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Hyperlipidemia and hypothyroidism

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ABSTRACT

Hypothyroidism is closely associated with increased serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG). The thyroid gland plays an important role in this process because thyroid hormones (THs) modulate cholesterol production, transformation and clearance. Although recent evidence suggests that thyroid-stimulating hormone (TSH) itself also participates in hyperlipidemia, the underlying mechanism remains unclear. Others demonstrated that the pathologic development of hypothyroidism-related hyperlipidemia was associated with down-regulated THs and up-regulated TSH in serum. This finding suggests a role for hypothyroidism in hyperlipidemia and potentially in related cardio-metabolic disease. Multiple newly identified modulatory biomarkers, such as proprotein convertase subtilisin/kexin type 9 (PCSK9), angiopoietin-like protein (ANGPTLs), and fibroblast growth factors (FGFs), might play a role in modulating the risk of hyperlipidemia induced by hypothyroidism. Moreover, hypothyroidism also contributes to the production of dysfunctional high-density lipoprotein (HDL) particles. In the present review, we examine the relationship between hypothyroidism with the risk and pathologic development of hyperlipidemia. We explore mechanisms by which hypothyroidism promotes hyperlipidemia in general and its contribution to cardio-metabolic disease specifically.

1. Introduction

Hypothyroidism is a common cause and independent risk factor for several diseases including depression, bradyarrhythmia and cretinism. There two important subtypes of hypothyroidism. Clinical hypothyroidism is characterized by the up-regulated thyroid-stimulating hormone (TSH) and down-regulated free peripheral thyroid hormones (PTHs) in serum [1]. In contrast, subclinical hypothyroidism is characterized by normal free serum PTHs. Recent epidemiologic studies have shown hypothyroidism poses severe risks to the human health leading to high mortality in the general population worldwide [2].

Among a series of concomitant symptoms of hypothyroidism, hyperlipidemia, which is characterized by the up-regulated circulating low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglyceride (TG), has been recently recognized as associated with hypothyroidism. [2]. Consistent with these findings, recent increasing evidence has demonstrated that hypothyroidism could induce the risk and the pathologil development of hyperlipidemia in several diseases. For example, patients with up-regulated serum total cholesterol (TC) presented with increased prevalence of clinical and subclinical hypothyroidism vs healthy subjects [3]. In contrast, hypothyroid individuals with the circulating TSH > 10 mIU/L were associated with increased prevalence of cardiovascular disease (CVD), suggesting that dysfunctional metabolism of thyroid hormones (THs) was an most important risk factors in lipid metabolic disorders [4]. Because the progression of up-regulated circulating LDL-C particles into the sub-endothelium is intimately involved in the cascade to atherosclerotic plaque formation which subsequently promotes

Abbreviations: LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; TG, triglyceride; TRL, TG-rich lipoprotein; NO, nitric oxide; Apo-B, apolipoprotein B; CM, chylomicron; RLP, remnant lipoprotein; LRP1, low-density lipoprotein receptor related protein 1; CRP, C-reactive protein; PCSK9, proprotein convertase subtilisin/kexin type 9; ANGPTL, angiopoietin-like protein; FGF, fibroblast growth factor; THR, thyroid hormones receptor; T3, triiodothyronine; SREBP, sterol regulatory element binding protein.

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atherosclerotic related CVDs, recent focus has shifted to elucidating the circulating lipid catabolism in hypothyroidism and clarifying the underlying mechanisms of hypothyroidism-induced hyperlipidemia [5].

On the other hand, multiple novel identified modulatory biomarkers, such as proprotein convertase subtilisin/kexin type 9 (PCSK9), angiopoietin-like protein (ANGPTLs), and fibroblast growth factors (FGFs), have been proposed to play an important role in modulating the risk of hyperlipidemia induced by hypothyroidism. Moreover, under the conditions of hypothyroidism, the dysfunctional HDL particles with impaired ability to induce the progression of reverse cholesterol transportation (RCT) could also been observed. In the present review, the current results of the associations between hypothyroidism with hyperlipidemia are well-listed. Furthermore, the understanding of the potential mechanisms by which hypothyroidism promotes hyperlipidemia and its cardio-metabolic diseases are also listed in our present review (see Fig. 1).

2. Clinical features of hyperlipidemia in patients with hypothyroidism

Due to the research advances, multiple eye-catching breakthroughs have been put forward to elucidate the characteristics of hyperlipidemia in the individuals with hypothyroidism. According to the results shown in the previous research, both TSHs and THs present diverse functions in regulating the circulating lipid profiles [6]. To be more specific, it has been demonstrated that the patients with subclinical hypothyroidism exhibited higher circulating levels of TC, LDL-C, and C-reactive protein (CRP); concurrently, these patients also presented relatively lower circulating levels of nitric oxide (NO) and omentin-1 compared with those in the euthyroid subjects. In addition, the circulating levels of TC, LDL-C, and CRP reduced significantly, whereas serum concentrations of NO and omentin-1 were up-regulated after using l-thyroxine treatment, suggesting a potential role of TSH in the risk of developing atherosclerotic related CVDs in the patients with subclinical hypothyroidism [7]. Consistent with these results, another research revealed that serum levels of TC were elevated significantly in patients with subclinical hypothyroidism compared with those in the control individuals, which also proposed a potential physiological function of TSH in regulating the catabolism of circulating lipid profiles in the individuals with subclinical hypothyroidism [8].

On the other hand, multiple large-scale clinical trials have demonstrated that the ratios of apolipoprotein B to apolipoprotein A1 (ApoB/ApoA1)-containing lipoprotein cholesterols, including the LDL-C/HDL-C and the TG/HDL-C, were significantly up-regulated compared with those in the euthyroid subjects [9,10]. Moreover, the hypothyroidism individuals are shown to be inclined to develop post-prandial hypertriglyceridemia (HTG), presenting with the up-regulating circulating levels of TG, TG-rich lipoproteins (TRLs), and remnant lipoprotein (RLP) [11]. Nonetheless, whether the pathological progression of hypothyroidism could influence the circulating concentrations and metabolism of ApoA1-containing lipoprotein cholesterol, such as HDL-C, is still not well elucidated. As a consequence, it is still necessary to conduct more large-scale clinical trials to deeply explore the metabolic alterations of serum ApoA1-containing lipoprotein cholesterol in patients with hypothyroidism.

