Lipids in Health and Disease

REVIEW

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Hypothyroidism/subclinical hypothyroidism and metabolic dysfunction-associated steatotic liver disease: advances in mechanism and treatment

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Abstract

Hypothyroidism is a risk factor for metabolic dysfunction-associated steatotic liver disease (MASLD) but it is not clear whether subclinical hypothyroidism (SCH) increases the risk of MASLD and whether SCH patients with MASLD require treatment. In this study, we reviewed articles published in PubMed from 2013 to 2024 with SCH/hypothyroidism and MASLD as keywords. According to the studies retrieved, SCH increases the likelihood of developing MASLD. Thyroid hormones influence energy metabolism and storage in adipose tissues, as well as fatty acid and cholesterol metabolism and transport in the liver. L-T_4 replacement therapy reduces the prevalence of MASLD, especially in patients with severe SCH or mild SCH with dyslipidemia. Recent studies showed that thyroid hormone analogues and thyroid hormone β receptor agonists obtained positive results in the treatment of MASLD in animal models and clinical trials, and Resmetirom has been approved by the US. Food and Drug Administration (FDA) under the name Rezdiffra for use in conjunction with dietary and exercise regimens for managing non-cirrhotic NASH in adults with moderate to advanced fibrosis.

Keywords Hypothyroidism, Subclinical hypothyroidism, Non-alcoholic fatty liver disease, Metabolic dysfunction-associated steatotic liver disease, Molecular roles, Thyroid-related medication

Introduction

Overt hypothyroidism is a prevalent clinical thyroid disorder characterized by elevated serum thyrotropin (TSH) levels as well as reduced free thyroxine (FT4) levels. Surveys have shown that the prevalence of overt hypothyroidism ranges from 0.25% to 4.2% in different areas [1]. Subclinical hypothyroidism (SCH) is often considered the early stage of hypothyroidism and it is characterized by elevated serum TSH levels and normal FT4 levels [2]. In endocrinology, it is widely accepted that a range of 4.2 mIU/L to 10 mIU/L for TSH signifies a mild form of SCH, and a TSH level of 10 mIU/L or higher indicates a more severe manifestation. SCH has become increasingly prevalent in modern times and it affects as many as 10% of the adult population [3]. The prevalence of SCH ranges from 0.76% to 16.7% [1].

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the prevailing chronic hepatic disorder in Western societies, where it is characterized by hepatic steatosis affecting more than 5% of hepatocytes in the absence of excessive alcohol consumption (≥30 g/day

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for men and ≥ 20 g/day for women), or other underlying chronic liver diseases, and it is commonly associated with metabolic risk factors such as obesity and type 2 diabetes [4]. The global prevalence of MASLD is 25.24% [5] and the primary causative factor is the buildup of hepatic fat, which may ultimately lead to cirrhosis or hepatocellular carcinoma [6].

According to recent studies, growing evidence supports the hypothesis that hypothyroidism significantly increases the likelihood of MASLD. However, further investigation is required to establish a definitive link between SCH and MASLD. Furthermore, the impacts of thyroid hormones (THs) on the progression of MASLD require elucidation. According to the guidelines for the primary care of hypothyroidism (2019) [7], individuals experiencing mild SCH accompanied by symptoms of hypothyroidism, thyroid peroxidase antibody (TPOAb) positivity, dyslipidemia, or atherosclerotic disease should receive levothyroxine (L-T_4) treatment. Therefore, it is necessary to determine whether patients with both SCH and MASLD require therapeutic intervention with L-T_4, as well as considering the side effects of L-T_4 and whether novel thyroid-related drugs can contribute to MASLD remission in addition to improving the thyroid function. To answer these questions, we reviewed articles published during the last 10 years and in the PubMed database by using the keywords SCH/hypothyroidism and MASLD.

Methods

The procedure for this narrative review included searching PubMed for peer-reviewed journal articles. The articles mainly published from 2014 to 2024 focused on the following three topics: hypothyroidism/subclinical hypothyroidism and MASLD, the mechanism of thyroid hormone in the liver, and medications for treating MASLD. The following search terms were used: hypothyroidism, subclinical hypothyroidism, non-alcoholic fatty liver disease, metabolic dysfunction-associated steatotic liver disease, molecular roles, lipid metabolism, thyroid-related medication, THRβ. Inclusion criteria included the following: 1) disease-related clinical manifestations are caused by thyroid hormone dysfunction; 2) thyroid hormones play a role through transcriptional or non-transcriptional effects; 3) treatment-related clinical trials and randomized controlled trials. Articles with the following relevant topics were excluded: 1) the correlation between SCH / hypothyroidism and MASLD was not discussed; 2) THs acts on other organs except liver; 3) the object of treatment is not MASLD but its related complications, such as diabetes; 4) articles published before 2000. We also analyzed 8 articles through the recommendations of reviewers. Overall, the articles used as references ranged from 2001 to 2024. Using this strategy, 68 journal articles were found (Fig. 1).

Results

Hypothyroidism/SCH and MASLD

Hypothyroidism and MASLD

Hypothyroidism is recognized as a risk factor for MASLD and the possible mechanism involves hypothyroidism-associated dyslipidemia leading to hepatic fat accumulation, which then contributes to insulin resistance and the development of MASLD [8]. Studies have identified evaluated TSH level as a risk factor for MASLD, more specifically, there is a positive linear association between TSH levels and MASLD risk and FT4 levels are negatively related with MASLD risk [9–11]. Alessandro et al. conducted a meta-analysis based on 44,140 individuals and found that criteria for different definitions of hypothyroidism were all associated with a significant increase in MASLD, and independent of common metabolic risk factors [12]. The results obtained in a cross-sectional study of 1276 subjects by Ludwig et al. showed that the incidence of hepatic steatosis increased significantly as serum thyroxine concentrations decreased [13]. Many studies have determined an association between hypothyroidism and MASLD, but these observational studies did not demonstrate a causal relationship, and randomized controlled trials (RCTs) to determine causality are often difficult to implement in clinical settings. A Mendelian randomization study by Qiu et al. ($n = 1483$) modeled RCT based on the random assignment of alleles obtained strong evidence that hypothyroid patients had a significantly increased risk of MASLD [14]. Hypothyroidism is associated with the risk of developing MASLD but it may also have an impact on the prognosis of MASLD. A cross-sectional study in a US population ($n = 3489$) demonstrated that low thyroid function (low-normal thyroid function[TSH:2.5–4.5mIU/L] and SCH[TSH > 4.5mIU/L and normal T4]) was associated with MASLD, and it also predicted elevated all-cause and cardiovascular mortality in patients with MASLD [15]. In general, the current opinion is that hypothyroidism is associated with MASLD, but not all studies are in full agreement regarding their relationship [16]. For example, a retrospective study by Escude et al. based on 10,116 individuals found no association between hypothyroidism and MASLD [17].

