Update on Lipid Metabolism and Thyroid Disorders

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Abstract

Thyroid hormone plays an important role in the regulation of lipid metabolism. It acts predominantly through its nuclear receptors (thyroid hormone receptor α and β) to regulate the gene expression related to lipid metabolism. Both overt hypothyroidism and hyperthyroidism result in abnormalities of lipid profile. However, changes in serum lipid profiles in patients with subclinical hypothyroidism have been inconsistent. In recent years, thyroid receptor β1-selective analogue represents a new class of hypolipidemic compound have been developed. Some of these T3 analogues are very potent in lowering serum cholesterol and triglyceride in animal models and human clinical studies. This mini review on the mechanisms that affect lipid profile under pathological thyroid conditions, and give brief touch on thyroid analogues.

ABBREVIATIONS

TR: Thyroid Hormone Receptor; L-T4: Levothyroxine; TC: Total Cholesterol; HMGCR: 3-hydroxy-3-methyl-Glutaryl coenzyme A reductase; SREBP: Sterol Regulatory Element Binding Protein; TRE: Thyroid Hormone Responsive Element; TG: Triglyceride; LDL-R: Low Density Lipoprotein Cholesterol Receptor; HDL: High-Density Lipoprotein cholesterol; IDC: Intermediate Density lipoprotein Cholesterol; VLDL-C: Very Low Density Lipoprotein Cholesterol; CYP7A1: Cholesterol 7-Hydroxylase; HL: Hepatic Lipase; LPL: Lipoprotein Lipase; CETP: Cholesteryl-Esters Transfer Protein; LCAT: Lecithin-Cholesterol Acyltransferase; Lp (a): Lipoprotein (a); CM: Chylomicron; apo (B): Apolipoprotein (B); Free thyroxine: FT3; FT3 Free triiodothyronine; TSH: Thyrotropin

INTRODUCTION

Thyroid Hormone (TH) has multiple effects on the regulation of lipid digestion, absorption, synthesis, and catabolism [1]. Cumulative evidence shows that both overt hypothyroidism and subclinical hypothyroidism can result in hyperlipidemia, leading to increased risk of cardiovascular disease. With the elucidation of the molecular mechanism of thyroid hormone action, we have gained much understanding the influences of thyroid hormone on lipid metabolism. This article intends to update the current knowledge concerning the impact of thyroid disorders on lipid metabolism and levothyroxine (L-T4) treatment, and also reviews the effect of thyroid hormone analogue treatment on hyperlipidemia.

Effects of thyroid hormone on cholesterol metabolism

TH regulates cholesterol synthesis through multiple mechanisms. Liver is the main organ for cholesterol synthesis.
Effects of thyroid hormone on circulating triglyceride level

Thyroid hormone plays a role in both lipogenesis and lipolysis. Thyroid hormone regulates Lipoprotein Lipase (LPL) an essential enzyme that responsible for removing Triglycerides (TG) from circulating chylomicrons and Very Low Density Lipoproteins (VLDL). LPL catalyzes TG breakdown into non-esterified fatty acid and transporting to adipose tissue where it re-esterified and storage as TG [12,15,16]. Also, the fatty acids yield from LPL hydrolysis TG as energy source for heart. Additionally, TH affects TG levels involves angioprotein-like 3 (ANGPTL3), a potent LPL inhibitor. Over expression of ANGPTL3 in mice significantly enhances total cholesterol, non-esterified fatty acid and TG. Patients carrying ANGPTL3 mutation have increased circulating TG levels [17]. Furthermore, in rats, thyroid hormone treatment reduced ANGPTL3 mRNA expression by 70%. At transcription level, ANGPTL3 is negatively regulated by thyroid hormone, which is mediated by TRβ but not TRα [18]. In hyperthyroid condition, TG level showed either no change or decrease, partly, due to T3 down regulate ANGPTL3 and stimulates PLP, leading to hydrolysis TG. Then, T3-mediated LDLR stimulation dramatically increases clearing capacity for LDL [17]. Thyroid hormone influences TG homeostasis also involves regulating APOA5 gene transcription. Apolipoprotein A-V (ApoA5) is associated with HDL, VLDL and chylomicrons. ApoA5 regulates TG level through stimulating LPL-mediated TG hydrolysis and inhibiting hepatic VLDL-TG formation. Patients with single nucleotide polymorphisms or mutation of APOA5 manifest markedly reduced plasma postheparin LPL activity and hypertriglyceridemia [19]. TH directly regulates ApoA5 gene transcription via TRβ in ApoA5 promoter and increases the protein level [20]. Animal experiment showed that ApoA5 mRNA significantly reduced in hypothyroid rats. After T3 treatment, ApoA5 mRNA level returned to normal. Thyroid hormone regulation of circulating TG level is more complex involving in multi-pathways and positive and negative gene regulations.

