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REVIEW

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Thyroid hormone and the Liver

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Abstract

It is known that thyroid hormone can regulate hepatic metabolic pathways including cholesterol, de novo lipogenesis, fatty acid oxidation, lipophagy, and carbohydrate metabolism. Thyroid hormone action is mediated by the thyroid hormone receptor (THR) isoforms and their coregulators, and THRβ is the main isoform expressed in the liver. Dysregulation of thyroid hormone levels, as seen in hypothyroidism, has been associated with dyslipidemia and metabolic dysfunction–associated fatty liver disease. Given the beneficial effects of thyroid hormone in liver metabolism and the advances illuminating the use of thyroid hormone analogs such as resmetirom as therapeutic agents in the treatment of metabolic dysfunction–associated fatty liver disease, this review aims to further explore the relationship between TH, the liver, and metabolic dysfunction–associated fatty liver disease. Herein, we summarize the current clinical therapies and highlight future areas of research.

Keywords: liver metabolism, MASLD, metabolic dysfunction–associated steatotic liver disease, THRβ, thyroid hormone, thyroid hormone receptor beta

INTRODUCTION

Thyroid hormones (THs), thyroxine (T4) and 3,5,3′-triiodothyronine (T3), are critical for normal development and maintenance of metabolic pathways after development.[1,2] T4 is the primary form of TH synthesized and released by the thyroid gland in humans. Once released, deiodinase enzymes, including type I (D1) and type II (D2) enzymes, convert T4 into T3, which is the bioactive form of TH. Type III deiodinases (D3) lead to the formation of reverse T3 (rT3), an inactive form of TH.[3,4] Most TH actions are mediated through the binding of T3 to the nuclear thyroid hormone receptors (THRs), which interact with T3 through its C-terminal ligand-binding domain.[5–7] There are 2 main isoforms of THR: *THRα* and *THRβ*. The expression of each THR is tissue-dependent. *THRα* is mainly expressed in the bone and heart, whereas *THRβ* is expressed in the liver and kidneys. The THRs form heterodimers with the retinoid X receptor, another nuclear receptor, and bind to thyroid hormone response elements in regulatory regions of target genes.[2,5,8–10] Classically, in the presence of T3, conformational changes in the ligand-binding domain lead to the recruitment of coactivators, including CREB

Abbreviations: DNL, de novo lipogenesis; FA, fatty acids; FAO, fatty acid oxidation; FASN, fatty acid synthetase; LDL-R, low-density lipoprotein receptor; MASH, metabolic dysfunction–associated steatohepatitis; MASLD, metabolic dysfunction–associated fatty liver disease; T3, 3,5,3′-triiodothyronine; T4, thyroxine; TH, thyroid hormone; THR, thyroid hormone receptor.

binding protein (CBP)/p300 and steroid receptor coactivator 1 (SRC1), promoting gene transcription (Figure 1). In absence or low levels of T3, corepressor proteins, the nuclear receptor corepressor 1 (NCoR1) and nuclear receptor corepressor 2 (NCoR2; also known as SMRT), are recruited to inhibit gene expression.[2,9,11] The THRα and THRβ proteins are structurally similar; however, they have different roles. This is manifested in the clinical conditions of resistance to thyroid hormones α and β where there are either mutations in THRα or THRβ, showing that the THR isoforms not only have a distinct tissue distribution but also have different effects.[8]

Metabolic dysfunction–associated fatty liver disease (MASLD), previously NAFLD, is a hepatic disorder with an incidence of approximately a quarter of the world's population.[12–14] MASLD is considered a complex metabolic disease often associated with obesity, insulin resistance, type 2 diabetes, high cholesterol, and metabolic syndrome.[15] MASLD can also be considered a state of intrahepatic hypothyroidism, as advanced liver fibrosis in humans has been associated with D3 induction, suppressing intrahepatic T3 levels and inhibiting known targets of TH.[16] MASLD represents a spectrum of liver disorders ranging from steatosis to steatohepatitis, advanced fibrosis, and cirrhosis.[17] MASLD is characterized by excess fat stored in the liver (hepatosteatosis) that can progress to metabolic dysfunction–associated steatohepatitis (MASH), which is defined by the presence of 5% or greater hepatic steatosis and also includes liver cell damage and inflammation. If untreated, MASH can further progress to cirrhosis, leading to HCC and liver failure.[12,18–20] While there continues to be a robust area of research into drug treatment for MASLD, currently there is only 1 (recently) approved pharmacological therapy, resmetirom, a THR agonist.[21] Consequently, there is an unmet need to develop models to address this disease, and there is significant untapped potential for benefit in leveraging the effects of thyroid hormone metabolism and signaling.