SCH and MASLD

SCH increases the risk of MASLD A recent retrospective cohort study of Eastern populations (n = 2901) also found an independent association between low thyroid function (TSH ⩾2.5mIU/L) and MASLD, but further stratification analysis showed that SCH, but not

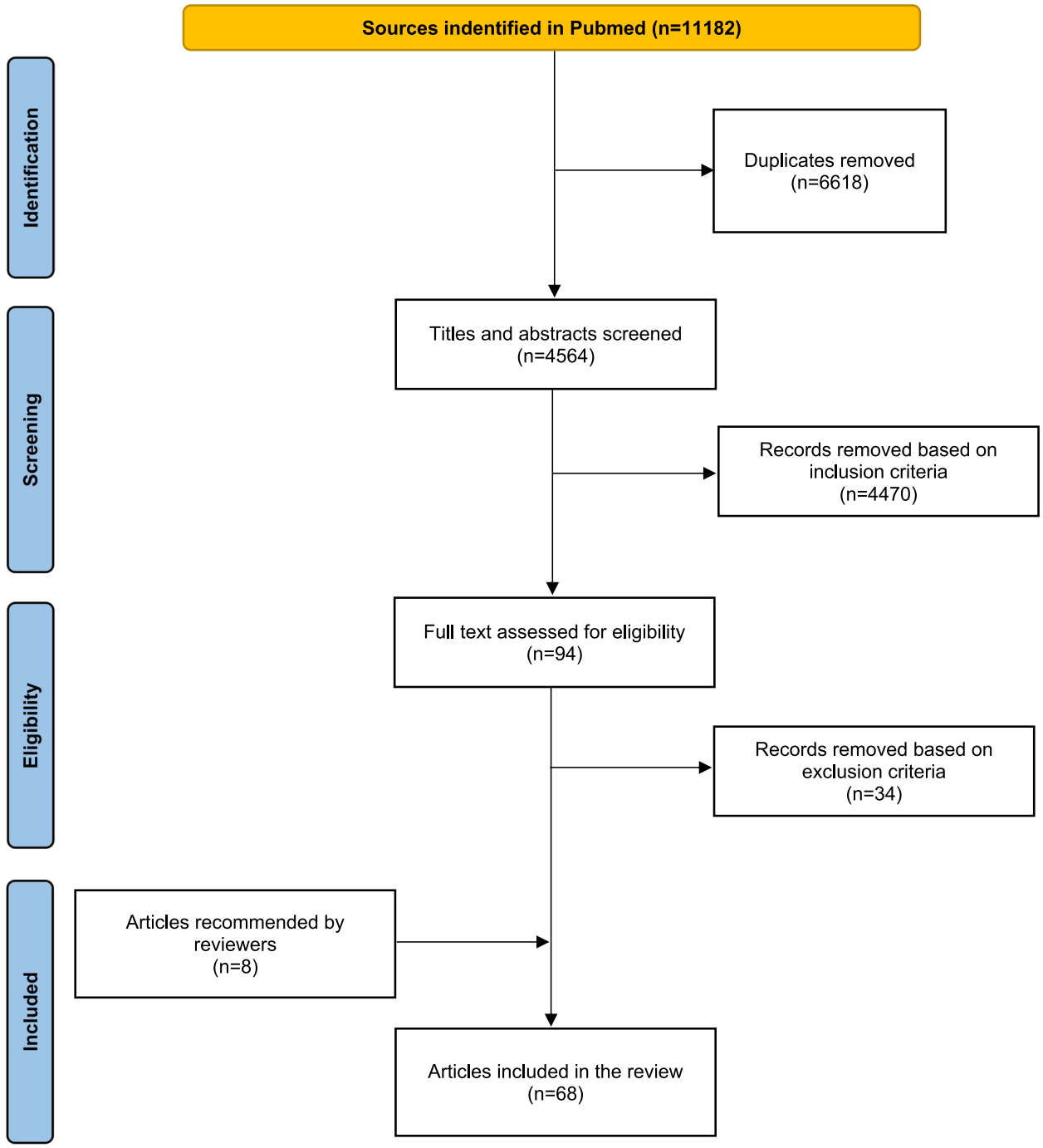

Fig. 1 PRISMA flow diagram

low-normal thyroid function, was still significantly associated with MASLD [18].The association of low thyroid function with cardiovascular and all-cause mortality was also highly consistent, but further study found that mild SCH (TSH:4.5-10mIU/L) carried significantly higher health risks than severe SCH (TSH > 10mIU/L). This may be due to the TSH values of the patients with severe SCH reached the intervention level recommended by the guidelines and received the corresponding treatment. So, a lower TSH cutoff value is of considerable importance to reduce the health risk of MASLD patients. In addition, the finding that elevated TSH levels, even in the

normal range, are strongly associated with cardiovascular and all-cause mortality in patients with MASLD also supports reevaluation of the TSH reference range [19]. Another recent study that included 44 cases also showed that SCH and clinical hypothyroidism were independent risk factors for the development of MASLD, and that clinical hypothyroidism had a stronger correlation [20], which is also consistent with the findings obtained in a cross-sectional study by Xu et al. (n = 654) [21]. The cross-sectional study by Chung et al. (n = 4648) showed that SCH continued to have a strong dose-dependent correlation with MASLD even in the range of high normal TSH levels [22]. Interestingly, a recent cross-sectional study by Fan et al. (n = 4567) showed that elevated TSH was associated with advanced fibrosis in MASLD, even in the presence of normal thyroid function [23]. A retrospective study based on a population of adolescents and children (n = 122) concluded that obesity-related SCH was associated with MASLD, although it is possible that this conclusion may have been tempered by age factors [24]. A large German population based cohort study (n = 40,583) provided evidence for a strong association between MASLD and SCH after excluding age and gender [25]. In the ongoing study of hypothyroidism and MASLD, serum IL-27 was found to predict the occurrence of MASLD in patients with hypothyroidism (both overt and subclinical hypothyroidism), it was negatively correlated with the incidence of MASLD, and showed a compensatory increase in patients with hypothyroidism, which means that it may be a potential therapeutic target for MASLD in patients with hypothyroidism [26].