LIPID PROFILES IN OVERT HYPOTHYROIDISM

Serum Total Cholesterol (TC), LDL-C, lipoprotein a (Lp[a]), oxi-LDL, ApoB [1,21], remnants of VLDL and Chylomicron (CM) levels are increased in overt hypothyroidism [22], while serum levels of triglyceride, High-Density Lipoprotein Cholesterol (HDL) and VLDL are normal or slightly increased [1,2]. All of the lipid abnormalities in overt hypothyroidism are reversible with levoxiloxine (L-T4) therapy unless the patient has underlying hyperlipidemia [12].

In overt hypothyroidism, thyroid hormone effects on LDL receptor expression and cholesterol absorption outweigh the effects of decreased hepatic cholesterol synthesis, leading to high serum levels of LDL, Intermediate Density Lipoprotein Cholesterol (IDC), and total cholesterol levels [23]. Additionally, LPL activity is decreased in hypothyroidism, resulted in higher level of VLDL-TG. Studies showed that Lipoprotein (a) [Lp(a)] levels are increased in patients with overt hypothyroidism and decrease after L-T4 treatment. Lp(a) is a complex of low density lipoprotein in which apolipoprotein (apo) B-100 is linked to apo(a) by a disulfied bridge. Lp(a) promotes foam cell formation and deposition of cholesterol, resulting in increased atherosclerotic and thrombogenic potential. The mechanism may be related to the decreased clearance of Lp(a) mediated by the LDL-R degradation pathway [23]. The levels of apolipoprotein (B) are higher in both overt and subclinical hypothyroidism and have been shown to decrease after L-T4 treatment [24-26].

Cholesterol ester transfer protein (CETP) transfers cholesterol from HDL-cholesterol (C) to LDL-C and VLDL-C. Plasma CETP concentrations are decreased in hypothyroidism and increased in hyperthyroidism, which may lead to the higher serum HDL-C concentrations in hypothyroidism [27]. Thyroid hormone analogue (GC-1) can also increase hepatic HDL-C receptor (scavenger receptor B1) [28], and accelerate the clearance of HDL-C by the liver. HDL-C particles can be subdivided into the smaller HDL2 (primarily incorporating Apo A-I) and larger HDL3 (incorporating Apo A-I and Apo A-II) subfractions. HL can catabolize TG within HDL-C, and regulate the hydrolysis of HDL-2 to HDL3. HL is decreased in hypothyroidism, leading to the higher HDL2 levels [12,13,30,31]. Apo A-I and Apo A-II are major constituents of HDL-C. Hypothyroidism inhibits the transcription of the Apo A-I gene, but the decreased activity of HL results in slower clearance of Apo A-I, thus leading to increased Apo-AI levels. Human studies show that Apo A-I levels are decreased in hypothyroidism and increased in hyperthyroidism, whereas Apo A-II levels are not influenced by either hyperthyroidism or hypothyroidism [13,30,31].

Patients with overt hypothyroidism usually have higher LDL-C, leading to increased oxidized (oxi)-LDL. Oxi-LDLs are taken up by macrophages in the arterial walls to produce foam cells, and as such may be a risk factor for atherosclerosis. The high levels of oxi-LDL are reversible with L-T4 treatment [32,33]. Both overt hypothyroidism and subclinical hypothyroidism can levels. However, studies show that thyroid status does not affect LDL particle size [34].

Lipid profiles in subclinical hypothyroidism

The results of serum lipid levels in patients with subclinical hypothyroidism are inconsistent. The results of cross-sectional studies of serum lipid levels in patients with subclinical hypothyroidism have been inconsistent, and are well reviewed by Pearce and Duntas [1,21]. Generally, serum total cholesterol and LDL-C levels are normal or increased [1,21]; oxi-LDL [33], apo B (B), remnants of VLDL and CM are increased [35]. TG and HDL may be normal [36,37], increased [38], or decreased [39]. The lipid abnormality in subclinical hypothyroidism may be related to the values of serum TSH. The lipid profile of patients with subclinical hypothyroidism with higher serum TSH level is similar to that in patients with overt hypothyroidism.

The mechanisms involved in the hypercholesterolemia resulting from subclinical hypothyroidism are the same as overt hypothyroidism. Although Free Thyroxine (FT4) and Free Triiodothyronine (FT3) levels in patients with subclinical hypothyroidism are within the normal reference range, TSH level is higher. Over time, the subclinical may develop to overt hypothyroidism. The abnormality of lipid profiles in subclinical hypothyroidism may be related to gradually decreased TSH levels in the serum and tissues [35,40]. Additionally, high TSH
level stimulates *HMGR* expression by stimulating the cyclic adenosine monophosphate/protein kinase A/cyclic adenosine monophosphate-responsive element binding protein (cAMP/PKA/CREB) cassette [41].