It is also worth noting that there are significant discordances of the alterations of serum lipid profiles among the individuals with clinical hypothyroidism or subclinical hypothyroidism. For instance, an independent research demonstrated that in the patients with hypothyroidism, both the circulating levels of homocysteine and LDL-C were significantly higher compared with those in the control healthy subjects. By the levothyroxine treatment, the patients exhibited a significant

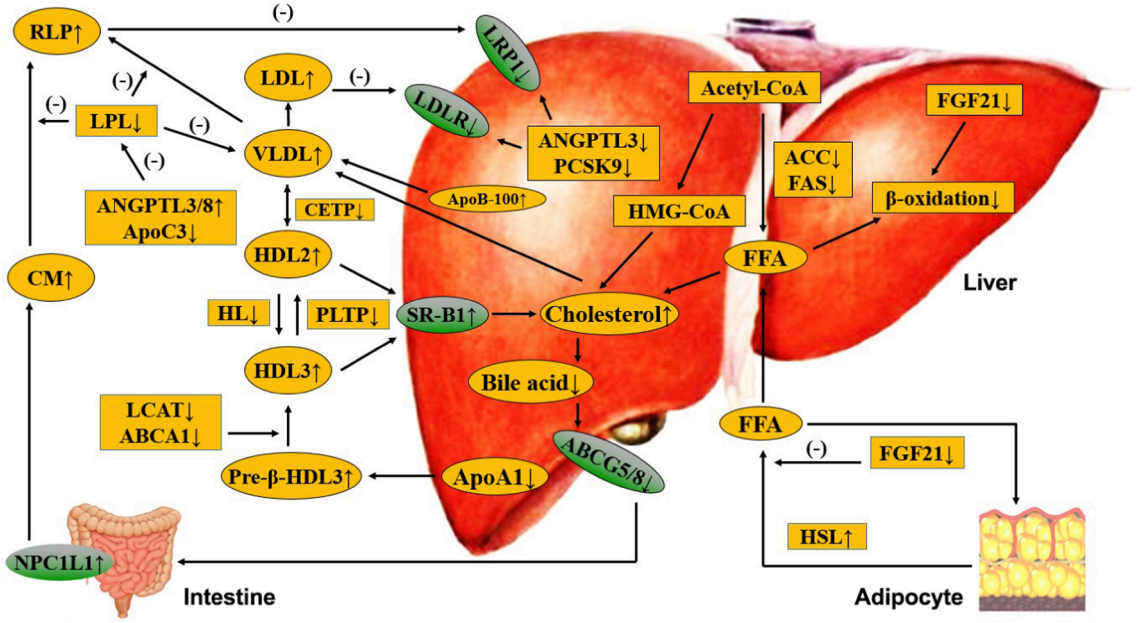

Fig. 1. The altered functions are labeled in the presence of hypothyroidism. Thyroid hormones (THs) decreases in hypothyroidism, then *de novo* lipogenesis (DNL) and the activity of HMG-COA reductase (HMGCR) reduces, leading to declined cholesterol production, but free fatty acid (FFA) β-oxidation also decreases. TH reduction reduces the activity of Cholesterol 7α-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 low-density lipoprotein (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 protein3/8; ApoC3, apolipoprotein C3; CETP, cholesterol transport protein transporter; HL, hepatic lipidosis; 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.

decreased body mass index (BMI) with the circulating levels of TC, LDL-C, and TG [12]. Another independent investigation showed that among approximately 12,000 participants, the thyroid functions were more closely associated with the circulating lipid profiles. Mean differences of LDL-C were approximately +15.2 mg/dL and approximately +3.2 mg/dL in the patients with moderate/severe and mild chemical hypothyroidism, respectively [13]. Similar discordances were observed in serum levels of TG, suggesting that hypothyroidism is closely correlated with the pathological development of hyperlipidemia, whereas the magnitude of hyperlipidemia is small in mild chemical hypothyroidism [14]. Importantly, no matter the thyroid function is normal or not, it is certainly demonstrated that the circulating concentrations of TSH are positively associated with serum ApoB-containing lipoprotein cholesterol concentrations [15]. Hence the higher serum levels of TSH are, the greater the risks of hyperlipidemia are. Taken together, we could make a reasonable speculation that the dysfunctional thyroid is closely associated with the pathological progression of hyperlipidemia. Besides the modulatory role of THs, the TSH also embraces a vital function in modulating the metabolism of circulating lipid profiles.

3. Altered regulation of LDL catabolism in patients with hypothyroidism

3.1. Functions of THs in regulating circulating LDL metabolism

By analysis the results of previous literatures, THs presents contradictory effects on influencing the production and release of circulating cholesterol. To be more specific, THs has been demonstrated to directly induce the expression extent of HMG-CoA reductase in the hepatocyte. Given that the HMG-CoA reductase has been considered as a rate-limiting enzyme in LDL-C synthesis, we could infer from these findings that THs could further promote the LDL-C synthesis via, at least partly, influencing the metabolism of HMG-CoA reductase [16]. Another independent investigation revealed that besides binding to thyroid hormones receptor (THR), the triiodothyronine (T3) hormone was found to stimulate the gene expression of sterol regulatory element binding protein 2 (SREBP-2) which has been identified as a major transcription factor during the adipogenic progression of pre-adipocytes [17]. As the excessive differentiation of adipocyte induces the pathological development of obesity/over-weight which is closely associated with hyperlipidemia, T3 hormone could affect the metabolism of circulating LDL-C via influencing the metabolism of SREBP-2. Recently, it is also demonstrated that SREBP-2 could activate the gene transcription of HMG-CoA reductase, indicating another potential mechanism by which dysfunctional thyroid modulates the pathological progression of hyperlipidemia [18].