No significant correlation between SCH and MASLD In contrast to the conclusion that SCH increases the risk of MASLD, some studies found no significant correlation between SCH and MASLD. A 4-year retrospective cohort study analyzed 18,544 subjects and found that the incidence of MASLD in the SCH group was not higher than that in the control group, and the results did not change significantly even after multivariate adjustment [16]. Jaruvongvanich et al. conducted a systematic review and meta-analysis based on 14 studies, and found no association with MASLD for either SCH or overall hypothyroidism (both SCH and hypothyroidism) [27].

Thus, views still differ regarding the relationship between clinical hypothyroidism/SCH and MASLD, but most consider that there is a correlation between the two diseases. Several possible reasons may explain the different results obtained in observational studies. First, the populations selected in different studies were often quite different due to geographical and other factors. Second, the definitions used in different studies were not completely consistent. Finally, the accuracy of the research results may have been limited by diagnostic methods and the degree of error.

Thyroid function and MASLD are associated with sarcopenia

Sarcopenia is a condition associated with aging, characterized by a progressive decline in skeletal muscle mass, weakening of muscle strength, and deterioration of muscle function, often coexisting with various diseases. Prior research has identified pleiotropic genes shared between MASLD and sarcopenia, demonstrating a positive genetic association [28]. The interaction between MASLD and sarcopenia also contributes to an increased risk of cardiovascular and all-cause mortality [29]. Furthermore, thyroid function appears to influence the occurrence of sarcopenia. In a cross-sectional study involving 6,974 Brazilian middle-aged and elderly community residents, the findings indicated no association between subclinical thyroid dysfunction and sarcopenia. However, a U-shaped association was observed between TSH levels and both sarcopenia and low muscle strength in older adults, while FT3 levels exhibited a negative correlation with muscle mass [30]. Another study indicated that hyperthyroidism, hypothyroidism, and subclinical hyperthyroidism are associated with an increased risk of sarcopenia [31]. However, one study suggested that there is no significant causal relationship between thyroid function and sarcopenia-related traits [32]. Therefore, further investigations are required to elucidate the relationship between thyroid function and sarcopenia. In the realm of interventions and therapies for sarcopenia, research has indicated that, alongside essential physical exercise, polyphenolic natural compounds may mitigate or delay the progression of sarcopenia through the improvement of pro-inflammatory states [33].

Molecular roles of THs in metabolism in adipose and liver tissues

The two main sources of fatty acids in the liver are exogenous comprising fatty acids produced by the breakdown of adipose tissue, which enter the liver via the bloodstream, and endogenous via de novo lipogenesis (DNL). The liver uses fatty acids for two main purposes comprising lipid metabolism and the synthesis of cholesterol or triglycerides. In the presence of hypothyroidism, triglyceride metabolism is slowed down and triglycerides accumulate more in the liver, thereby leading to the high accumulation of fatty acids [34]. Toxic lipid substances accumulate when the ability of the liver to process primary metabolic energy substrates, carbohydrates, and fatty acids is overwhelmed. Excess metabolites induce hepatocyte stress, injury and death, which subsequently leads to hepatic insulin resistance, changes in the gut

microbiota, and other harmful phenomena, such as mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress, and the generation of reactive oxygen species (ROS). These harmful factors eventually make the liver chronically inflamed, which promotes MASLD [6, 35].

Molecular roles of THs in metabolism in the liver

Transcriptional effects There are two main types of TH where T_3 is the active form and T_4 is a prohormone that is activated at the cellular and circulation levels by deiodinase. Type 2 deiodinase (D_2) has the ability to convert T_4 into T_3 [36]. It was shown that higher D_2 activity in mouse adipose tissue enhanced oxygen consumption [37]. Thyroid hormone receptors (THRs) are nuclear hormone receptors that function as ligand-dependent transcription factors and they are found mainly in the nucleus with few in the cytoplasm. THRα and THRβ are the two main isoforms of THRs. THRs exhibit tissue-specific expression patterns, where THRα is primarily expressed in the heart and bone, whereas THRβ is primarily expressed in the liver [38]. In the absence of ligands, THRs can bind to the thyroid hormone response elements of their target genes and recruit co-repressor complexes with histone deacetylase activity to inhibit the transcription of positively regulated genes. After ligand