**Overt hyperthyroidism and lipid profiles**

In overt hyperthyroidism, serum levels of total cholesterol, LDL-C, and HDL-C (mainly HDL2) are decreased, while triglyceride levels are slightly elevated, normal or reduced [13,42,43], and oxLDL levels are increased [44,45]. Whether the decreased HDL-C levels and increased oxLDL levels lead to atherosclerosis in hyperthyroidism is not known. Reason for this mild hypertriglyceridemia is unclear. Lipolysis is augmented in hyperthyroidism with elevation of free fatty acids in plasma, but hepatic lipogenesis is also augmented due to increased free fatty acid flux from adipose tissue to the liver [21,46]. After treatment for hyperthyroidism, the hypertriglyceridemia caused by overt hyperthyroidism can be reversed.

**ASSOCIATION OF SUBCLINICAL AND OVER HYPOTHYROIDISM WITH CARDIOVASCULAR DISEASES**

The higher levels of serum total cholesterol, LDL-C, remnants of VLDL and CM, oxLDL, and apoB that result from subclinical hypothyroidism are risk factors for cardiovascular disease. Subclinical hypothyroidism has been associated with an increased risk of cardiovascular disease and mortality in some prospective population-based cohort studies [47-49]. By contrast, the incidence of coronary heart disease and mortality due to coronary heart disease were not increased in other prospective population-based studies [50-53]. In a meta-analysis from 11 prospective cohort studies, the risk of cardiovascular disease was negatively related to initial TH levels [54].

L-T4 treatment has a hypolipemic effect on subclinical hypothyroidism. Treatment with L-T4 can prevent the progression from subclinical to overt hypothyroidism and improve hyperlipidemia, thus decreasing the risk of atherosclerotic disease. A number of small-scale (N=20 to100), randomized, placebo-controlled, double-blind clinical trials have recently been conducted to study the effects of L-T4 therapy on lipid profiles, and the results are inconsistent [1]. Generally speaking, the higher the initial levels of serum cholesterol and TSH, the greater the therapeutic benefit. Patients whose serum TSH levels exceed 10 mIU/L are at increased risk for heart failure and cardiovascular mortality and should be treated with L-T4 [55]. Patients whose TSH levels are greater than the upper limit of a given laboratory reference range but less than 10 mIU/L should be considered for treatment if they have symptoms of hypothyroidism, positive antithyroid antibody or cardiovascular risk factors (eg. hypertension, hypercholesterolemia, insulin resistance or diabetes) [56]. The treatment of mild subclinical hypothyroidism (serum TSH concentration of 4.5-10mIU/L) is not recommended in older patients because available evidence suggests the benefit of treatment may be reduced in patients above 65 years of age [57,58].

**Perspectives of thyroid hormone analogues in treatment of hyperlipidemia**

Thyroid hormone plays an important role in the regulation of lipid metabolism [59]. There are mainly two TR genes (TRα and TRβ), with different patterns of expression in different tissues. In liver, TRβ exerts approximately 80% T3 action. TRα/T3 mediates cholesterol reduction and lipid metabolism in liver. In past decade, TRβ1 selective ligand has been one of the focal points for developing cholesterol reducing drugs. The idea is that T3 analogues should preserve the beneficial effect of T3 in reducing cholesterol levels while minimizing the harmful effects on heart and bone. The research on the selective thyroid hormone receptor β1 analogues has made significant progress. These TRβ1-selective ligands include L-9490 [60], CGS23425 [61], Triac [62], GC-1 [63], GC-24 [64], KB141 [65], KB2115 [66] and MB07811 [67]. Among them, GC-1, KB2115, and MB07811 are higher liver-selective T3 analogues and KB141 is a non-tissue selective analogue. Theoretically, these highly liver-targeting ligands are higher cholesterol-lowering potential with fewer side effects. For example, KB141 induced weight loss and an increased metabolic rate when tested in animals. Besides KB141, the liver-selective TRβ1 analogues GC-1, MB07811 and KB2115 increased expression of hepatic LDL-R and hepatic HDL receptor SR-B1, stimulated the activity of CYP7A1, and increased fecal excretion of bile acids. TRβ1 analogues also decreased levels of serum triglycerides and Lp(a) without adverse effects on heart and bone [68-71].

Presently, three selective TRβ1 analogues (KB2115, GC-1, and MB07811) reached human clinical trials for hypercholesterolemia and displayed impressive early results for this indication [66,70,71]. The studies demonstrated that the analogues took effect quickly (1-2 weeks after commencing treatment). Patients had a significant reduction in serum LDL-C levels (as high as 40% within 3 months) without side effects on heart, bone or muscle [66,70,71]. Addition of KB2115 ( Eprotirome) to statin therapy resulted in further substantial reduction in levels of LDL-C, triglycerides, apolipoprotein B, and Lp(a) in human clinical trials, which suggests that these two classes of medication may work through complementary mechanisms [72].

Unfortunately, the development of KB2115 was discontinued in 2012, after a 12-month toxicology study revealed that prolonged exposure to the drug led to cartilage damage [72]. This led to termination of this trial and all other related studies (such as GC-1 and MB07811). Although the development of selective TRβ1 analogues has been halted at present, their unique lipid-lowering mechanism indicates that the selective TRβ1 may still be a potential drug to aid in lowering lipid levels and augmenting weight loss.

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