More recently, Yen et al. found that THs could activate the β-oxidation progression of free fatty acids (FFAs) and subsequently delivered the FFAs into mitochondria which was coupled with the promotion of hepatic autophagy, revealing that TH could regulate the circulating LDL homeostasis via, at least partly, the autophagy process and up-regulating the oxidative metabolism [19]. Another research also found that the THs could also activate the biological activity of carnitine palmitoyl-transferase I-α (CPTI-α), which has been considered as a rate-limiting enzyme during the β-oxidation progression, and consequently regulate the catabolism of circulating lipid profiles [20]. Importantly, by using hypothyroidism mouse model, Chen et al. observed that compared with the pre-pregnant hypothyroidism mouse, the gestational hypothyroidism mouse exhibited more prominent increased circulating LDL-C levels and more TG accumulation within the hepatocytes. With in-depth investigation, the authors also demonstrated a significant up-regulation of *SREBP-1C* gene expressions in murine livers with gestational hypothyroidism [21]. Taken together, these results provided the evidence that THs might regulate hyperlipidemia via influencing the biological metabolism of several adipokines, such as SREBP-1C and SREBP-2. Furthermore, two research has also found that the THs could also directly down-regulate the circulating levels of ApoB-48 and ApoB-100, which consequently reduced the synthesis and secretion of VLDL and chylomicron (CM) within circulation [22,23].

Besides the direct function in regulating the LDL metabolism, THs has also been demonstrated to regulate the expression contents of LDL receptor (LDLR) by combining with the thyroid-responsive element (TRE) of *LDLR* gene on the hepatocyte surface which further promotes the clearance progression of serum cholesterol and reduced the risk of hyperlipidemia [24]. Likewise, SREBP-2 could combine with the sterol regulatory element (SRE) on the *LDLR* gene promoter, thereby induce the transcription of *LDLR* gene [25]. As demonstrated above, T3 hormone could activate the expression of *SREBP-2* gene, we could make a reasonable speculation that THs could modulate the *LDLR* gene expression by *SREBP-2* gene. As a consequence, the number of LDLR and the extent of LDL-C clearance rate decreased prominently in patients with hypothyroidism.

Aside from the important roles of THs, the regulatory functions of TSH on regulating the circulating LDL-C concentrations have been given substantial attention recently. As mentioned in previous literatures, the TSH could directly influence the circulating LDL-C synthesis. To be more specific, mice with deficient TSH-receptor presented the relatively lower circulating TC and LDL-C concentrations compared with those in the healthy control mice [26]. Another research suggested that the combination of TSH and its receptor on hepatocyte membrane could promote the expression and biological activity of HMG-CoA reductase via the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling pathway [27]. On the other hand, it is also firmly demonstrated that TSH could directly activate the expression of *SREBP-2* gene to regulate HMG-CoA reductase [16,28]. Consistent with this finding, by using the adipocytes, Manuel Fernández-Real observed that the TSH could significantly up-regulate the expression contents of HMG-CoA reductase which subsequently affected the intra-cellular contents of LDL-C [29]. Otherwise, Sorisky et al. demonstrated that TSH up-regulated the phosphorylation of perilipin and hormone sensitive lipase (HSL) which further promoted the lipolytic progress and reduce the circulating concentrations of LDL-C [30].

It is worth noting that the TSH has been identified to play an important function in facilitating the progression of LDL clearance. A research conducted by Zhao et al. demonstrated that TSH could facilitate the phosphatidylinositol 3 kinase (PI3K)/SREBP-2 signaling pathway and further inhibit the production of hepatic bile acids (BAs) through TSH receptor [31]. In patients with hypothyroidism and hypercholesterolemia, the circulating concentrations of TSH and BAs were negatively associated which were also independent of circulating levels of TH [7]. Since BA embraces a vital function in regulating the circulating concentrations of LDL-C, we could infer from these results that THs could affect the circulating concentrations of LDL-C and the development of hyperlipidemia through modulating the synthesis and secretion of BA. Nevertheless, it is still needed multiple other research to further explore the underlying mechanisms.

3.2. Functions of THs in regulating factors involved in hypothyroidism-induced LDL-C metabolism

3.2.1. Acetyl-CoA carboxylase and fatty acid synthase (ACC/FAS)

According to the results of previous research, ACC and FAS play a catalytic function in regulating the intra-cellular metabolism of lipid profiles in the liver and the adipose tissue. Alterations of ACC/FAS could promote the pathological development of hyperlipidemia and its related atherosclerotic related diseases [32]. Recently, the important functions of THs in modulating the metabolism of ACC/FAS have begun to gain more appreciation. To be more specific, Fujimori et al. found that T3 could modulate the expression of *ACC/FAS* gene via two different pathways, as named the direct pathway and the indirect pathway. As demonstrated, T3 could directly up-regulate the expression contents of *ACC/FAS* gene via influencing the TRE [33]. On the other hand, T3 has

also been shown to combine with SREBP-1C/carbohydrate response element-binding protein element binding protein (ChREBP) which subsequently influences the intracellular metabolism of ACC or FAS, indicating a unique mechanism by which THs regulate the metabolism of lipid profiles within circulation [34]. Notably, it has also been demonstrated that the TSH could regulate the expression of *ChREBP* gene in hepatocytes and adipocytes [35]. As the gene expression levels of *ACC* and *FAS* have been shown to be positively modulated by ChREBP, we could make a reasonable speculation that TSH could also regulate the metabolism of lipid profiles through influencing *ChREBP* gene expression [36]. In conclusion, these findings proposed that TH and TSH could significantly regulate the circulating lipid metabolism by affecting the gene expression of *SREBP-1C* and *ChREBP*.

