chylomicron remnants in patients with hypothyroidism. *J Clin Endocrinol Metab* 84:2532–2536
 29. Brenta G, Berg G, Zago V, Muzzio ML, Schnitman M, Sinay I, Arias P, Schreier L 2008 Proatherogenic mechanisms in subclinical hypothyroidism: hepatic lipase activity in relation to the VLDL remnant IDL. *Thyroid* 18:1233–1236
 30. Tanaci N, Ertugrul DT, Sahin M, Yucel M, Olcay I, Demirag NG, Gursoy A 2006 Postprandial lipemia as a risk factor for cardiovascular disease in patients with hypothyroidism. *Endocrine* 29:451–456
 31. Ito M, Takamatsu J, Matsuo T, Kameoka K, Kubota S, Fukata S, Tamai H, Miyauchi A, Kuma K, Hanafusa T 2003 Serum concentrations of remnant-like particles in hypothyroid patients before and after thyroxine replacement. *Clin Endocrinol (Oxf)* 58:621–626
 32. Sundaram V, Hanna AN, Koneru L, Newman HA, Falko JM 1997 Both hypothyroidism and hyperthyroidism enhance low density lipoprotein oxidation. *J Clin Endocrinol Metab* 82:3421–3424
 33. Dickman T, Demacker PN, Kastelein JJ, Stalenhoef AF, Wiersinga WM 1998 Increased oxidizability of low-density lipoproteins in hypothyroidism. *J Clin Endocrinol Metab* 83:1752–1755
 34. Gjedde S, Gormsen LC, Rungby J, Nielsen S, Jørgensen JO, Pedersen SB, Riis AL, Weeke J, Møller N 2010 Decreased lipid intermediate levels and lipid oxidation rates despite normal lipolysis in patients with hypothyroidism. *Thyroid* 20:843–849
 35. Duntas LH, Mantzou E, Koutras DA 2002 Circulating levels of oxidized low-density lipoprotein in overt and mild hypothyroidism. *Thyroid* 12:1003–1007
 36. Pearce EN, Wilson PW, Yang Q, Vasan RS, Braverman LE 2008 Thyroid function and lipid subparticle sizes in patients with short-term hypothyroidism and a population-based cohort. *J Clin Endocrinol Metab* 93:888–894
 37. Ozcan O, Cakir E, Yaman H, Akgul EO, Erturk K, Beyhan Z, Bilgi C, Erbil MK 2005 The effects of thyroxine replacement on the levels of serum asymmetric dimethylarginine (ADMA) and other biochemical cardiovascular risk markers in patients with subclinical hypothyroidism. *Clin Endocrinol (Oxf)* 63:203–206
 38. Kim CS, Kang JG, Lee SJ, Ihm SH, Yoo HJ, Nam JS, Ahn CW, Kim KR 2009 Relationship of low-density lipoprotein (LDL) particle size to thyroid function status in Koreans. *Clin Endocrinol (Oxf)* 71:130–136
 39. Bakker SJ, ter Maaten JC, Popp-Snijders C, Slaets JP, Heine RJ, Gans RO 2001 The relationship between thyrotropin and low density lipoprotein cholesterol is modified by insulin sensitivity in healthy euthyroid subjects. *J Clin Endocrinol Metab* 86:1206–1211
 40. Chubb SA, Davis WA, Davis TM 2005 Interactions among thyroid function, insulin sensitivity, and serum lipid concentrations: the Fremantle diabetes study. *J Clin Endocrinol Metab* 90:5317–5320
 41. Müller B, Zulewski H, Huber P, Ratcliffe JG, Staub JJ 1995 Impaired action of thyroid hormone associated with smoking in women with hypothyroidism. *N Engl J Med* 333:964–969
 42. Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, Doré CJ, Finer N, Naoumova P 2002 A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med* 112:348–354
 43. Iqbal A, Jorde R, Figenschau Y 2006 Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromsø Study. *J Intern Med* 260:53–61
 44. Adrees M, Gibney J, El-Saiey N, Boran G 2009 Effects of 18 months of L-T4 replacement in women with subclinical hypothyroidism. *Clin Endocrinol (Oxf)* 71:298–303
 45. Razvi S, Ingoe L, Keeka G, Oates C, McMillan C, Weaver JU 2007 The beneficial effect of L-thyroxine on cardiovascular risk factors, endothelial function, and quality of life in subclinical hypothyroidism: randomized, crossover trial. *J Clin Endocrinol Metab* 92:1715–1723
 46. Duman D, Sahin S, Esertas K, Demirtunc R 2007 Simvastatin improves endothelial function in patients with subclinical hypothyroidism. *Heart Vessels* 22:88–93
 47. Villar HC, Saconato H, Valente O, Atallah AN 2007 Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev* 3:CD003419
 48. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, Rodondi N 2008 Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med* 148:832–845
 49. Razvi S, Shakoor A, Vanderpump M, Weaver JU, Pearce SH 2008 The influence of age on the relationship between subclinical hypothyroidism and ischemic heart disease: a metaanalysis. *J Clin Endocrinol Metab* 93:2998–3007
 50. Ineck BA, Ng TM 2003 Effects of subclinical hypothyroidism and its treatment on serum lipids. *Ann Pharmacother* 37:725–730
 51. Tanis BC, Westendorp GJ, Smelt HM 1996 Effect of thyroid substitution on hypercholesterolemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clin Endocrinol (Oxf)* 44:643–649
 52. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, Smith SA, Daniels GH, Cohen HD 2000 American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med* 160:1573–1575
 53. 2002 Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final report. *Circulation* 106:3143–3421
 54. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ 2004 Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 291:228–238
 55. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT 2005 Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *J Clin Endocrinol Metab* 90:581–585; discussion 586–587
 56. The Coronary Drug Project Research Group 1972 The coronary drug project: findings leading to further modifications of its protocol with respect to dextrothyroxine. *JAMA* 220:996–1008
 57. Baxter JD, Webb P 2009 Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. *Nat Rev Drug Discov* 8:308–320
 58. Pearce EN 2004 Hypothyroidism and dyslipidemia: modern concepts and approaches. *Curr Cardiol Rep* 6:451–456