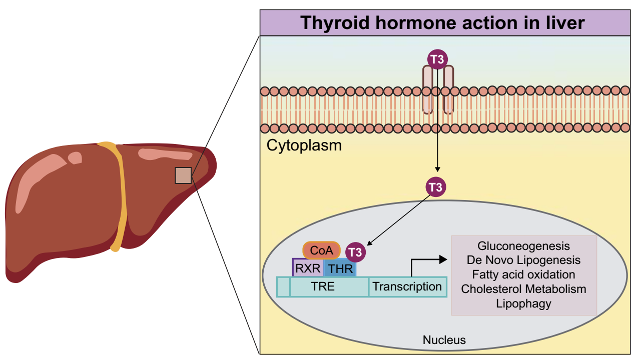

FIGURE 1 Overview of TH action in the liver. TH enters the cell through transporters on the cell membrane. The nuclear THR forms a heterodimer with the RXR receptor at TRE sequences on DNA. In the presence of T3, coactivators are recruited to facilitate gene expression that regulates gluconeogenesis, de novo lipogenesis, fatty acid oxidation, cholesterol metabolism, and lipophagy. Abbreviations: RXR, retinoid X receptor; T3, 3,5,3′-triiodothyronine; TH, thyroid hormone; THR, thyroid hormone receptor; TRE, thyroid hormone response element.

TH is a potent regulator of cellular metabolism and plays a role in regulating carbohydrate and lipid metabolic pathways and mitochondrial biogenesis.[22,23] Numerous studies have shown that THs have beneficial effects in preventing and reversing hepatic steatosis.[24,25] Nevertheless, the use of TH as a specific liver disease therapy has been limited due to the lack of selectivity and systemic adverse effects, such as in the heart, muscle, and bones, mainly due to the activation of THRα. Selective activation of THRβ has, therefore, been targeted for the development of novel therapeutic drugs to treat MASLD and MASH. In this context, THRβ agonists have been studied as potential therapeutic agents for treating both serum dyslipidemia and MASLD. Not surprisingly, the studies revealed the beneficial THRβ agonist's effects on decreasing liver lipid accumulation in the absence of harmful effects primarily mediated by THRα activation, including loss of bone density or elevated heart rate.[26–28] In this review, we examine the effects of TH on hepatic lipid and carbohydrate metabolism and the regulation of cholesterol metabolism, and we summarize the advances in using TH agonists as therapeutic agents to address liver diseases, particularly MASLD.

THE INTERACTION BETWEEN TH-THRβ AND LIVER

TH is an important regulator of several physiological processes both globally and in the liver and is critical for maintaining metabolic balance.[29] Dysregulation of thyroid hormone levels is often associated with metabolic diseases, including dyslipidemia and hepatic steatosis.[30,31] Hyperthyroidism is characterized by low thyroid-stimulating hormone levels and high levels of TH, whereas hypothyroidism is defined by increased plasma thyroid stimulating hormone and low levels of free T4.[32,33] An inverse relationship has been observed between TH levels and MASLD; however, the pathogenesis involved in this relationship is complex and not fully understood. Hypothyroidism is associated with MASLD, and even low, but normal TH levels are associated with a higher risk of MASLD with risk increasing as TH levels drop.[34,35] The impact of hypothyroidism in MASLD is extensive. Patients with hypothyroidism often have hyperlipidemia, which is involved in the pathophysiology of MASLD,[36] and may contribute to the increased risk of cardiovascular events observed with MASLD.[37,38] THs modulate glucose and lipid metabolism in the liver by regulating essential metabolic pathways such as lipogenesis, fatty acid oxidation (FAO), bile acid synthesis, cholesterol metabolism, insulin sensitivity, and gluconeogenesis. These actions are mediated by T3 binding THR, controlling gene expression, or in association with other nuclear receptors, including peroxisome proliferator–activated receptor (PPAR) and liver X receptor (LXR).[39,40] In addition, hepatic activation of THRβ is associated with the reduction of lipids and an increase in bile acid synthesis and FAO.[41]