3.2.2. Fibroblast growth factor-21 (FGF-21)

It is well demonstrated that the FGF family contains 22 structurally similar proteins. According to the diverse sequence homology and phylogeny of each members of FGF family, it could be classified into seven diverse subgroups, including the paracrine FGFs (including FGF-1 to FGF-10, FGF-16 to FGF-18, and FGF-20/22), the endocrine FGFs (including FGF-15/19/21/23), and the intracrine FGFs (including FGF-11 to FGF-14). In addition, different members of FGF family has been shown to be involved in a wide variety of biological metabolic processes in mammals [37]. To be more specific, among different members, FGF-21 is one of the most important and novel discovered cytokines which is significantly up-regulated under the status of multiple lipid disorder diseases, such as hyperlipidemia, obesity, and the related CVDs [38]. Recently, increasing evidence revealed that FGF-21 plays an essential function in modulating carbohydrate, lipid and phosphate catabolism, and as a result, FGF-21 could modulate the pathological development of lipid disorder diseases [39]. Similar with these notion, treatment with FGF-21 has been shown to improve the energy catabolism within the hepatocyte in both rodents and non-human primates, supporting the evidence that FGF-21 could be identified as a potential therapeutic method for hyperlipidemia [40].

Given that it has been well-established that FGF-21 is strongly correlated with circulating lipid catabolism, recent focus is shifting to illuminating the association between FGF-21 and the changes of circulating LDL-C levels in patient with hypothyroidism. As demonstrated in several published results, it has been shown that the circulating FGF-21 levels were significantly down-regulated in hypothyroidism patients whereas up-regulated or did not alter in patients with hyperthyroidism [41,42]. Another investigation has shown that circulating FGF-21 levels were significantly up-regulated in hypothyroidism patients which were strongly associated with the serum levels of TSH, revealing that the TSH could also modulate the metabolism of FGF-21 [43]. Nonetheless, the accurate relationship between TSH with the altered of circulating FGF-21 is needed to be further illustrated by more investigations.

Emerging results has demonstrated that T3 could up-regulate the gene and protein levels of FGF-21 within the hepatocyte in mice through the combination between TH-receptor with TRE in the intron 2 of *FGF-21* gene [44]. Moreover, another two research found that THs could also facilitate hepatic *FGF-21* gene expression and promote the β-oxidation via stimulating AMP-activated protein kinase (AMPK) and Sirtuin-1 (SIRT-1) in a proliferator-activated receptor α (PPARα)-dependent manner in mice [45]. In mice treated with exogenous T3, the expression of FGF-21 increased significantly in a dose-dependent manner [46]. By contrast, another research has demonstrated that the peripheral administration of FGF-21 could down-regulate the circulating levels of THs [47].

Recently, it is worth noting that FGF-21 could down-regulate serum concentrations of FFAs by suppressing lipolysis in white adipose tissue (WAT) [48] and activating FFAs uptake into WAT, which consequently inhibits the secretion of VLDL by the hepatocyte [38]. Treatment with recombinant FGF-21 protein could reduce circulating and hepatic TG levels in diet-induced obese mice by suppressing the gene expression of *SREBP-1C* gene [49]. More recently, two independent basic experiment using mice which were treated with recombinant FGF-21 protein and demonstrated that the circulating levels of TG, VLDL-C, and LDL-C were down-regulated in rodents [50,51]. Moller et al. demonstrated that in patients who were injected with recombinant FGF-21 mimic peptide, the circulating levels of LDL-C and TG were significantly lower whereas the circulating levels of HDL-C were higher compared with those in the control individuals [52]. Using Ad-ChREBP-infected mice, the authors demonstrated that these mice presented lower circulating TG and VLDL-C levels, consistent with higher FGF-21 gene and protein expression levels. On the other hand, infection of ChREBP has been confirmed to up-regulate uncoupling protein-1 (UCP-1) gene contents with increased circulating FGF21 concentrations in the WAT. Given that FGF-21 could activate the process of lipolysis in the adipocyte, ChREBP appears to regulate the circulating TG levels by influencing the *FGF-21* expression contents [53]. In a conclusion, these results put forward multiple novel potential mechanisms by which FGF-21 promotes the development of hyperlipidemia in patient with hypothyroidism.

FGF19, which is mainly secreted from the ileum after the storage of BA, is shown to participate in the negative feedback modulation of BA synthesis by suppressing hepatic cholesterol 7α-hydroxylase [54]. Notably, THs has been demonstrated to play a direct role on regulating the circulating concentrations of FGF-19. In details, the serum FGF-19 levels were dynamically up-regulated in patients with hypothyroidism which were further confirmed to be independently associated with circulating levels of TSH [55]. Another research revealed that the SREBP could down-regulate the expression levels of *FGF-19* gene [56]. Nevertheless, whether the SREBP could be considered as the underlying mechanism by which FGF-19 induces hyperlipidemia in patients with hypothyroidism is still not elucidated and is needed more deeply investigations.

3.2.3. MicroRNAs

The effect of diverse microRNAs on modulating serum lipid levels has also been given substantial attention in recent years. MicroRNAs, which contains approximately 21 nucleotides in length, are widely identified as the post-transcriptional regulators of gene expression, which are demonstrated to further influence multiple processes in eukaryotic organisms [57]. Actually, the roles of microRNAs in regulating the pathological progression of cardio-metabolic disorder diseases, such as hyperlipidemia, has begun to gain appreciation during the past decades. In details, a number of microRNAs have been shown to influence the HDL metabolism from synthesis to clearance within circulation in mammals [58]. Emerging evidence also shed light on the vital functions of microRNAs, such as microRNA-148, microRNA-128, or microRNA-30, in regulating the serum LDL-C concentrations and controlling the VLDL secretion process [59]. Concerning on that reason, in patients with hypothyroidism, it has been suggested that diverse microRNAs may hold the functionality and the potentiality in affecting the pathological development of hyperlipidemia.

