Hypothyroidism and Dyslipidemia: Modern Concepts and Approaches

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Subclinical and overt hypothyroidism are relatively common disorders in the general population. Thyroid hormone is known to play a role in regulating the synthesis, metabolism, and mobilization of lipids. In patients with overt hypothyroidism there is an increase in serum total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein B, lipoprotein(a) [Lp(a)] levels, and possibly triglyceride levels. The effects of subclinical hypothyroidism on serum lipid values are less clear. The preponderance of evidence suggests that total cholesterol, LDL cholesterol, and possibly triglycerides are increased in patients with subclinical hypothyroidism, whereas high-density lipoprotein (HDL) cholesterol and Lp(a) remain unchanged. Most lipid abnormalities in patients with overt hypothyroidism will resolve with thyroid hormone replacement therapy. However, clinical trials to date have not shown a beneficial effect of thyroid hormone treatment on serum lipid levels in patients with subclinical hypothyroidism. The lipid-altering effects of thyroid hormone make it an appealing target for drug development. The development of specifically targeted thyroid hormone analogues that could potentially treat hyperlipidemia without causing systemic thyrotoxicosis is currently ongoing.

Introduction

An association between thyroid dysfunction and dyslipidemia was first reported in 1930 [1]. Although they have been the focus of numerous clinical studies over the past 70 years, the relationships between thyroid function, lipid status, and cardiovascular outcomes remain incompletely understood. Although hyperthyroidism has adverse effects on the cardiovascular system, most of its effects on serum lipid concentrations are beneficial. Therefore, this review focuses on the effects of overt and subclinical hypothyroidism on serum lipid levels. The prevalence of thyroid dysfunction and the lipid effects of overt hypothyroidism are described. Several of the most recent and most important clinical studies regarding lipid changes in subclinical hypothyroidism, approaches to screening, and the impact of thyroid hormone treatment on those changes are detailed here. It may be possible in the future to take advantage of the effects of thyroid hormone on lipid metabolism by developing highly selective thyroid hormone analogues that could treat hyperlipidemia without causing potential adverse effects of thyroid hormone excess on peripheral tissues; early research efforts in this direction are described.

Thyroid Dysfunction

Thyroid dysfunction is relatively common in the US population. In the third National Health and Nutrition Survey (NHANES III) [2], conducted between 1988 and 1994, hyperthyroidism was present in 1.3% and hypothyroidism in 4.6% of the population. The prevalence of thyroid dysfunction increases with age. Data from the Framingham Heart Study [3] demonstrate that some degree of hypothyroidism is present in 10.3% of unselected patients over age 60, with a higher incidence in women (13.6%) than in men (5.7%).

An elevated serum thyroid-stimulating hormone (TSH) level is the hallmark of hypothyroidism. As thyroid function diminishes, serum TSH levels begin to rise. Elevated serum TSH levels with normal free thyroxine (T4) and triiodothyronine (T3) concentrations is termed *subclinical hypothyroidism*, or *mild thyroid failure*. Symptoms are usually subtle or absent. As thyroid failure progresses, serum free T4 levels fall, and the combination of elevated TSH and low free T4 concentrations is termed *overt hypothyroidism*. Serum total and free T3 levels may not fall until disease is far advanced, because increased TSH levels stimulate T3 release from the thyroid. When patients develop overt hypothyroidism, they exhibit the classic symptoms and signs of hypothyroidism such as fatigue, weight gain, cold intolerance, constipation, dry skin, hoarseness, mental impairment, depression, decreased appetite, or arthralgias.

