REVIEW

Update on dyslipidemia in hypothyroidism: the mechanism of dyslipidemia in hypothyroidism

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Abstract

Hypothyroidism is often associated with elevated serum levels of total cholesterol, LDL-C and triglycerides. Thyroid hormone (TH) affects the production, clearance and transformation of cholesterol, but current research shows that thyroid-stimulating hormone (TSH) also participates in lipid metabolism independently of TH. Therefore, the mechanism of hypothyroidism-related dyslipidemia is associated with the decrease of TH and the increase of TSH levels. Some newly identified regulatory factors, such as proprotein convertase subtilisin/kexin type 9, angiogenin-like proteins and fibroblast growth factors are the underlying causes of dyslipidemia in hypothyroidism. HDL serum concentration changes were not consistent, and its function was reportedly impaired. The current review focuses on the updated understanding of the mechanism of hypothyroidism-related dyslipidemia.

Key Words

- ▶ dyslipidemia
- ▶ hypothyroidism
- ▶ ANGPTL
- ▶ FGF
- ▶ PCSK9

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Introduction

Hypothyroidism, including overt and subclinical hypothyroidism is a common disease among people. The former is defined as increased serum thyroid-stimulating hormone (TSH) levels and reduced free peripheral thyroid hormone (TH) concentrations. The latter is characterized by normal free peripheral TH concentrations. The association between thyroid dysfunction and dyslipidemia was first reported in 1930. Since then, it has been gradually recognized that hypothyroidism could cause disorders of lipid metabolism (1), mainly with increased total cholesterol (TC) and LDL-C (2) in blood. Elevated LDL-C can lead to progressive lipid accumulation, plaque formation in the arteries and increase the risk of cardiovascular disease (CVD), the leading cause of death worldwide. Regardless of TSH or TC concentration, cholesterol levels will return to normal (3, 4) and cardiac function improves (5) after T4 replacement treatment. Furthermore, T4 treatment has a more significant impact on blood lipid profiles in overt than subclinical hypothyroidism (6). Therefore, it is

exceedingly important to pay attention to the relationship between hypothyroidism and lipid metabolism.

Previous observations have found that the prevalence of overt hypothyroidism is about 4.3% (7) and of subclinical hypothyroidism is about 11.1% (8) among hypercholesterolemic patients, both of which are higher than that of general people. Overt and subclinical hypothyroidism patients with serum TSH >10 mIU/L had an increased risk of CVD and mortality (9). These findings suggested that TH and TSH are two important risk factors for lipid metabolic disorders.

TH is a key regulator of metabolism, development and growth, which plays an important role in regulating the anabolism and catabolism of lipids. However, the deeper mechanism between hypothyroidism and blood lipid profile is still not fully understood, like the signaling pathway of TSH and other regulatory factors involved in lipid disturbance. This review focuses on mechanisms of hypothyroidism related to dyslipidemia, including

the established mechanisms and the newly identified mechanisms.

Dyslipidemia in hypothyroidism

Hypothyroidism has a different impact on blood lipid components; generally, it tends to increase levels of TC, especially apolipoprotein B (ApoB)-containing lipoprotein cholesterol, like LDL-C and triglyceride (TG) (1, 10, 11), while its influence on ApoA-containing lipoprotein cholesterol, like HDL-C, is uncertain (12). However, the ratios of ApoB to ApoA-containing lipoprotein cholesterol (LDL-C/HDL-C and TG/HDL-C) were consistently higher in hypothyroidism than the euthyroid ones (13, 14, 15). In addition, hypothyroidism patients are more likely to develop postprandial hypertriglyceridemia (16), generally with elevated TG, TG-rich lipoproteins (TRLs) and remnant lipoprotein (RLP).

Hypothyroidism has a different impact on blood lipid profiles. A higher degree of ApoB-containing lipoprotein cholesterol is found in patients with TSH >10 mIU/L compared to those with TSH 4.0–10.0 mIU/L (17, 18, 19). Regardless of the thyroid status, circulating TSH level is always positively correlated with levels of ApoB-containing lipoprotein cholesterol (20, 21, 22, 23, 24, 25). Hence the higher TSH level is, the greater the risks of dyslipidemia are (26). If there is no significant impairment of thyroid function with a low TSH level, blood lipids even improve over time (27). Therefore, we could initially speculate that besides TH, TSH also plays an important role in regulating lipid metabolism.