Previous research has also revealed that the THs could significantly modulate cholesterol synthesis via influencing the metabolism of diverse microRNAs. To be more specific, a research conducted by Yen et al., which used a microRNAs microarray to explore whether diverse microRNAs could be directly modulated by THs in a human hepatic cell line, has demonstrated that the microRNA-181 could be significantly regulated by THs. By the in-depth investigations, the authors also confirmed two novel THs-regulated target genes, including caudal type homeo-box 2 and sterol O-acyltransferase-2, which were on the downstream of *microRNA-181* gene. Given that the sterol O-acyltransferase-2 has been considered to release the cholesteryl esters which are further packaged into lipoproteins, these results suggested that the microRNA-181 embraced a vital role in regulating the metabolic genes by THs within the hepatocyte [60]. Furthermore, another research conducted by Xu et al. used the human HepG2 cells and the serum obtained from 12 Chinese hyperthyroidism patients and demonstrated that circulating

microRNA-206 was down-regulated in patients with hyperthyroidism compared to those in the control individuals. Treatment of HepG2 cells with T3 could induce the significantly decreased intracellular TG contents and the lower expression contents of *microRNA-206* gene. Additionally, inhibition of endogenous *microRNA-206* gene expression decreased intracellular TG concentrations in the HepG2 cells. By contrast, over-expressing *microRNA-206* gene in the HepG2 could partially suppress the reduction in TG levels induced by treatment with T3 [61]. Taken together, the findings mentioned above revealed that diverse microRNAs could regulate the lipid catabolism in patients with hypothyroidism. However, due to the lack of published results, whether other microRNAs could also influence the pathogenic progression of hyperlipidemia in patients with hypothyroidism is still needed to be further explored and elucidated by conducing more large-scale clinical trials and basic experiments.

3.2.4. PCSK9

As shown in previous studies, a relatively clear epidemiological link between hyperlipidemia and cardiovascular risk has been well-established. Among multiple novel-discovered candidate mediators, PCSK9 is attracting a growing attention during the past few decades, due to a combined function on serum lipid metabolism and the whole-body inflammatory response. As shown in previous research, PCSK9 is a serine protease which could combine with the LDLR on the hepatocyte surface and subsequently promotes LDLR degradation in lysosomes [62]. Through this mechanism, PCSK9 could regulate the clearance progression of LDL-C which further disrupts the circulating cholesterol homeostasis and promotes the risk of hyperlipidemia.

On the other hand, PCSK9 could also interact with low-density lipoprotein receptor related protein 1 (LRP1). As demonstrated in previous research, LRP1 has been postulated to take part in multiple diverse physiological and pathological progression ranging from the serum lipoprotein homeostasis, atherosclerotic related CVDs, tumor evolution, and fibrinolysis to neuronal regeneration and survival [63]. Aside from the direct effects in regulating circulating metabolism of lipid profiles, LRP1 has been also shown to compete with LDLR and induce the development of hyperlipidemia [64]. Consistent with these results, increasing evidence has demonstrated that TH could down-regulate the circulating PCSK9 levels [65]. With in-depth investigations, it has been demonstrated that both SREBP-1C and SREBP-2 could modulate the expression levels of *PCSK9* via combining with the SRE-1 site on the *PCSK9* gene promoter [66]. Since THs could significantly interact with SREBP-1C and SREBP-2, we could make a reasonable speculation form these findings that THs could down-regulate the serum PCSK9 levels through these two important regulators. By this mechanism, THs play an important function in regulating the gene expression of *LDLR* and facilitating the clearance process of cholesterol from the circulation in mammals.

Recently, emerging evidence has also demonstrated that the circulating levels of TSH is significantly positively associated with the circulating PCSK9 concentrations, which may be partly dependent on the gene expression of *SREBP-1C* and *SREBP-2* [67,68]. Since the PCSK9 plays an important role in modulating the pathogenic development of hyperlipidemia, it could be proposed that TSH affects the progression of hyperlipidemia is partly through regulating the metabolism of PCSK9. However, it is necessary to conduct more clinical studies to further explore the relationship between TSH with PCSK9. On the other hand, the mechanisms by which TSH regulate the circulating concentrations of PCSK9 and the risk of hyperlipidemia in patients with hypothyroidism should also be further investigated.

4. Regulation of TG metabolism in patients with hypothyroidism

4.1. Roles of THs in regulating serum TG metabolism

According to the previous studies, TG comes from the exogenous or intracellular FFAs within circulation which are produced by glycolysis and fat mass. The functions of THs in regulating circulating TG catabolism has been researched during the past several decades. Notably, the THs could reduce the synthesis of VLDL-TG within hepatocytes [69]. In addition, Rodríguez et al. found that T3 played an important role in up-regulating the *APOA5* mRNA and protein concentrations in the hepatocyte. Given that the ApoA5 is a key determinant of serum TG concentrations which has been identified as a major risk factor for atherosclerotic artery disease and a biomarker for the metabolic syndrome, it is well-accepted that THs influenced VLDL-TG metabolism via modulating the metabolism of ApoA5, indicating that the identification of ApoA5 as a T3 target gene provides a new potential mechanism by which THs could influence circulating TG homeostasis [70]. Molina et al. demonstrated in patients with hypothyroidism, the circulating contents of TC, TG, HDL-C, LDL-C, ApoA1, and ApoB-100 down-regulated after THs replacement treatment. Meanwhile, the circulating Lp(a) levels decreased significantly after treatment of THs. According to the reports of recent research, hypothyroidism is correlated with the risk of hyperlipidemia, and a reduction in lipid and lipoprotein metabolism after THs replacement which further resulted in a less atherogenic lipid profiles [71]. Intriguingly, research has also demonstrated the impaired activity of hepatic lipidosis (HL) in hypothyroidism patients may be also associated to the excessive accumulation of TRL [72]. Another research found that the transferring of TG to HDL was significantly impaired in patients with subclinical hypothyroidism, suggesting that although intra-vascular metabolism of triglyceride-rich lipoproteins was normal, patients with subclinical hypothyroidism exhibited abnormalities in HDL metabolism which could be improved by levothyroxine treatment and achievement of euthyroidism [73].