In the United States and other regions where dietary iodine intake is generally sufficient, the vast majority of cases of hypothyroidism are caused by chronic autoimmune thyroiditis (Hashimoto's thyroiditis). Hypothyroidism can also be iatrogenic, resulting from thyroid surgery or radioactive iodine therapy for hyperthyroidism. Most of the causes of subclinical hypothyroidism are

Table 1. Causes of subclinical hypothyroidism

Endogenous causes
Hashimoto's thyroiditis
Transient hypothyroid phase of silent sporadic thyroiditis, postpartum thyroiditis, or subacute thyroiditis
Exogenous causes
Inadequate L-thyroxine treatment for overt hypothyroidism
Overtreatment with antithyroid medications for hyperthyroidism
Radioactive iodine ablation
Subtotal or total thyroidectomy
External beam radiation to the neck
Inadequate dietary iodine
Excess iodine (from iodine-containing medications or iodinated radiographic contrast agents)
Treatment with lithium, interferon-α, or interferon-2

similar to those for overt hypothyroidism (Table 1.) Subclinical disease progresses to overt hypothyroidism at the rate of 2% to 4% per year, especially in the presence of detectable serum thyroid antibodies [4].

Levothyroxine sodium (L-T4) is the treatment of choice for hypothyroidism. The goal of therapy is the normalization of serum TSH values. The undertreatment of overt hypothyroidism will result in subclinical hypothyroidism.

Mechanisms for Lipid-Thyroid Interactions

Elevations in total cholesterol and low-density lipoprotein (LDL) cholesterol 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 [5]. Therefore, in hypothyroidism, hepatic cholesterol synthesis is decreased. However, thyroid hormone also increases the expression of cell surface LDL cholesterol receptors expressed in fibroblasts, liver, and other tissues. LDL cholesterol receptor levels are regulated by negative feedback in the presence of high intracellular cholesterol levels. This is mediated through the sterol regulatory element-binding protein (SREBP)-2. It has recently been discovered that the *SREBP2* gene is directly regulated by T3 [6]. A decrease in LDL cholesterol receptors leads to reduced clearance of LDL cholesterol from the serum. This thyroid hormone effect on LDL cholesterol receptor expression outweighs the effects of decreased hepatic cholesterol synthesis, leading to a net accumulation of serum LDL cholesterol in hypothyroidism.

Cholesteryl ester transfer protein (CETP) transfers cholesterol from high-density lipoprotein (HDL) cholesterol to LDL cholesterol 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 cholesterol concentrations [7]. Thyroid hormone also appears to play a role in the regulation of hepatic lipase, which alters HDL cholesterol subfractions [7].

Lipoprotein lipase lowers triglyceride levels through hydrolysis of triglyceride-enriched lipoproteins and facilitation of cholesterol transfer from these lipoproteins to HDL cholesterol. Lipoprotein lipase activity is increased by thyroid hormone [8]. Therefore, hypertriglyceridemia may develop in hypothyroidism.

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. However, this is unlikely to be a primary mechanism for lipid changes in patients with thyroid dysfunction [9].

Overt Thyroid Dysfunction and Lipid Levels

Serum lipid levels are decreased in patients with hyperthyroidism when compared with euthyroid controls (Table 2) [10]. Of considerably more clinical importance, over 90% of overtly hypothyroid patients have hyperlipidemia [11]. Serum total cholesterol and LDL cholesterol levels are increased by approximately 30% in patients with overt hypothyroidism [12,13•]. Interestingly, this LDL cholesterol increase is enhanced in patients with insulin insensitivity [14]. The effect of hypothyroidism on lipid levels is also mediated by cigarette smoking; serum LDL cholesterol and total cholesterol concentrations are approximately 25% higher in hypothyroid smokers compared with hypothyroid nonsmokers [15]. Triglyceride levels and VLDL are normal to increased in overt hypothyroidism [11,13•,16]. Effects of overt hypothyroidism on HDL cholesterol have been variable, with some studies showing HDL cholesterol to be increased, some showing it to be normal, and others showing it to be increased [17–19]. However, the preponderance of evidence suggests that HDL cholesterol levels are normal to slightly elevated in overt hypothyroidism, resulting in an unfavorable ratio of LDL cholesterol to HDL cholesterol [11]. The lipid abnormalities in overt hypothyroidism are generally reversible with L-T4 therapy [12]. Patients who have higher baseline serum lipid values when hypothyroid will have greater reductions in serum lipid concentrations after the initiation of thyroid hormone replacement [20].