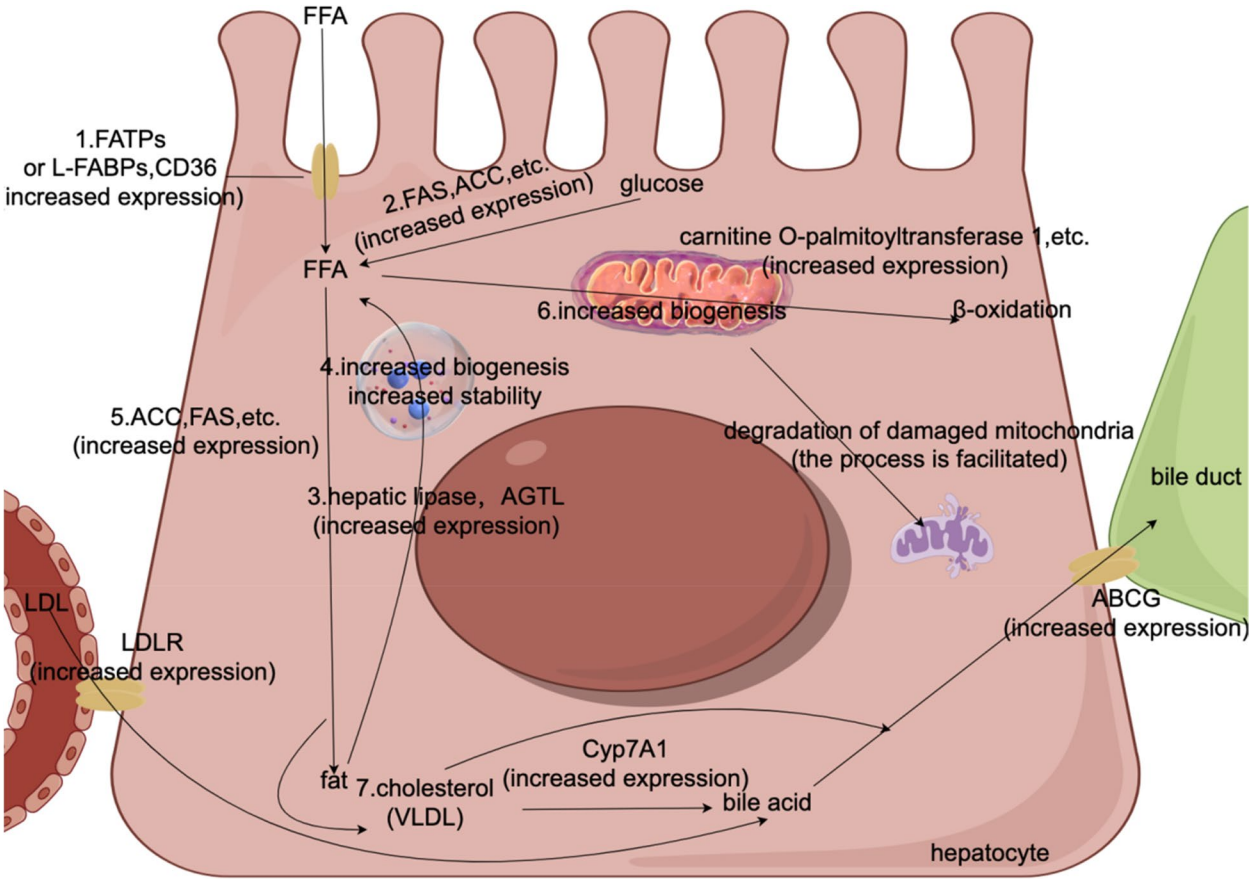

Fig. 2 Mechanism of action for thyroid hormones in the liver. Sources of intrahepatic FFAs: 1. Extrahepatic FFAs enter hepatocytes via transport proteins, such as FATPs, L-FABPs, and CD36. T_3 promotes the expression of these transport proteins. 2. Glucose is converted into FFA through the DNL pathway by enzymes, such as FAS and ACC, and T_3 promotes the expression of related enzymes. 3. Hepatic lipase and AGTL break down triglycerides into FFAs and T_3 promotes the expression of related enzymes. 4. Lysosomes are involved in lipophagy, which breaks down triglycerides into FFAs. T_3 increases lysosomal biogenesis, improves LAMP expression, and increases lysosomal stability. Destinations of FFAs in the liver: 5. Conversion to triglycerides stored in the liver by FAS and ACC, and T_3 promotes the expression of related enzymes. 6. Involved in β-oxidation in mitochondria and eventually metabolized. T_3 increases mitochondrial biogenesis, promotes the expression of β-oxidation related rate-limiting enzymes, and facilitates autophagic degradation of damaged mitochondria to maintain the quality of mitochondria at a high level. 7. Conversion to cholesterol, where LDL is converted into bile acids or excreted directly into the bile. T_3 promotes the expression of rate-limiting enzymes and LDL-R during cholesterol synthesis. ABCG, a transporter protein required for the transfer of bile acids and part of the cholesterol into bile, is also upregulated by T_3

binding, the conformations of THRs change, thereby leading to the release of co-repressors and the recruitment of co-activator complexes with histone acetyltransferase activity to enhance gene transcription [39]. The routes that allow THs to act on the liver are described as follows (Fig. 2).

THs regulate the transport of extrahepatic free fatty acids (FFAs) to the liver

THs stimulates lipolysis in white adipose tissue (WAT) and dietary fat sources to produce circulating FFAs, which are the main source of liver lipids. FFAs enter hepatocytes through protein transporters such as fatty acid transfer proteins, liver fatty acid binding proteins (L-FABPs), and fatty acid translocase (FAT; also known as CD36) [40]. Fatty acid transporters are regulated by THRs. THs promote upregulation of the transcription factor Peroxisome proliferator-activated receptors (PPAR) -γ by binding to THRs, which then leads to an increase in the expression of these transporter proteins [41]. When the THs level decreases in the body, the expression levels of FAT and FABP are also suppressed in the liver, which reduces the uptake of triglyceride-derived fatty acids in the liver.

THs regulate intrahepatic lipogenesis

In hepatocytes, the DNL pathway is initiated when an excess of substrate leads to an increase in mitochondrial citrate. The DNL pathway converts selectable carbon sources to FFAs, and the core enzymes involved in the process include acetyl-CoA carboxylase and fatty acid synthase [42]. Among these enzymes, acetyl-CoA carboxylase and fatty acid synthase are also involved in triglyceride synthesis in the liver [43]. T_3 can facilitate this process by amplifying cAMP signaling and enhancing the transcription of associated DNL enzymes [44].

THs promote hepatic lipid metabolism

THs stimulate lipogenesis but the net amount of triglycerides is reduced in the presence of elevated THs levels because the metabolism of fatty acids occurs more quickly than the synthesis of fatty acids. THs increase the activity of hepatic lipolysis and fatty acid metabolism, which is the main process that allows the liver to reduce steatosis.

A Generation and release of FFAs in the liver

THs promote lipolysis primarily through the breakdown of stored triglycerides into FFAs and their subsequent β-oxidation. The ability of hepatocytes to release accumulated FFAs from triglycerides depends on cytoplasmic lipases. Hepatic lipase and adipose triglyceride lipase are the two main cytoplasmic lipases in the liver. The expression and activity of hepatic lipase are sensitive to the THs level [45].

In the lipophagy process, lipid droplets fuse with lysosomes and are eventually broken down into FFAs, which are transported to mitochondria. Mucolipin 1 on lysosomes also regulates and can enhance the FFA efflux process [46]. T_3 promotes lipid autophagy and increases the number of autophagosomes and lysosomes [47]. In addition to promoting the expression of lysosomal genes, T_3 increases the expression of lysosomal-associated membrane protein (LAMP) [48, 49], which is a protein associated with stabilizing lysosomes and enhancing their resistance to the autophagosome burden activity to enhance the lysosomal activity [50].