Remnant lipoprotein is another kind of small lipoprotein particle which contains apolipoprotein E (ApoE). Within human circulation, the intra-cellular concentrations of TG, phospholipid, ApoA1, and ApoC3 within TRL particles gradually reduced significantly by LPL and as a consequence, the TRL particles might transfer to remnant lipoprotein. Consistent with this notion, increasing evidence has demonstrated that hypothyroidism is associated with increased serum levels of remnant lipoprotein [74]. On one hand, the excess production of TRL particles by hepatocyte could also induce the increasing plasma concentrations of remnant lipoprotein observed in hypothyroidism patients. On the other hand, LRP1 is expressed on the hepatocyte surface which could combine with ApoE, resultantly contributing to the clearance process of remnant lipoprotein. As demonstrated, THs could increase the transcription of *LRP1* gene in the mice and in the human beings which subsequently altered the circulating lipid concentrations in hypothyroid patients [75]. By contrast, another independent research has shown that the *SREBP-1* gene and *SREBP-2* gene could also down-regulate the transcription of *LRP1* gene in human vascular smooth muscle cells (VSMCs) and macrophages through combination with SRE [76]. As a consequence, these findings put forward that the dysfunctional thyroid could lead to a reduction in circulating LRP1 levels hand in hand with the impaired clearance process of remnant lipoprotein though modulating the *SREBP* gene and protein contents.

Aside from TH, the TSH has also been demonstrated to facilitate the synthesis of TG. To be more specific, Ma et al. found that the TSH could combine with the TSH-receptors which subsequently promote the synthesis of TG within differentiated adipocytes via AMPK/PPARγ signaling pathway [77]. In addition, the TSH could significantly up-regulate the circulating concentrations of TG in hepatocytes through TSHR/cAMP/PKA/PPARα and PPARα/AMPK/SREBP-1C signaling pathways [78]. Recently, Dullaart et al. demonstrated that in euthyroid individuals, the

higher concentrations of TSH may affect TG metabolism via regulating the circulating levels of ApoE, which may explain the circulating ApoE concentrations could increase in patients with hypothyroidism [79].

4.2. Roles of THs in regulating factors involved in hypothyroidism-induced TG modulation

4.2.1. Angiogenin-like proteins (ANGPTLs)

It is recently demonstrated that among the eight members of ANGPTLs family, ANGPTL3, ANGPTL4, and ANGPTL8 have been given substantial attention due to they could regulate TG catabolism by influencing the biological activity of LPL. According to the reports, diverse members of ANGPTLs have similar structure and different functions. As reported in previous studies, these three ANGPTL proteins shared a common structure whereas differ in tissue expression [80]. Given that their established function in regulating plasma TG metabolism and the risk of hypertriglyceridemia, ANGPTLs have been also identified for the treatment of hypertriglyceridemia and its related atherosclerotic CVDs. For instance, ANGPTL3, encoded by *ANGPTL3* gene, is produced mainly by the hepatocytes with minor expression by the renal cells. Additionally, it is also demonstrated that the ANGPTL3 protein is a 460-amino-acid peptide which includes a distinctive signal peptide sequence, an N-terminal coiled-coil domain, and a C-terminal globular fibrinogen homology domain [81]. Recently, TH has been confirmed to suppress the expression of *ANGPTL3* gene [82]. By contrast, the circulating concentrations of VLDL-TG and LDL-C were declined importantly in patients who carried the LOF mutation of *ANGPTL3* gene [83]. When the circulating concentrations of ANGPTL3 were up-regulated, it could crack LPL through Furin protease which inhibited the catalytic activity of LPL [84]. In addition, another study also demonstrated that ANGPTL3 could inactivate the LPL activity by catalyzing the irreversible unfolding of its hydrolase domain [85]. Using the mice with *ANGPTL3* gene deficiency, the authors of two independent research found that these mice presented declined post-prandial lipid concentrations which was possibly due to the stimulated catabolic metabolism of TRLs and the reduced flow of FFAs into the hepatocyte [86]. Consistent findings could also been seen from the basic experiments which used the treatment of ANGPTL3 mono-clonal anti-body. Nevertheless, it is suggested that the transformation from VLDL to LDL reduced partially given that the enhanced clearance process of ApoB [87]. Recently in 2019, Zhao et al. confirmed that the circulating concentrations of ANGPTL3 were significantly up-regulated in the hypothyroid patients compared with those in the control individuals. Nevertheless, there were no significant differences in circulating concentrations of ANGPTL4. Moreover, the positive relationship were verified between ANGPTL3 with the serum concentrations of HDL-C, and there was a significantly negative relationship between ANGPTL3 with the serum T3 concentrations, revealing that the circulating concentrations of ANGPTL3 were up-regulated in the patients with clinical and subclinical hypothyroid. In addition, it has been suggested that ANGPTL3 could also considered as the possible biomarker of hypothyroid disease [88].

ANGPTL8, which is encoded by *Gm6484* gene in mice and *C19* gene in humans, is synthesized and released by the liver and the adipose tissue. As shown in published literatures, the circulating concentrations of ANGPTL8 were importantly up-regulated under the conditions of hypothyroidism, which has also been verified to be positively associated with circulating levels of TG and TC [89,90]. On the other hand, in patients with Graves' disease, the circulating concentrations of ANGPTL3 were positively associated with the circulating levels of TSH [91]. Another investigation demonstrated that within HepG2 cells, the expression content of *ANGPTL8* gene could be significantly affected by THs [92]; concurrently, the expression of *ANGPTL8* gene could also be specifically stimulated via SREBP-1C and SREBP-2 in the liver isolated from mice [93]. By analyzing the mice with *ANGPTL8* gene deficiency, it has been shown that the clearance rate of TG was enhanced significantly due to the stimulated biological activity of LPL which concurrently down-regulating the circulating levels of TG [94]. On the other hand, using the mouse models, the authors demonstrated that ANGPTL8 could significantly interact with ANGPTL3 which subsequently facilitate the combination between ANGPTL3 with LPL. By this method, ANGPTL8 could facilitate the lysis progression of LPL, leading to the upregulated circulating TG levels [95]. Nevertheless, due to the lack of published literatures, the accurate relationship and the potential mechanism by which the ANGPTL8 regulates the pathological development of hyperlipidemia are needed to be further explored.