Subclinical Hypothyroidism and Lipid Levels

The results of observational studies of lipid levels in patients with subclinical hypothyroidism have been inconsistent. In a cross-sectional study of 7000 thyroid clinic outpatients, Vierhapper *et al.* [21] concluded that, although total cholesterol and LDL cholesterol were clearly elevated in overtly hypothyroid patients, there were no significant differences in serum total cholesterol, LDL cholesterol, HDL cholesterol, or triglyceride levels between subclinically hypothyroid patients and the

Table 2. Lipid effects of thyroid dysfunction

	Hyperthyroidism	Overt hypothyroidism	Subclinical hypothyroidism
Total cholesterol	Decreased	Increased 30%	Increased
LDL cholesterol	Decreased	Increased 30%	Increased
HDL cholesterol	Decreased	Normal to slightly increased	No change
Triglycerides	No change	Normal to increased	Normal to increased
Lp(a)	Decreased	Increased	No change
ApoB	Decreased	Increased	Increased

ApoB—apolipoprotein B; HDL—high-density lipoprotein; LDL—low-density lipoprotein; Lp(a)—lipoprotein (a).

euthyroid control group. By contrast, in a population-based sample of 2799 elderly black and white subjects, Kanaya *et al.* [22] reported that total cholesterol was significantly increased in subclinical hypothyroidism. In the largest cross-sectional study to date, Canaris *et al.* [23••] examined thyroid function tests from 25,862 participants in a statewide health fair in Colorado. They documented elevated serum TSH levels in 9.5% of this population. The majority of this group (9.0% of the total) had normal serum T4 levels, consistent with subclinical hypothyroidism. There was a significant, gradual increase in fasting total cholesterol, triglyceride, and LDL cholesterol levels as thyroid function declined, with higher mean lipid levels in subclinically hypothyroid subjects than in euthyroid subjects.

Several studies have evaluated the effects of L-T4 treatment on lipid profiles in patients with subclinical hypothyroidism, with mixed results. Tzotzas *et al.* [24] 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.* [25] randomly assigned 40 patients with subclinical hypothyroidism to L-T4 treatment versus 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, since serum TSH averaged 3.4 mU/L in the treatment group at 6 months. By contrast, Caraccio *et al.* [26•] randomly assigned 49 patients with subclinical hypothyroidism to treatment with L-T4 or placebo [26•]. Serum total cholesterol and LDL cholesterol 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 cholesterol values, although HDL cholesterol and triglyceride levels did not change. In a double-blinded study Meier *et al.* [27•] randomly assigned 66 women with subclinical hypothyroidism to L-T4 treatment or placebo. Following treatment, they found reductions from baseline total cholesterol and LDL cholesterol concentrations in the L-T4 group, with more marked reductions seen in patients with initial LDL cholesterol levels above 155 mg/dL or serum TSH levels greater than 12 mU/L. However, LDL cholesterol changes did not differ significantly between the L-thyroxine and placebo groups. Similarly, they did not detect significant differences in HDL cholesterol or triglyceride levels in the L-T4 group compared with the controls.

Because a large number of small studies have shown conflicting results regarding the effects of L-T4 treatment on serum lipid profiles in subclinical hypothyroidism, Danese *et al.* [28••] performed a meta-analysis of 13 published studies, which included a total of 247 subjects. Their conclusion was that serum total cholesterol and LDL cholesterol are both reduced by L-T4 treatment in patients with subclinical hypothyroidism, but that HDL cholesterol and triglyceride levels are not altered. The mean decrease in total cholesterol with L-T4 treatment was 7.9 mg/dL whereas the mean decrease in LDL cholesterol was 10 mg/dL.

