Update in Lipid Alterations in Subclinical Hypothyroidism

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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

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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.

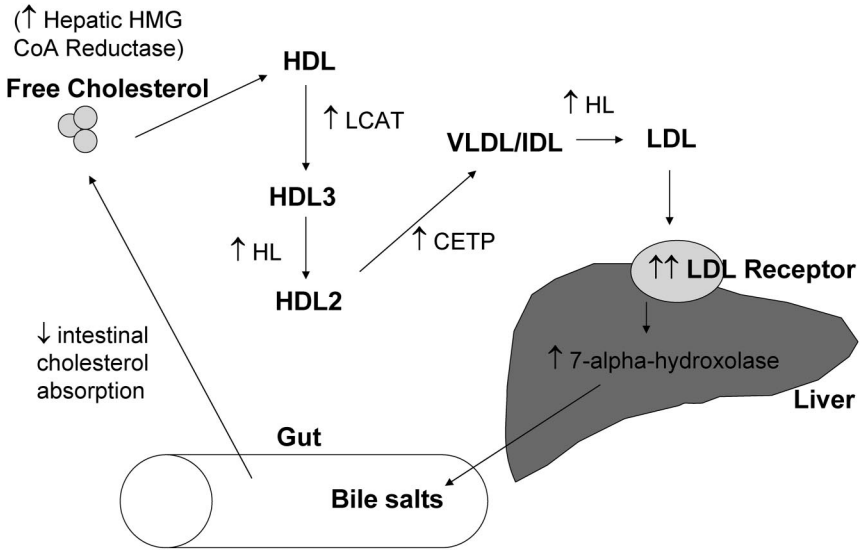

FIG. 1. Effects of thyroid hormone on cholesterol metabolism. Thyroid hormone increases LDL receptor expression, increases CETP concentrations, and increases hepatic lipase (HL) concentrations. Thyroid hormone also increases hepatic cholesterol synthesis by inducing hydroxymethylglutaryl coenzyme A (HMG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

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.]

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.

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 T_4 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 HDL_2 (primarily incorporating the protein ApoA-I) and larger HDL_3

(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. T_4 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]
LT-4 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 LT-4 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

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