ANGPTL6, which is confirm to embrace an important function in regulating the development of hyperlipidemia in patients with hypothyroidism, is recently being paid attention [96]. Notably, it is confirmed that the circulating ANGPTL6 levels were up-regulated and were positively associated with the circulating contents of TSH and LDL-C under the pathological condition of hypothyroidism [97]. Furthermore, it has been demonstrated that the circulating ANGPTL6 levels were considered as an independent predictor of the lower circulating HDL-C concentrations and the increased circulating TG concentrations, which could be identified as the characteristic of hypertriglyceridemia [98]. With further investigation, it was shown that the ANGPTL6 could facilitate the gene expression of *PPAR-α* via the extra-cellular regulation of protein kinases/mitogen-activated protein kinase (ERK/MAPK) signaling pathway, which further resulted in the higher gene expression of *FGF21* and consequently induced the β-oxidation process [99]. Since the circulating concentrations of FGF21 are more prone to be down-regulated under the condition of hypothyroidism as mentioned above, it could be suggested that the TSH could promote *FGF21* gene expression via affecting the metabolism of ANGPTL6 whereas the THs might have opposite function on regulating the circulating concentrations of FGF-21 compared with TSH.

Since the gene domains are similar with those within *ANGPTL3* gene cluster, *ANGPTL4* gene has also been demonstrated to suppress the biological activity of LPL and promote the disruption of TG metabolism with circulation [100]. By contrast, another research also demonstrated that the average circulating levels of ANGPTL4 was extremely low which could not further affect the LPL activity and metabolism [101]. Importantly, the roles of ANGPTL4 in regulating hyperlipidemia were also discordant according to the published results provided by diverse research. In details, two recent clinical trials demonstrated that the LOF mutation of *ANGPTL4* gene was strongly correlated with the down-regulated circulating TG concentrations and the up-regulated circulating HDL-C concentrations [102], whereas another independent investigation found that ANGPTL4 could not significantly regulate the circulating TG levels in patients with hypothyroidism [88]. Concerning on the discordant results, it is still needed to conduct more large-scale clinical trials and in-depth basic experiment in the future to further illustrate the essential function of ANGPTL4 in regulating the pathological development of hyperlipidemia in patients with hypothyroidism.

4.2.2. Apolipoprotein C3 (ApoC3)

ApoC3, encoded by the *APOA1/C3/A4/A5* gene cluster in mammals, has been identified as a critical modulator of circulating or intra-cellular TG metabolism. According to the results of several previous studies, deficiency or silencing of *APOC3* gene could facilitate significantly decreased circulating TG levels. Emerging evidence indicated that serum ApoC3 also played an important regulatory function in serum remnant cholesterol (RC) and HDL-C. In addition, another large-scale population genetic investigations revealed that the loss of function (LOF) mutation in *APOC3* gene also conferred the decreased risk of atherosclerosis and its related coronary artery disease (CAD).

On the other hand, it is also worth noting that the circulating levels of ApoC3 was found to be significantly decreased in hypothyroidism mice with or without pregnancy. To be more specific, by comparison with the normal control mice, the mice with gestational hypothyroidism presented more prominent increase compared to the pre-pregnant mice

with hypothyroidism in circulating levels of LDL-C and hepatic TG storage [21]. Consistent with these results, another independent research demonstrated that the suppressed expression of *APOC3* gene could lead to significantly increased biological activity of LPL which subsequently induced the decreased circulating TG levels [103]. In conclusion, the net effect of ApoC3 in regulating plasma lipid metabolism in patients with hypothyroidism is more inclined to suppressing the biological activity of LPL and influencing the TG metabolism within circulation.

5. Regulation of HDL catabolism in patients with hypothyroidism

5.1. Roles of THs in regulating circulating HDL metabolism

Since the firmly established regulatory functions of THs in circulating LDL-C and TG, recent attention is also paid to illustrate the role of THs in regulating circulating metabolism of HDL particles. As shown in the previous reports, it has been demonstrated that synthesis progression of HDL particles are decreased in the patients with hypothyroidism. For instance, Dullaart et al. found a positive association between free T4 with the formation of pre-β-HDL particles in patients with type 2 diabetes mellitus, proposing that variations in thyroid function within the euthyroid range could potentially affect the metabolism of pre-β-HDL particles [138]. Alternatively, another research found that the THs could strongly induced gene and protein expression contents of ApoA1; concurrently, the THs have been also firmed to enhance the ability of accept cellular cholesterol via the ATP-binding cassette transporter A1 (ABCA1), which consequently facilitates the pathological progression of cholesterol efflux from peripheral tissues to HDL by a classical pathway which is named as RCT [104]. Conclusively, this function is most likely attributable to increase in small HDL and poor lipid-containing ApoA1 in response to THs.

It is worth noting that homocysteine could decrease the serum levels of HDL-C by inhibiting the ApoA1 protein synthesis, which consequently suppresses the progression of RCT [105]. Given that it has been verified that in mice with hypothyroidism, the circulating levels of homocysteine were significantly up-regulated, proposing that the potential function of THs in regulating plasma HDL-C concentrations might be via affecting the circulating concentrations of homocysteine. Nevertheless, after thyroidectomy, the serum levels of ApoA1 were significantly up-regulated in hypothyroidism patients [106]. The potential causes of contradictory result are inclined to be owing to the diverse species in different research.

Importantly, the aberrant circulating concentrations of THs have also been shown to present diverse functions on clearance process of HDL particles from circulation. According to the results of recent research, it is demonstrated that this process is significantly suppressed in the patients with hypothyroidism. Further research revealed that THs could also activate the biological activity of HL, which consequently promoted the degradation of HDL particles and altered components of HDL particles [107]. On the other hand, circulating levels of cholesterol transport protein transporter (CETP) have been demonstrated to be down-regulated significantly in patients with hypothyroidism. Since CETP plays an important function in inhibiting plamsa concentrations of HDL-C, the positive regulatory function of THs in CETP could make a reasonable explanation which illustrates the alterations of circulating HDL-C concentrations in patients with hypothyroidism [108]. Additionally, down-regulated biological activity of CETP and phospholipid transfer protein (PLTP) has also been demonstrated to promote the decreased circulating contents of HDL-2 whereas the increased circulating concentrations of HDL-3 in patients with hypothyroidism [109].