B Metabolism of FFAs

Mitochondria are major sites for fatty acid metabolism and classical targets for TH action in the liver. THs induces estrogen-related receptor α (ESRRA) expression by stimulating the expression of the transcription factor PPARGC1A. Thyroid hormone ultimately promotes mitochondrial biogenesis in an ESRRA-dependent manner [51, 52]. THs also indirectly increase the upregulation of genes related to mitochondrial transcription factors and cytochrome c by increasing the levels of nuclear respiratory factor (NRF) −1 and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) [53]. The rate-limiting enzyme for related mitochondrial β-oxidation is carnitine O-palmitoyltransferase 1 and its gene expression level can also be upregulated by T_3 [54].

In addition to increasing mitochondrial genesis and promoting fatty acid β-oxidation, THs improve the overall quality of mitochondria by removing ROS-damaged mitochondria due to increased oxidative phosphorylation [48]. The Ca^{2+}-calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2)−5′-AMP-activated protein kinase (AMPK) signaling cascade pathway can be triggered by ROS produced by TH-mediated oxidative phosphorylation, which can facilitate the autophagy of damaged mitochondria and ultimately increase the overall quantity of mitochondria. ROS can also initiate mitophagy, thereby increasing mitochondrial biogenesis and preventing mitochondrial loss of function and aging, and reducing mitochondrial oxidative stress [55].

THs promote cholesterol metabolism and transport

THs improve cholesterol metabolism in the liver by promoting cholesterol biosynthesis, low density lipoprotein-receptor (LDL-R) mediated endocytosis, and reverse cholesterol transport [56].

Sterol regulatory element-binding protein 2 (SREBP) is positively transcribed by T_3, which allows SREBP to enter the nucleus and activate the transcription of the LDL-R and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) genes [57]. In particular, LDL-R mediates LDL endocytosis and the HMG-CoA enzyme limits the rate at which cholesterol is synthesized. These two enzymes work together to keep the serum LDL level low.

In the reverse cholesterol transport process, high density lipoprotein transports peripheral cholesterol to the liver, where it is ultimately excreted from the body in the form of bile acids. Sobetirome (GC-1) (specific THRβ) treatment resulted in a decrease in the serum cholesterol levels in food-fed mice, stimulated the activity of cholesterol 7α-hydroxylase (Cyp7A1), increased the amount of hepatic high density lipoprotein receptors, and facilitated the excretion of bile acids [58]. Cyp7A1 is the rate-limiting enzyme in the conversion of cholesterol to bile acids. An in vitro study showed that T_3 promoted the expression of Cyp7A1 in human hepatocytes [59]. In addition, an ATP-binding cassette subfamily G member transport protein is required for the excretion of bile acids and cholesterol into the bile, and it is also upregulated by T_3 [56].

Non-transcriptional effects

In THR mutant mice, when THR loses its ability to bind to DNA, some TH-related functions remain, such as the heart rate, body temperature, and blood glucose and triglyceride concentrations, thereby suggesting that THs have non-transcriptional effects [60]. In addition to nuclear receptor-mediated genomic effects that increase or decrease gene transcription, T_3 can exert non-transcriptional effects via intracytoplasmic THRs or membrane integrin receptor αvβ3 [61]. T_3 alters the phosphorylation state of several kinases in a tissue-specific manner in vivo, and stimulates mitochondrial ontogeny, fatty acid oxidation, and autophagy via AMPK [39].

Molecular roles of THs in metabolism in adipose tissue

The body's adipose tissue is mainly divided into WAT and brown adipose tissue (BAT). WAT is divided into subcutaneous adipose tissue and visceral adipose tissue, which store excess energy in the form of triglycerides. The WAT capacity expands when the triglyceride content storage increases [62]. The increased accumulation of WAT, particularly in visceral depots, is a key determinant of the relative risk for cardiometabolic disorders, hypertension, and cardiovascular disease [63]. Thus, an increase in WAT is biased toward a pathological nature. BAT is distributed in the cervical, supraclavicular, axillary, paraspinal, mediastinal, and abdominal regions. BAT protects animals from hypothermia by dissipating energy as heat through a process known as non-shivering thermogenesis [63].

In human adipose tissue, WAT depends primarily on the storage and release of lipids to control energy homeostasis, whereas BAT depends primarily on the consumption of stored energy in the form of calories [64]. T_3 can enhance the adrenergic effects in WAT and cause WAT to undergo catabolism. T_3 can also promote BAT thermogenesis effects [39], which are mainly mediated by T_3 in BAT stimulating the proliferation of brown adipose progenitor cells [65], increasing mitochondrial proliferation and Ucp1 expression, and increasing the mitochondrial β-oxidation capacity [66, 67].

THs lower the lipid burden in the liver by promoting the transfer of extrahepatic FFAs to the liver, intrahepatic lipid synthesis, intrahepatic lipid metabolism, and intrahepatic cholesterol metabolism and transport. THs also stimulate lipid metabolism in peripheral adipose tissue, where this mechanism allows THs to reduce the excessive accumulation of metabolites such as FFAs, thereby maintaining the liver in a healthy state.

Thyroid-related medications for MASLD

L-T_4 is the standard medication for hypothyroidism and its efficacy in the treatment of patients with SCH and MASLD has been investigated. In addition, numerous studies conducted to explore the use of TH analogs or THRβ-selective agonists in MASLD treatment have yielded valuable insights and novel approaches[9]. In recent years, many studies have focused on THRβ-selective agonists, primarily due to their specific action on the liver. This class of medications is currently the focus of various ongoing clinical trials, thereby highlighting the growing interest and potential therapeutic benefits associated with these compounds (Table 1).