The mechanism of dyslipidemia in hypothyroidism

Hypothyroidism influences lipid profiles mainly via TH. TH could bind to thyroid hormone receptor β (THR β), mainly expressed in the liver, to regulate the expression of downstream target genes (28). The total effect of TSH on TC level includes the direct effect and the indirect effect (TH) (29, 30). Multiple regression analysis showed that the increase of cholesterol levels was closely related to declined TH levels after injection of TSH in levothyroxine-treated thyroidectomized patients (31). TSH alone also can increase TC levels in CVD patients independent of TH (32). It has been reported that TSH regulates cholesterol metabolism through binding to TSH receptors (TSHRs)

on the surface of hepatocytes (33) and adipocytes (34). Therefore, current evidence suggests that both TH and TSH affect cholesterol metabolism. Some regulatory factors are involved in cholesterol metabolism regulating as following. The major effect of TH and TSH on lipid metabolism in hypothyroidism has been outlined in Fig. 1.

Hypothyroidism and LDL-C metabolism

Hypothyroidism affects the production and clearance of LDL-C

TH has contradictory effects on cholesterol absorption and production. TH can directly induce the expression of liver HMG-CoA reductase (HMGCR), a rate-limiting enzyme in cholesterol synthesis (35), achieving greater cholesterol synthesis (36). Besides binding to THR, TH could activate sterol regulatory element-binding protein 2 (SREBP2) (37), a major transcription factor, and SREBP2 can stimulate the transcription of HMGCR gene. Hence, hypothyroidism can cause reduced cholesterol synthesis by affecting HMGCR. But the effect of TH on the Niemann-Pick C1-like 1 protein (NPC1L1) in the intestine leads to increased cholesterol absorption in hypothyroidism (38). In hypothyroidism, free fatty acid (FFA) oxidation is also reduced, leading to increased very low-density lipoprotein (VLDL) secretion in the liver. TH could enhance β -oxidation of FFA by increasing the autophagy of hepatocytes (39). It could also stimulate carnitine palmitoyltransferase 1 α (CPT1A), a rate-limiting β -oxidation enzyme (40). Accordingly, CPT1A mRNA and enzyme activity in the hyperthyroidism animal livers increase significantly (41); CPT1A is inhibited in the hypothyroidism mice (42). TH can also reduce the production of ApoB48 and ApoB100, thus reducing the production of VLDL and chylomicron (CM) (43, 44). Moreover, ApoB48 levels are negatively correlated to TH (45). Overall, the reduction of TH inhibits cholesterol synthesis via HMGCR but promotes the absorption of cholesterol through NPC1L1 and reduces catabolism through β -oxidation.

The LDL receptor (LDLR) is a transmembrane glycoprotein on the hepatocyte surface that recognizes lipoproteins containing ApoB, promoting cholesterol clearance. TH can upregulate the expression of LDLR mRNA through binding to thyroid-responsive element (TRE) of LDLR gene on the hepatocyte surface (46). Meanwhile, SREBP2 binds to the sterol regulatory element (SRE) on the LDLR promoter, thereby promoting the transcription of the LDLR gene (47). Therefore, the number of LDLR and LDL-C clearance rates decreased in hypothyroidism. The combined impact of TH on cholesterol production