The function of THs in affecting the progression of RCT has also been given substantial attention in recent several decades. As firmed in previous research, THs could increase the gene transcription of cholesterol 7α-hydroxylase [110]. By this pathway, THs could facilitate the transformation of cholesterol into BA within circulation which subsequently exhibit the progression of hyperlipidemia. Recently, another research found that THs could also activate the secretion of BA from the liver and the intestine by promoting the gene transcription of ATP-binding cassette transporter G5/8 (ABCG5/ABCG8) in rats [104]. Given that this transcriptional process is the last stage of RCT, we could speculate from these findings that the THs may regulate the circulating metabolism of lipid profiles via, at least partly, influencing the expression of *ABCG5/ABCG8* gene [111]. Interestingly, a report demonstrated the degradation process of HDL particles was predominantly up-regulated under the status of hypothyroidism. Nevertheless, it is also demonstrated that the clearance progression of cholesterol was also accelerated since the THs could facilitate the gene expression of scavenger receptor b1 (SRB1), as another important receptor on the surface of HDL particle which embraced a vital function in RCT [112]. In conclusion, the discordant functions mentioned above might cancel each other out. Thereby, the circulating HDL-C concentrations in patients with hypothyroidism present not consistent in diverse clinical observation trials.

More recently, it is also well-confirmed that the TSHs are strongly correlated with the activity of cholesteryl ester transfer protein (CETP) within circulation. Importantly, Dullaart et al. found that the up-regulated circulating concentrations of CETP could significantly accelerate the lipid exchange progression between HDL particles and LDL particles, resultantly facilitated the dysfunctional HDL particles and the up-regulated cholesterol ester-rich LDL particles and VLDL particles [113].

5.2. Roles of THs in regulating cholesterol efflux capacity of HDL particles

Besides the quantity of HDL particles within circulation and the circulating concentrations of HDL-C could be regulated by dysfunctional thyroid, the capacity of cholesterol efflux, which has been considered as an important metric of HDL function, has been demonstrated to be impaired in patients with hypothyroidism. To be more specific, Dullaart et al. enrolled 17 patients who had undergone a total thyroidectomy for differentiated thyroid carcinoma and explored the HDL particle characteristics, such as nuclear magnetic resonance spectrometry), the capacity of cholesterol efflux, and the anti-oxidative capacity. As demonstrated in the previous findings, the patients exhibited increased circulating levels of TC, HDL-C, and ApoA1. Though the quantity of HDL particles were unchanged, there was a shift in HDL subtypes toward larger HDL particles. Moreover, the capacity of cholesterol efflux was significantly down-regulated. The anti-oxidative capacity of HDL particles exhibited not significantly changes [106]. The other independent research conducted by Moon et al. put forward the similar findings. Nevertheless, the latter research found that the activity of paraoxonase-1 (PON-1), as an important anti-oxidative enzyme, remains unaltered after thyroidectomy; but the activity was significantly decreased after expressed as the PON-1/ApoA1 ratio [79]. In conclusion, the above findings shed light on that in patients with hypothyroidism, dysfunctional thyroid may influence the HDL function. However, the potential underlying mechanisms are still needed more research to further investigations.

6. Conclusion and further perspectives

In the present review, we provide a summary of several results of latest research which has demonstrated that the characteristics of hypothyroidism-related hyperlipidemia; furthermore, we also demonstrated that the hypothyroidism-related hyperlipidemia is strongly correlated with the changed circulating levels of TH and TSH, indicating that hypothyroidism could induce hyperlipidemia and its related atherosclerotic related CVD. In addition, several novel identified biomarkers, which play an important role in modulating hyperlipidemia induced by hypothyroidism including PCSK9, ANGPTL3, ANGPTL8,

FGF-21, FGF-19, and several microRNAs, is also listed in our current review.

Due to the eye-catching breakthrough, it is well-established that besides the regulatory function of THs, the TSH is also demonstrated to be another important modulator in influencing the serum or intracellular lipid metabolism under the condition of hypothyroidism. As demonstrated, even in patients with normal thyroid and subclinical hypothyroidism, higher serum TSH concentrations could also significantly regulate the serum lipid metabolism. Concerning on these findings, it seems that maintaining the circulating concentrations of TSH at a low normal concentrations to minimize cholesterol concentrations could be considered as an important therapeutic strategy to hypothyroidism in daily clinical practice. Nonetheless, the main alteration of the hormones in patients with hypothyroidism is THs, and TSH could be influenced though a negative feed-back regulation of THs. As a consequence, whether TSH metabolic pathway makes up a large proportion in patients with hypothyroidism is still needed to be further elucidated. As shown in our recent findings, several regulatory factors, including SREBPs, ChREBP, ANGPTLs, microRNAs, and FGFs, also participated in the tissue related-lipid metabolism in the liver and the adipose tissue isolated from the patients with hypothyroidism. Additionally, it has also been firmed that the status of hypothyroidism could influence HDL particle function, especially the regulatory function of RCT, in Chinese patients. According to the findings, these important regulatory factors could be considered as the novel and potential therapeutic targets of hypothyroidism. Further basic research and large-scale clinical trials are still required to deeply clarify the accurate roles and the respective mechanisms by which these modulatory factors influence serum or intra-cellular lipid metabolism which further subsequently facilitates the risk and the pathological development of hyperlipidemia in patients with hypothyroidism.

Author contributions

X.J.W., B.W., and X.C. contributed to the study design; X.S. and H.P. wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

Ethical statement

This article does not contain any studies with human participants performed by any of the authors.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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