Subclinical Hypothyroidism and Atherosclerosis

Subclinical hypothyroidism has also been suggested to increased cardiovascular events. Two groups have recently reported an association between subclinical hypothyroidism and increased carotid artery intima-media thickness, which may be a marker for early atherosclerosis [29,30]. L-T4 therapy was associated with decreases in intima-media thickness in both studies, suggesting that these adverse effects of hypothyroidism are reversible.

Finally, the Rotterdam Study group [31••] reported that subclinical hypothyroidism was associated with aortic atherosclerosis and myocardial infarction in a cohort of postmenopausal women. This was true despite the fact that, surprisingly, the women in the cohort with subclinical hypothyroidism had a significantly lower mean total cholesterol value than the euthyroid controls. These data are provocative, but have not yet been replicated.

Other Lipid Alterations and Hypothyroidism

In addition to changes in conventional fasting lipid profiles in patients with hypothyroidism, recent studies have noted alterations in some less traditional lipid measures in patients

with thyroid dysfunction. Concentrations of apolipoprotein (Apo) B, a major constituent of LDL cholesterol and VLDL, are significantly increased in hypothyroidism [29,32]. Lipoprotein(a) [Lp(a)] is a form of LDL cholesterol in which the large lipoprotein Apo(a) and ApoB are covalently bound by a disulfide bridge; it may be particularly atherogenic and thrombogenic. Some studies have suggested that Lp(a) levels are increased in patients with overt hypothyroidism and decrease following L-T4 treatment [13•,24,32]. 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 [24,26•,27•]. Also, Apo(a) size does not differ in patients with subclinical hyperthyroidism compared with euthyroid controls [33].

Although it has not been clearly demonstrated to have an effect on total HDL cholesterol serum concentrations, thyroid hormone does appear to play a role in determining the size and density of HDL cholesterol particles. HDL cholesterol particles can be categorized by size into the smaller HDL_2 (primarily incorporating the protein ApoAI) and larger HDL3 (incorporating both ApoAII and ApoAI) subfractions. HDL cholesterol that incorporates more ApoAI is more antiatherogenic. The HDL_2 subfraction is decreased in hyperthyroid patients and increased in hypothyroid patients [34]. ApoAI concentrations are decreased in hyperthyroidism and increased in hypothyroidism, whereas ApoAII levels are unchanged [35]. A beneficial change in HDL cholesterol subfractions may help to moderate the atherogenic LDL cholesterol changes seen in hypothyroidism.

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. Recent studies have determined that T4 increases the clearance of chylomicron remnants from the serum [36]. Therefore, hypothyroidism is associated with increased serum concentrations of remnant lipoproteins. This effect is reversible with L-T4 treatment [37].

Qualitative as well as quantitative changes in serum lipids may result from thyroid dysfunction, and may add to cardiovascular risk. It has been demonstrated, for example, that oxidizability of LDL cholesterol is increased in overt hyperthyroidism and overt hypothyroidism [38,39]. Levels of oxidized LDL cholesterol are also higher in patients with subclinical hypothyroidism than in euthyroid controls [40]. The significance of these findings is not entirely clear, but such oxidative modifications of LDL cholesterol may play a role in the initiation of atherosclerosis.

Recommendations for Screening and Therapy

Hyperlipidemia and hypothyroidism are both relatively common in the general population, and therefore may occur concomitantly. Estimates of the prevalence of subclinical hypothyroidism among patients with dyslipidemia range from 1.4% to 11.2% [41]. 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 [20]. The American Thyroid Association has recommended that all patients with hypercholesterolemia be screened for thyroid dysfunction [42]. This approach has been demonstrated to be cost effective [43]. A serum TSH value should be the initial screening test. If the serum TSH value is elevated, some measure of the serum free T4 concentration should be obtained to discriminate between overt and subclinical disease.