Figure 1

Effect of decreased TH and increased TSH on lipid metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. TH decreases in hypothyroidism and then *de novo* lipogenesis (DNL) and the activity of HMG-CoA reductase (HMGCR) reduce, leading to declined cholesterol production, but free fatty acid (FFA) β -oxidation also decreases. TH reduction reduces the activity of cholesterol 7 α -hydroxylase (CYP7A1) and ATP-binding cassette transporter G5/8 (ABCG5/8) to reduce cholesterol clearance. In general, triglyceride (TG)-rich very low-density lipoprotein (VLDL) level is increased in hypothyroidism, and the elevation of Niemann-Pick C1-like 1 protein (NPC1L1) concentration leads to an increase of TG-rich chylomicron (CM). The decrease of TH causes the declined function that lipoprotein lipase (LPL) hydrolyzes CM and VLDL, and the clearance of LDL and remnant lipoprotein (RLP) by LDL receptor (LDLR) and LDL receptor-related protein 1 (LRP1) decreases too, so TG level increases. However, the net concentration of HDL is not consistent. TSH mainly results in the increase of proprotein convertase subtilisin/kexin type 9 (PCSK9), HMGCR and hormone-sensitive lipase (HSL) levels and the decrease of CYP7A1. RLP, remnant lipoprotein; ANGPTL3/8, angiogenin-like protein 3/8; ApoC3, apolipoprotein C3; CETP, cholesterol transport protein transporter; HL, hepatic lipase; PLTP, phospholipid transfer protein; LCAT, lecithin cholesterol acyltransferase; ABCA1, ATP-binding cassette transporter A1; SRB1, scavenger receptor b1; FGF19/21, fibroblast growth factors 19/21; HMG-CoA, 3-hydroxy-3-methyl glutaryl coenzyme A; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; CPT1A, carnitine palmitoyltransferase 1 α ; WAT, white adipose tissue.

and clearance leads to a net accumulation of serum LDL-C in hypothyroidism.

On the one hand, TSH can directly affect cholesterol synthesis. Mice with liver TSHR knockout had low TC levels, especially serum LDL-C (48). The binding of TSH to TSHR of hepatocyte membrane upregulates the expression and activity of HMGCR through the cAMP/PKA/CREB signaling pathway (49). TSH can also stimulate the expression of SREBP2 to regulate HMGCR (35, 50). In adipocytes, TSH β elevates HMGCR mRNA levels, and TSH β expression levels in mice's s.c. adipocytes are directly related to circulating cholesterol levels (51). TSH β gene expression is also positively correlated with the

expression of fatty acid mobilization (CAV1, ENGL1) (52). It has been found that TSH increased the phosphorylation of perilipin and hormone-sensitive lipase (HSL) to increase lipolysis, and circulating FFA increased significantly after TSH injection *in vitro* studies (53). Also, TSH could stimulate the increase of ApoB (31, 45). So, we could speculate that TSH is capable as a stand-alone hormone to produce a physiological response on lipid metabolism and have an effect independent of TH.

On the other hand, TSH plays an important part in LDL clearance. TSH induces PI3K/AKT/SREBP2 and SREBP2/HNF4/ Cholesterol 7 α -hydroxylase (CYP7A1) signaling pathways to inhibit the synthesis of hepatic bile

acids through TSHR (54). In patients with hypothyroidism and hypercholesterolemia, serum TSH was significantly negatively correlated with bile acid levels, independent of TH (10). Interestingly, the association between TSH and total serum bile acid was stronger in patients under 65 (55).

The decrease of TH and increase of TSH share similar pathogenic mechanisms of LDL-C accumulation in hypothyroidism, both of which could induce the cholesterol production and inhibit clearance. The effect of TH and TSH on LDL-C in hypothyroidism has been outlined in Fig. 2.

Factors involved in hypothyroidism-related LDL-C elevation

Fatty acids are obtained from the diet or *de novo* lipogenesis (DNL), where acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) play catalytic roles in the liver and adipose tissue (AT). TH regulates the expression of target genes in two different ways: TH could directly upregulate ACC/FAS through TRE (the direct mechanism) (56) or SREBP1/carbohydrate response element-binding protein

(ChREBP) (the indirect mechanism). The transcription of SREBP1 is negatively regulated via TRE (56, 57), but TH can also improve the translation efficiency of SREBP1 mRNA through non-genomic actions (58). Then SREBP1 combines with SRE in ACC and FAS genes to stimulate the expression (59, 60). Meanwhile, the inhibition of SREBP1C expression downregulates the expression of HSL gene, thus inhibiting lipid lipolysis (56). It is known that TH β influences the expression of ChREBP in hepatocytes (61) and ACC/FAS genes are positively regulated by ChREBP (62). ChREBP and SREBP1C can regulate each other to some extent (63). These new observations suggest that TH fine-tunes lipid adipogenesis by regulating the expression of SREBP-1C and ChREBP genes respectively.