L-T_4

L-T_4 is the standard care for the treatment of hypothyroidism, lowering total cholesterol,low density lipoprotein cholesterol,and increasing liver lipase activity and is also effective in patients with MASLD [68–70]. Liu et al. conducted a post-hoc analysis of an RCT to evaluate the effects of SCH treatment on MASLD, where their objective was to identify novel therapeutic possibilities for the management of MASLD. Furthermore, they conducted subgroup analysis to examine the impacts of

Table 1 Current status of research into thyroid-related therapeutic agents for MASLD

Compound	Mechanism	Objects	Main effects	Adverse reaction	Research status	References
L-T4	Direct regulation of hepatic cholesterol and triglyceride metabolism	NASH mouse models	Liver TAG↓ Liver Hyp↓ Liver Lipid Types↓ Fatty acid oxidation↑	Adverse effects of high doses of TH on the heart and bones	Further clinical trials are still needed to validate the benefits of L-T4 supplementation in MASLD	[70]
		SCH patients (363 persons)	Prevalence of MASLD↓ Serum AST↓ Serum TC↓ Weight and BMI↓			[71]
		Patients with T2DM combined with MASLD (47 persons)	IHLC↓ BMI↓ Visceral adipose tissue volume↓ Subcutaneous adipose tissue volume↓			[69]
3,5-diiodo-L-thyronine (T2)	To increase hepatic mitochondrial oxygen consumption and fatty acid metabolism	High-fat diet rat models	Weight↓ Fatty acid oxidation↑ SerumTAG↓,TC↓,ALT↓ Carnitine palmitoyltransferase activity↑ Serum TH and TSH are not affected	No adverse effects were observed at the cardiac level for the time being	Lack of larger trials; now focusing on the therapeutic potential of functional T2 analogs	[73, 74]
		Subjects with normal thyroid function (2 persons)	RMR↑ Weight↓ Serum FT_3,FT_4,TSH are not affected			[75]
TRC150094	Functional T2 analog	High-fat diet rat models	Visceral adipose tissue volume↓ Fatty acid oxidation↑	Adverse effects in subjects were not related to treatment	Phase III clinical trial underway	[76]
		Dyslipidemic subjects (225 persons)	FPG↓ Fasting insulin↓ Mean arterial pressure↓ Non-HDL cholesterol↓			[77]
Sobetirome (GC-1)	Hepatic selective THR agonist	Cholesterol-Fed Rats and Crab-Eating Monkeys	Weight↓ Serum TC,TAG↓ Lp-a ↓ MVO2 ↑	Some degree of TSH suppression was observed as well as reduced hepatic insulin sensitivity	Subsequent clinical trials were not performed due to decreased hepatic insulin sensitivity and increased endogenous glucose production	[79, 80]
eprotirome (KB2115)	Liver-specific THR agonist	High-fat diet rat models	Liver TAG↓ Serum LDL↓	Decreased glucose uptake in skeletal muscle; Potential for liver injury; cartilage damage in dogs	Phase III clinical trial terminated early due to cartilage damage identified in dog toxicology study	[80]

Table 1 (continued)

Compound	Mechanism	Objects	Main effects	Adverse reaction	Research status	References
		Patients with high cholesterol or overweight (24 persons)	Serum LDL↓ Serum TC↓ Serum apoB↓ Bile acid synthesis↑			[59]
		Familial high cholesterol patients (236 persons)	SerumLDL↓ Liver TAG↓ Bile acid synthesis↑ Transaminases, bilirubin↑			[81]
VK2809 (MB07811)	Prodrug for hepatic THRβ-selective active drug (MB07344)	Rabbits, dogs, monkeys	Serum TC↓	No significant cardiovascular effects observed	Another Phase II clinical trial is underway	[83]
		Mouse models of glycogen storage disease	Hepatic steatosis↓ Mouse liver mass↓ Intrahepatic TAG↓ Hepatic fatty acid oxidation↑			[85]
		High cholesterol and MASLD patients (45 persons)	Liver fat content↓ Hepatic steatosis↓ Hepatic fatty acid oxidation↑			[86]
TG68	Novel selective agonist of THRβ	High-fat diet mouse model	Liver weight↓ Hepatic steatosis↓ Serum TAG↓	No adverse reactions have been detected for the time being	More preclinical studies are lacking, but current evidence shows its therapeutic potential	[87]
		DEN induction with high-fat-fed rat models	Liver weight↓ Hepatic steatosis↓ Serum TAG↓ Regression of pre-tumor lesions			[88]
Resmetirom (MGL-3196)	Liver-directed, THRβ-selective agonist	NASH patients (348 persons)	Liver fat content↓ Liver TC↓ Indicators of Liver Injury and Liver Fibrosis↓ HRQL Improvement	Generally well tolerated	Further phase III clinical trials are underway	[89, 90]
		NASH patients (1143 persons)	The majority of TEAEs were of mild to moderate severity Atherogenic lipid levels↓			[91]
		NASH patients (966 persons)	NASH resolution without worsening fibrosis Fibrosis improvement Low-density lipoprotein cholesterol↓			[92]

Table 1 (continued)

Compound	Mechanism	Objects	Main effects	Adverse reaction	Research status	References
		Late-stage NASH mouse model	Liver fat content↓ Liver TC↓ Serum TAG↓			[93]

L-T_4levothyroxine, *THR* thyroid hormone receptor, *NASH* non-alcoholic steatohepatitis, *SCH* subclinical hypothyroidism, *T2DM* Type 2 Diabetes Mellitus, *MASLD* metabolic dysfunction-associated steatotic liver disease, *DEN* diethylnitrosamine, *TAG* triacylglycerol, *Hyp* hydroxyproline, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TC* total cholesterol, *BMI* body mass index, *IHLC* intrahepatic lipid content, *TH* thyroid hormone, *TSH* thyroid stimulating hormone, *RMR* resting metabolic rate, FT_3 free triiodothyronine, FT_4 free thyroxine, *FPG* fasting blood glucose, *Lp-a* lipoprotein a, *MVO2* maximum voluntary oxygen consumption, *LDL* low density lipoprotein, *apoB* apolipoprotein B, *HRQL* health-related quality of life, *TEAEs* treatment-emergent adverse events