All patients with hyperlipidemia and overt hypothyroidism should be treated with L-T4. Once serum TSH values have normalized, usually by 2 to 4 months of adequate L-T4 therapy, serum lipid values should be repeated. Up to a 30% to 50% decrease in the ratio of total cholesterol to HDL cholesterol can be expected with L-T4 treatment [11]. If the hyperlipidemia has not resolved with L-T4 therapy alone, therapeutic lifestyle changes should be instituted and lipid-lowering medications should be added as appropriate. It is preferable to start statins, if required, after patients become euthyroid, as overt hypothyroidism may be a risk factor for statin-associated myopathy [44].

The question of treatment for patients with subclinical hypothyroidism remains controversial. A consensus panel convened by the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society recently concluded that L-T4 therapy should be instituted in patients with subclinical hypothyroidism and serum TSH values greater than 10 mU/L, and that there is currently insufficient evidence to recommend L-T4 treatment for patients with subclinical hypothyroidism and serum TSH values of 4.5 to 10 mU/L [45••]. Although observational studies and meta-analyses have suggested that there are mild elevations in serum lipid values in patients with subclinical hypothyroidism, there are no sufficiently large clinical trials to date that have showed a significant lipid-lowering benefit of L-T4 therapy alone. Therefore, in patients diagnosed with both subclinical hypothyroidism and 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. Azezli *et al.* [46] compared combination treatment with L-T4 and a statin to treatment with L-T4 alone in postmenopausal women with subclinical hypothyroidism and noted that the combination treatment significantly reduced total cholesterol, LDL cholesterol, and triglycerides, and increased HDL cholesterol.

Future Directions

Although L-T4 therapy can be extremely effective for the treatment of hyperlipidemia in patients with overt hypothyroidism, is not possible to use supraphysiologic thyroid hormone therapy to treat hyperlipidemia in euthyroid patients because of the adverse effects of thyrotoxicosis. However, different human tissues express different thyroid hormone receptor isoforms. It appears from mouse knockout models that α receptor isoforms are predominantly responsible for the effects of thyroid hormone on heart rate, whereas β isoforms regulate serum cholesterol levels [47•]. There has been recent interest in the development of thyroid hormone receptor isoform-specific thyroid hormone analogues. Such tailored drugs could eventually be used to target thyroid hormone therapy to relevant tissues while avoiding the adverse effects of systemic thyrotoxicosis. The experimental compound GC-1, which selectively targets the β isoform of the thyroid hormone receptor, has recently been reported to be effective, reducing body weight and serum cholesterol in animal studies, with minimal effects on heart rate [48]. Similarly, in animal studies an experimental thyromimetic compound (CGS 23425) has been reported to cause a dose-dependent increase in ApoAI expression without causing adverse cardiac effects [49]. This is a promising area for future study.

Conclusions

Thyroid hormone has multiple effects on lipid synthesis and metabolism. In hyperthyroid patients this results primarily in decreased fasting serum LDL cholesterol and total cholesterol values. The net effect in patients with overt hypothyroidism is an increase in serum total cholesterol, LDL cholesterol, ApoB, Lp(a) levels and possibly triglyceride levels. Treatment with L-T4 will reverse these changes, and should be instituted in all overtly hypothyroid patients. The effects of subclinical hypothyroidism on serum lipid values are less clear. The preponderance of evidence suggests that total cholesterol, LDL cholesterol, and possibly triglycerides are increased in patients with subclinical hypothyroidism, whereas HDL cholesterol and Lp(a) remain unchanged. Clinical trials to date have not shown a significant beneficial effect of L-T4 therapy on lipids in patients with subclinical hypothyroidism, most likely 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. Finally, the lipid-altering effects of thyroid hormone make it an appealing target for drug development. The development of specifically targeted thyroid hormone analogues that could potentially treat hyperlipidemia without causing systemic thyrotoxicosis is currently ongoing.

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