FGF21 is a member of the FGF superfamily. It is mainly released from hepatocytes and is considered as an important endogenous regulator of glucose-lipid metabolism (64), and endogenous FGF21 is mainly released from hepatocytes. When treated with recombinant FGF21, serum TG, VLDL-C and LDL-C of rodents significantly reduced (65, 66). The same situation was observed in the human study: LDL-C and TG were lower and HDL-C was higher in patients using FGF21 analog (67). Chronic treatment with recombinant FGF21 can even reduce

Figure 2

Effect of decreased TH and Increased TSH on LDL-C metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. The reduction of TH inhibits cholesterol synthesis via HMGCR, but the absorption of cholesterol through NPC1L1 increases; the catabolism through β -oxidation and LDL-C clearance through LDL-R decrease. TSH could increase cholesterol synthesis and lipolysis but inhibits the clearance of cholesterol independently. The decrease of TH and increase of TSH induce the net production and inhibit the clearance of LDL-C, thus leading to LDL-C accumulation.

serum and liver TG levels in diet-induced obese mice by inhibiting SREBP1 (68). FGF21 reduces circulating FFAs by inhibiting lipolysis in white adipose tissue (WAT) (69) and stimulating FFAs uptake into WAT, consequently decreasing the secretion of VLDL in liver (70). FGF21 could also increase TRL disposal in AT (70).

TH increases FGF21 transcription and peptide levels in mice's liver through THR β binding to TRE in FGF21 intron 2 (71). TH also induces liver FGF21 gene expression to promote β -oxidation by activating AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) in a proliferator-activated receptor α (PPAR α)-dependent manner in mice, and the expression of FGF21 reportedly increased in a dose-dependent manner in mice treated with exogenous TH (72, 73). ChREBP also regulates plasma TG levels by regulating FGF21 (74, 75). In turn, peripheral administration of FGF21 could decrease TH levels (76).

Studies have found that FGF21 levels were significantly lower in hypothyroidism patients (77) and increased or did not change in hyperthyroidism patients (78, 79) due to the effect of TH. However, another study has found that the increase of circulating FGF21 levels in hypothyroidism patients is related to serum TSH (80). So, it could be speculated that TH and TSH have contradictory effects on pathogenetic metabolism. Whether TSH could induce the expression of FGF21 needs further exploration.

FGF19, secreted from the ileum after the stimulation of bile acid (81), participates in the negative feedback regulation of bile acid synthesis by inhibiting liver CYP7A1 (82). TH has a direct effect on the secretion of FGF19 (79). Circulating FGF19 levels significantly decrease in hypothyroidism patients and are independently correlated with TSH levels (83). Further studies have shown that SREBP downregulates the transcription and expression of FGF19 (84).

TH could regulate cholesterol synthesis via miRNA, a kind of small regulatory RNA. TH induces the expression of miR-181d in humans, thereby reducing the expression of caudal type homeobox 2 (CDX2), a transcription factor that activates sterol O-acyl transferase 2 (SOAT2). SOAT2 is essential for converting cholesterol into cholesterol ester (CE), and the latter is the preferred form of LDL (85); and TH mediated the reduction of miR-206, so TG and TC in HepG2 cells declined (86). Also, TH could positively regulate hepatic miR-378, leading to the reduction of serum cholesterol levels through promoting bile acid synthetic pathways (87). Recently, a regulatory module containing three miRNAs (miR-34a-5p, miR-24-3p and miR-130a-3p) and four proteins (thioredoxin, selenium-binding protein

2, elongation factor 1 β and prosaposin) about hepatic lipid metabolism was identified in subclinical mice (88).