L-T_4 supplementation on MASLD among patients with mild SCH and dyslipidemia [71]. This post-hoc analysis involved 363 subjects comprising 33 patients with severe SCH (TSH ≥ 10 mU/L) and 330 patients with mild SCH (4.2 mU/L < TSH < 10 mU/L). All patients with severe SCH were treated with L-T_4, and among the patients with mild SCH, 181 patients were treated with L-T_4 (mild SCH-L-T_4 group) and 149 patients were not treated (mild SCH control group). In patients with severe SCH, the prevalence of MASLD decreased from 48.5% to 24.2% ($P=0.041$) [71]. In the sub-L-T_4 group comprising patients with mild SCH and dyslipidemia who were treated with L-T_4, there was a decrease in the prevalence of MASLD from the beginning to the end of the study (54.3% to 40.5%, $P=0.035$). In the sub-control group comprising patients with mild SCH and dyslipidemia who did not receive L-T_4, there was also a decrease in the prevalence of MASLD, although this decrease was not statistically significant compared with the sub-L-T_4 group (44.0% to 39.6%, $P=0.548$). In addition, this study analyzed the rate of MASLD remission in patients who started with MASLD and the incidence in patients without MASLD, where 26 of 63 patients with MASLD in the sub-L-T_4 group (41.3%) recovered, which was higher than the number in the sub-control group (35.0%, $P=0.525$). Among patients who started without MASLD, the incidence of MASLD at the end of the study was 18.9% in the sub-L-T_4 group, which was slightly lower than that in the sub-control group (19.6%, $P=0.924$) [71]. The results indicated that L-T_4 replacement therapy was advantageous for managing MASLD in individuals diagnosed with SCH, particularly for patients with severe SCH or mild SCH accompanied by dyslipidemia. Furthermore, L-T_4 replacement therapy has the potential to decrease the occurrence of MASLD. In clinical practice, it is common to encounter patients who have SCH combined with MASLD, and normal blood lipid levels. However, the impact of L-T_4 supplementation on MASLD in this specific patient group has not yet been documented and further investigations are required. It has been demonstrated L-T_4 is efficacious in the management of MASLD resulting from various diseases in both animal models and patients. Studies have shown that L-T_4 can significantly decrease hepatic triglyceride levels and enhance mitochondrial oxidation [69, 70]. Nevertheless, it is important to note that L-T_4 can potentially have impacts on cardiac and skeletal tissues that express THRα. Thyrotropin suppression therapy has the potential to decrease bone mineral density in certain premenopausal and postmenopausal women [72]. Therefore, additional clinical studies are required to further refine our understanding in order to establish the appropriate dosage.

TH analogues (3, 5-diiodo-L-thyronine and TRC150094)

The naturally occurring iodothyronine called 3,5-diiodo-L-thyronine (T2) substantially enhanced hepatic mitochondrial oxygen consumption and fatty acid metabolism in a rat model treated with a high-fat diet to effectively prevent the development of hepatic steatosis. In addition, T2 did not cause thyrotoxicity or adverse effects at the cardiac level in the animal models [73, 74]. In human studies, T2 also significantly increased the resting metabolic rate in subjects without causing changes in thyroid-related hormone levels [75]. Nevertheless, there have been no extensive clinical investigations of T2 because the focus has shifted toward examining its functional analog TRC150094. Similar to T2, TRC150094 acts at the mitochondrial level to increase fatty acid metabolism and reverse steatosis. The therapeutic efficacy of TRC150094 was observed in animal models and in a phase II clinical trial. At a dosage of 50 mg, a uniform reduction trend was observed across all lipid components associated with arteriosclerosis. At present, the compound is undergoing a phase III clinical trial (NCT03254446) to assess its effectiveness in mitigating cardiovascular risk in individuals with diabetes, dyslipidemia, and hypertension [76, 77]. However, research has also indicated that TRC150094 at a dose of 50 mg/day does not improve the metabolic stability of subjects at increased risk of cardiovascular metabolism [78]. To date, there is still no compelling evidence demonstrating the potential effects of T2 or TRC150094 in treating obesity or MASLD.

THRβ-selective agonists

GC-1 and eprotirome (KB2115) GC-1 and eprotirome (KB2115) were among the initial set of THRβ-selective agonists employed in clinical trials. Their application in preliminary trials conducted on animal models indicated good therapeutic effectiveness, with enhancements of aberrant metabolic parameters, such as the body weight, liver fat content, and serum cholesterol content. In addition, in early clinical trials, eprotirome exhibited excellent therapeutic efficacy in subjects, without significant side effects [59, 79]. Subsequent animal trials of sobetirome and eprotirome showed that both sobetirome and eprotirome were effective in treating steatosis in fat-fed rats, but they both impaired insulin sensitivity via discrete pathways [80]. The phase III clinical trial of eprotirome was ultimately halted after only six weeks due to concurrent toxicology studies in dogs demonstrating the adverse effects of eprotirome on canine cartilage [81]. Due to the detrimental impacts observed in these studies, both subsequent investigations of sobetirome and eprotirome were prematurely terminated [82].

VK2809 (MB07811) MB07811 is a hepatic THRβ-selective agonist and a prodrug of MB07344. In contrast to GC-1, MB07811 possesses a phosphate group in its side chain. Preclinical investigations obtained promising outcomes regarding cholesterol metabolism, with no notable adverse effects observed [83]. However, the clinical trials of MB07811 were prematurely terminated before initiation [84]. The renaming of MB07811 to VK2809 and subsequent recommencement of trials occurred recently. In mouse models of glycogen storage disease, VK2809 was efficacious in effectively lowering hepatic triglyceride levels by concurrently reinstating autophagy, mitochondrial biogenesis, and fatty acid β-oxidation [85]. A phase II clinical trial that investigated the efficacy of VK2809 found that participants who received VK2809 exhibited notable reductions in their liver fat contents as determined by the magnetic resonance imaging proton density fat fraction (MRI-PDFF) technique compared with those who received a placebo. In addition, the improved tolerability of VK2809 was demonstrated among the subjects involved in the study [86]. In order to further investigate the therapeutic effectiveness of VK2809, a phase II clinical trial is currently underway (NCT04173065). This trial aims to assess the efficacy, safety, and tolerability of administering VK2809 over a period of 52 weeks.

TG68 TG68 is a novel selective agonist of THRβ. A comparative study conducted using a mouse model treated with a high-fat diet assessed the effects of TG68 and MGL-3196 (a THRβ-selective agonist that is currently undergoing phase III clinical trials). The findings showed that when administered in equal doses, both drugs obtained comparable outcomes in terms of reducing the liver weight, alleviating hepatic steatosis, and lowering blood triglyceride levels in mice [87]. A recent preclinical investigation showed that in addition to its significant impact on diminishing liver fat levels, brief exposure to TG68 induced the reversal of diethylnitrosamine-induced preneoplastic lesions in the livers of rats, among other benefits [88]. Clinical studies of TG68 are still lacking but the results obtained in current trials have demonstrated the notable therapeutic potential of TG68.