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease, binds to the LDLR on the hepatocyte surface, facilitating LDLR degradation in lysosomes and reducing its recycling. PCSK9 could also regulate LDL receptor-related protein 1 (LRP1), which competes with LDLR (89). Studies have shown that TH significantly reduces PCSK9 levels (79). Both SREBP1 and SREBP2 can affect PCSK9 mRNA (90). Studies have found that SREBP2 can bind to the SRE1 site on the PCSK9 promoter (47). The expression of SREBP1C and FAS in liver is involved in circulating PCSK9 and its mRNA levels (91, 92). Combined, TH reduces PCSK9 through SREBPs, thereby increasing the expression of LDLR, promoting the clearance of cholesterol in the plasma and reducing cholesterol levels. Currently, studies have found that TSH is significantly positively correlated with plasma PCSK9, which partly depends on SREBP1C, SREBP2 and HMGCR (93, 94).

Regulatory factories like ACC/FAS of DNL, FGF21 and miR-181d/206 could affect the synthesis of LDL-C, while factories like FGF19 and PCSK9 influence the degradation of LDL-C. The detailed metabolisms are shown in Fig. 3.

Hypothyroidism and hypertriglyceridemia

Hypothyroidism affects TG production and transformation

TG comes from circulating exogenous or intracellular FFAs produced by glycolysis and fat. TH could reduce the production of VLDL-TG in liver (95). When the rate of lipolysis remains unchanged, hypothyroidism will lead to decreased lipid oxidation rates and elevated TG (96). TH could also increase ApoA5 mRNA and protein levels in hepatocytes, leading to a decline of TG (97). TH mainly upregulates the activity of lipoprotein lipase (LPL), which could lead to the lipolysis of TRLs, including CM and VLDL; the decrease of TH leads to the attenuation of these effects, thus promoting the elevation of serum TG in hypothyroidism (98). Studies have shown that impaired hepatic lipase (HL) activity in hypothyroidism patients may also be related to the accumulation of TRL (45). The transfer of TG to HDL is impaired in subclinical hypothyroidism patients (99).

Remnant lipoprotein (RLP) is composed of cholesterol, CE and ApoE-riched smaller particles. TRL particles gradually lose TG, phospholipid, ApoA and ApoC then transfers to RLP after being hydrolyzed by LPL. Existing studies have shown that hypothyroidism is associated with

Figure 3

Regulatory factors involved in hypothyroidism-related dyslipidemia. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. ACC/FAS, FGF21 and miR-181d/206 could affect the synthesis of LDL-C, while factors like FGF19 and PCSK9 influence the degradation of LDL-C. In hypothyroidism, FFA synthesis via DNL decrease, and the indirect mechanisms of TH on SREBP1 is stronger than the direct mechanisms through TRE. The oxidation and lipolysis of FFA decreases partly because of hypothyroidism-induced decreased FGF-21. FGF-19 inhibits bile acid synthesis and PCSK9 increases the degradation of LDLR, thus inhibiting the clearance of cholesterol in hypothyroidism.

increased serum RLP levels (100). On the one hand, the excess production of TRL particles in the liver can explain the elevated RLP levels in hypothyroidism patients. On the other hand, LRP1 is expressed on the hepatocyte surface and binds to ApoE, internalizing TRL and contributing to RLP clearance. TH influences the lipid profile by increasing the transcription of LRP1 in mice and humans (101). Interestingly, SREBP1 and SREBP2 could downregulate the transcription of LRP1 in human vascular smooth muscle cells and macrophages through binding to SRE (102, 103). Therefore, hypothyroidism can lead to LRP1 reduction and RLP clearance through SREBP.

TSH could also promote the synthesis of TG. It binds to TSHR to promote TG synthesis in differentiated adipocytes via AMPK/PPAR γ /GPAT3 axis (104). TSH could

also significantly increase TG levels in hepatocytes in a dose-dependent manner through TSHR/cAMP/PKA/PPAR α and PPAR α /AMPK/SREBP1C signaling pathways (49, 105). Higher TSH levels in the euthyroid population may affect TG-rich metabolism via ApoE (106), which could explain increased ApoE levels in hypothyroidism patients (107).

Hypothyroidism and newly identified mechanisms factors in TG metabolism

ANGPTL1-8 are secretory glycoproteins composed of an N-terminal helical domain and a C-terminal fibrinogen-like domain. Angptl3 is identified for proteolysis at positions 221–224 to produce N-terminal domains.

TH could inhibit mRNA of ANGPTL3 TR β dependently (108), and there was a positive correlation between ANGPTL3 and TSH in Graves' disease patients (109). Circulating VLDL-TG and LDL-C declined in ANGPTL3 loss-of-function heterozygotes (110, 111) because some studies have shown that ANGPTL3 at high concentration could inhibit LPL (112, 113). ANGPTL3 cleaves LPL through furin protease (114) and shows reversible inhibition of LPL catalytic activity. However, other studies also found that ANGPTL3 inactivates LPL by catalyzing the irreversible unfolding of its hydrolase domain, which is similar to ANGPTL4 (115). Furthermore, ANGPTL3 deficiency could lead to declined postprandial lipid levels, possibly due to accelerated catabolic metabolism of TRLs and reduced flow of fatty acids into liver (116, 117). One study demonstrated that ANGPTL3 gene siRNAs induced increased expression of LDLR/LRP1 and reduced the secretion of apoB100, resulting in increased uptake of LDL/VLDL (118). However, in another study, it was reported that the use of ANGPTL3 MAB, the reduction of LDL-C could be independent of the LDLR pathway, and it was speculated that the transformation from VLDL to LDL reduced partially because of increased ApoB clearance (111). Circulating ANGPTL3 levels elevated and were positively correlated with HDL-C in hypothyroidism patients (119). ANGPTL3 acts as an inhibitor of endothelial lipase, which could hydrolyze HDL-phospholipid to reduce plasma HDL levels, and ANGPTL3 is also involved in promoting the elevation of plasma HDL-C in humans and rodents (120).

ANGPTL8, known as TD26, re-feeding induced in fat and liver, lipasin and betatrophin, is an atypical member of ANGPTL family. It is expressed mainly in liver of humans, while in AT and liver of mice. The TG clearance rate and LPL activity in Angptl8 knockout mice increase significantly, thus reducing the plasma TG levels (121, 122). ANGPTL8 can cooperate with ANGPTL3 to improve the binding of ANGPTL3 to LPL and promote LPL lysis to increase the plasma TG level in mice (123, 124, 125). ANGPTL3 and ANGPTL8 can even promote each other somehow (125). Circulating Angptl8 levels increase in hypothyroidism patients and positively correlate with TSH, TG and TC (119, 122, 126, 127, 128). However, ANGPTL8 mRNA in HepG2 cells is induced by TH (129), and its expression can also be specifically activated in the liver of mice through SREBP1a and SREBP2 (124). These pieces of evidence could suggest that TH and TSH regulate ANGPTL8. TH could also convert lipid droplets through the autophagy process activated by ANGPTL8 to regulate lipid metabolism (129). In addition, the lipid contents in adipocytes significantly reduced after the deletion of ANGPTL8 gene (130). ANGPTL8

protein levels are positively related to TC, LDL-C in patients with morbid obesity and type 2 diabetes (131), but whether it is related to hypothyroidism or not, the answer remains uncertain.

ANGPTL6, also known as AGE, does not bind to angiogenin receptors. In patients with hypothyroidism, serum ANGPTL6 levels increase and are positively correlated with TSH and TC (132). Serum ANGPTL6 levels are also an independent predictor of low HDL and high TG (133). Studies have found that ANGPTL6 could mediate increased expression of PPAR α through the extracellular regulated protein kinases/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, leading to increased expression of FGF21, thereby promoting β -oxidation (134). It is possible to predict that TSH could induce FGF21 through ANGPTL6; however, TH has the opposite effect on FGF21 from TSH and the effect prevails, so serum FGF21 level is more prone to decrease in hypothyroidism as mentioned above.

The domain of Angptl4 is similar to Angptl3 (135). But, TH could not inhibit the expression of Angptl4 mRNA (108), and there is no significant change of Angptl4 levels in hypothyroidism (119). So, we could speculate that TH could not influence lipid metabolism through Angptl4.