Resmetirom (MGL-3196) Resmetirom (MGL-3196) is a liver-directed, THRβ-selective agonist, which has obtained positive therapeutic effects in patients with non-alcoholic steatohepatitis(NASH) in several recent clinical trials [89–92], and has been approved by the U.S. Food and Drug Administration (FDA) under the name Rezdiffra for use in conjunction with dietary and exercise regimens for managing non-cirrhotic NASH in adults with moderate to advanced fibrosis. In the 36-week phase II trial of Resmetirom, in week 12, the measurements of liver fat content indicated a significant reduction of 32.9% in the group treated with Resmetirom compared with a decrease of 10.4% in the placebo group ($P<0.0001$). Similarly, by week 36, a highly significant reduction of 37.3% was found in the Resmetirom group compared with a decrease of 8.5% in the placebo group ($P<0.0001$). Moreover, Resmetirom had significant effects on lowering liver enzymes, atherogenic lipids, lipoproteins, and markers of inflammation and fibrosis, and improving liver biopsies in NASH compared with the placebo [89]. During the course of the trial, researchers observed that the administration of Resmetirom for the treatment of NASH could lead to improvements in the health-related quality of life among patients. This positive change was found to be most significant at week 12 and continued consistently until week 36 [90]. Furthermore, subsequent investigations involving animal models substantiated the therapeutic efficacy of Resmetirom in the treatment of advanced NASH [93]. Results from several Phase 3 clinical trials of Resmetirom have been recently reported. One of these trials, known as MAESTRO-NAFLD-1, was a 52-week randomized, double-blind, placebo-controlled Phase 3 trial (NCT04197479) with the aim of assessing the safety profile of Resmetirom in clinical settings. During the 52-week treatment period and 4-week follow-up, the incidence rates of treatment-emergent adverse events (TEAEs) in adult patients receiving 100 mg Resmetirom (325 patients), 80 mg Resmetirom (327 patients), placebo (320 patients), and 100 mg Resmetirom in an open-label trial (171 patients) were 86.1%, 88.4%, 81.8%, and 86.5%, respectively. There were no significant differences among them, and the majority of TEAEs were of mild to moderate severity. The study results demonstrate that Resmetirom is safe and well-tolerated in adult patients presumed to have NASH [91]. The trial results at the 52nd week of a 54-month randomized, double-blind, placebo-controlled study (NCT03900429) involving Resmetirom were subsequently published [92]. The two primary endpoints of the trial at week 52 were defined as the resolution of NASH with non-worsening fibrosis, and an improvement (reduction) in at least one stage of fibrosis with non-worsening of the MASLD activity score. In this clinical trial, a total of 966 primary participants were randomly distributed into three groups in a 1:1:1 ratio, with 322 individuals in the 80 mg Resmetirom group, 323 in the 100 mg Resmetirom group, and 321 in the placebo group. The results at the 52-week mark revealed that 25.9% of patients in the 80 mg group and 29.9% in the 100 mg group achieved NASH resolution without worsening fibrosis, in contrast to 9.7% in the placebo group ($P<0.001$). Furthermore, 24.2% and 25.9% of patients in the 80 mg and 100 mg groups, respectively, displayed a minimum of one stage improvement

in fibrosis without worsening the MASLD activity score, compared to 14.2% in the placebo group (P < 0.001). At the 24th week of the study, participants receiving 80 mg and 100 mg doses exhibited decreased LDL cholesterol levels compared to their initial measurements, showing a reduction of 13.6% in the 80 mg group and 16.3% in the 100 mg group. Conversely, there was no reduction (0.1%) in the placebo group (P < 0.001). Notably, this observed effect persisted up to the 52nd week of the research period. Compared to the placebo group, patients in the Resmetirom group showed a decrease in levels of triglycerides, non-high-density lipoprotein cholesterol, apolipoprotein B, apolipoprotein C-III, and lipoprotein (a) at weeks 24 and 52. Furthermore, liver enzyme levels also decreased more significantly in the Resmetirom group compared to the placebo group [92]. The subsequent phases of the trial will assess the safety implications associated with the extended administration of Resmetirom as well as its impact on the advancement of cirrhosis. The findings indicate that Resmetirom indeed exerts a noteworthy impact on the resolution of NASH and the improvement of liver fibrosis. However, the observation that fewer than one-third of participants administered Resmetirom during the clinical study attained remission implies that it may not be a miracle drug for all individuals with NASH.

Future perspectives

In the field of epidemiology, numerous studies have suggested that SCH is a potential risk factor for MASLD; however, this association remains controversial. The interplay between thyroid function, MASLD, and sarcopenia warrants further investigation to elucidate potential mechanistic links.

Regarding pharmacological interventions, L-T4 therapy is currently primarily indicated for patients with severe SCH or those with mild SCH accompanied by dyslipidemia. Nevertheless, the effect of L-T4 supplementation on MASLD has not been reported in patients with mild SCH and concurrent MASLD who are dyslipidemic, and thus further research is needed. Additionally, the potential therapeutic role of TH analogues in managing obesity or MASLD remains an area of active exploration. It is noteworthy that most of the pharmacological agents discussed in this review are still in the clinical research phase. Should subsequent clinical trials demonstrate the long-term efficacy and safety of these drugs, they may offer novel therapeutic avenues for managing MASLD in patients with SCH. Further research is essential to validate these potential treatment options and optimize clinical outcomes.

Conclusions

Hypothyroidism is widely recognized as a significant risk factor for MASLD. While the association between SCH and an increased risk of MASLD remains a subject of debate, the majority of research supports this correlation. Studies have demonstrated that THs play a crucial role in promoting lipid metabolism and excretion in both hepatic and adipose tissues, thereby significantly mitigating hepatic lipid accumulation. In response to this mechanism of action, several therapeutic agents targeting MASLD, including L-T4, thyroid hormone analogues, and THRβ-selective agonists, have advanced to the clinical research stage. L-T4 therapy has been shown to reduce the prevalence of MASLD, especially in patients with severe SCH or mild SCH patients with dyslipidemia, and these patient populations should be prioritized for active clinical intervention. Furthermore, THs and numerous THRβ-selective agonists have yielded positive results in animal models or clinical trials. Notably, Resmetirom, a THRβ-selective agonist, has received approval from the U.S. Food and Drug Administration (FDA) under the trade name Rezdiffra. It is indicated for use in conjunction with dietary and exercise regimens to manage non-cirrhotic NASH in adults with moderate to advanced liver fibrosis.

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The authors have nothing to disclose.

Authors' contributions
Zhao, Pu and Jiang wrote the main manuscript.Zhao prepared Figs. 1 and 2. Pu prepared Table 1.Cui revised the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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