Serum ApoC3, another LPL inhibitor, was found to decrease in hypothyroidism mice with or without pregnancy (42). The suppressed expression of ApoC3 gene leads to increased LPL activity and decreased plasma TG levels (136). Taken together, ApoC3 decrease leads to LPL increase in the presence of hypothyroidism.

Angptl3/6/8 and ApoC3 play important roles in TG transformation, especially Angptl3 and Angptl8 make a synergic reaction. More basic and epidemiological studies are needed to verify the deeper relationship between Angptl6/FGF21 and TSH. The detailed effects of TH and TSH on TG metabolisms are shown in Fig. 4.

Hypothyroidism and HDL-C metabolism

Thyroid hormone affects HDL levels

HDL synthesis decreases in hypothyroidism. A study has documented a positive relationship between FT4 and plasma pre- β -HDL formation in type 2 diabetes mellitus patients (137). TH strongly induces ApoA1 gene and protein expression (138), thereby increasing cholesterol efflux from peripheral tissues to HDL in reverse cholesterol transport (RCT). Homocysteine levels significantly increase in hypothyroidism mice; and homocysteine can reduce circulating HDL-C by inhibiting ApoA1 protein synthesis, thereby inhibiting RCT (139). However, ApoA1 levels

Figure 4

Effect of decreased TH and increased TSH on TG metabolism in hypothyroidism. The altered functions are labeled in the presence of hypothyroidism. Red arrows mark actions of declined TH, and blue arrows mark actions of elevated TSH. The increase of Angptl3 in hypothyroidism could inhibit LDL degradation via LDL-R and inhibit cholesterol transport via LPL and EL. TSH is related to Angptl6, influencing β -oxidation to some extent.

increase in hypothyroidism patients after thyroidectomy (140, 141). The potential causes of the contradictory result are not clear yet. TH could also stimulate cholesterol efflux from macrophages to HDL via transporter protein ATP-binding cassette transporter A1 (ABCA1) (138). The activity of ABCA1 and lecithin cholesterol acyltransferase decreases in hypothyroidism, which leads to the inhibition of the synthesis and maturation process of HDL particles (142).

The HDL clearance and transformation process decrease in hypothyroidism. TH stimulates HL, thus promoting HDL degradation and changing HDL components (143). Plasma cholesterol transport protein transporter (CETP) concentrations decrease in hypothyroidism, resulting in elevated plasma HDL-C levels (144). TH can increase the transcription of CYP7A1, a rate-limiting enzyme in RCT, thus promoting the transformation of cholesterol into bile acid (145). TH could also stimulate the secretion of bile acid in liver and intestine by stimulating the transcription of ATP-binding cassette transporter G5/8 (ABCG5/ABCG8) in rats (138), which is the last step of RCT (146). Hypothyroidism could inhibit cholesterol clearance by decreasing scavenger receptor b1 (147). These effects of TH on HDL synthesis and clearance counteract each other; therefore, the HDL-C level is not constant.

Patients with a moderate increase in TSH had reduced CETP and phospholipid transfer protein activities, which resulted in decreased HDL2 and elevated HDL3 levels (148). However, in T2DM patients, there is a positive correlation between TSH and CETP, thereby raising the possibility that hyperglycemia has strong effects on the ability of VLDL to accept cholesteryl esters from HDL (149). Hence, HDL-C levels could be affected by numerous conditions. The detailed effects of TH and TSH on HDL levels are shown in Fig. 5.

Hypothyroidism impairs HDL cholesterol efflux capacity

Though HDL levels were not consistent, cholesterol efflux capacity (CEC) was impaired in overt hypothyroidism, reflecting HDL function losses (107, 141). Paraonase-1 (PON1) is an important anti-oxidative enzyme that resides on HDL. Recent reports showed that after thyroidectomy, PON1 activity remained unaltered (140) but the PON1/ApoA1 ratio decreased (107). Altogether, hypothyroidism may affect HDL function through several unclear mechanisms.

Even though elevated HDL-C levels could not always protect humans from CVD and mortality, CEC is a

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Author contribution statement

H X L and D Q P contributed to the study design; H X L wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

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