LIVER METABOLIC PATHWAYS REGULATED BY TH THROUGH THE THRβ

De novo lipogenesis

De novo lipogenesis (DNL) is a process in which non-lipid precursors such as glucose or fructose are used to synthesize fatty acids (FAs) in times of excess energy (Figure 2, blue arrows). DNL is an essential metabolic pathway for storing excess energy, and dysregulation of this process can contribute to metabolic disorders such as MASLD, obesity, and dyslipidemia.[42] TH regulates the expression and activity of key genes involved in DNL, directly and indirectly. Acetyl-CoA carboxylase (ACC), which is the enzyme that carboxylates acetyl-CoA in the first, committed step of DNL is under the control of TH with T3 increasing *Acc* transcription.[43] Fatty acid synthetase (FASN) is an additional key enzyme under the control of TH with *Fasn* expression stimulated by TH.[44,45] FASN catalyzes the formation of palmitate, a long-chain saturated fatty acid.[46] Finally, TH regulates TH-responsive Spot14 (*Thrsp*), which is required for DNL.[47,48] *Acc*, *Fasn*, and *Thrsp* all have thyroid hormone response elements in their promoters, where THRs are recruited, providing a mechanism by which TH acts to increase transcription of these genes.[42,43,48–50] While these studies have primarily been done in murine models, similar activation of these enzymes was seen in vivo in a human line of induced pluripotent stem cells differentiated to hepatocytes (iHEPs) treated with T3.[51] iHEPs represent a novel model to investigate not only TH action but also TH agonists for the treatment of MASLD.

Indirectly, TH activates carbohydrate-responsive element-binding protein (ChREBP), a transcription factor that plays a key role in DNL through the activation of *Acc*, *Fasn*, and ATP citrate lyase (*Acly*).[52,53] In addition, the malic enzyme (*ME*), which generates NADP and provides energy for DNL, is activated by TH.[54,55] Thus, TH has both direct and indirect roles in DNL, a key

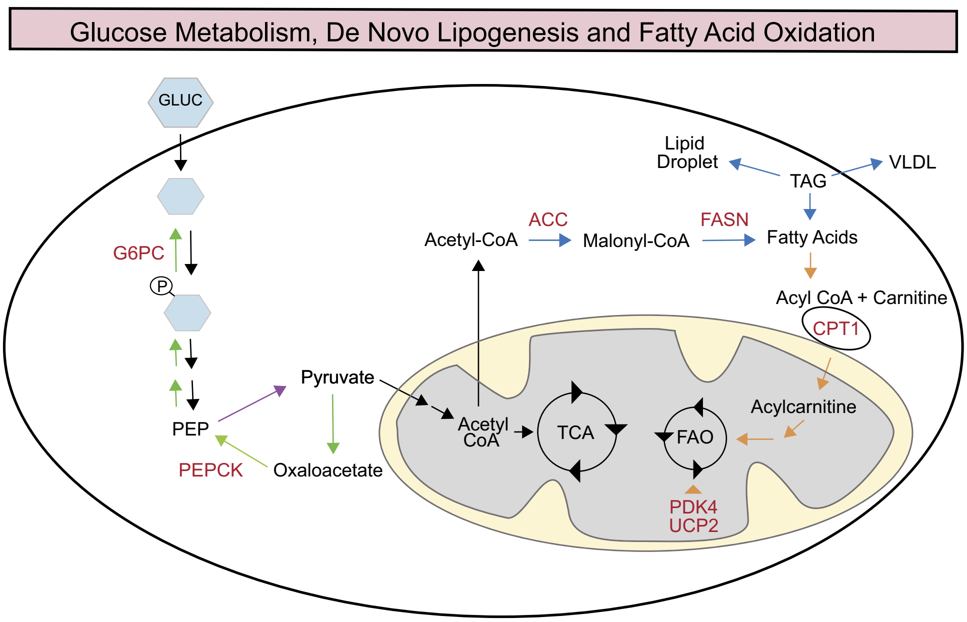

FIGURE 2 Key enzymes of glucose metabolism (gluconeogenesis, green arrows), DNL (blue arrows), and FAO (orange arrows) are activated by TH (in red). Glycolysis is a metabolic pathway that converts glucose into pyruvate. Gluconeogenesis is the metabolic process that synthesizes glucose from non-carbohydrate precursors. TH regulates key enzymes involved in these pathways, including G6PC and PEPCK. PEPCK is the rate-limiting step of gluconeogenesis and catalyzes the reaction of oxaloacetate to PEP. DNL is the process by which glucose or other carbohydrates are converted to fatty acids for triglyceride synthesis. Key enzymes activated by TH in this process include ACC, which catalyzes the carboxylation of acetyl-CoA to malonyl-CoA in the first step of DNL. Downstream of this reaction, FASN catalyzes the formation of palmitate, a long-chain fatty acid. Conversely, FAO is the process by which long-chain fatty acids are oxidized for energy during energy-deficient states. TH acts on CPT1, the rate-limiting enzyme of FAO. Additional enzymes regulated by TH critical for FAO include PDK4 and UCP2. Abbreviations: ACC, acetyl-CoA carboxylase; CPT1, carnitine palmitoyltransferase 1; DNL, de novo lipogenesis; FAO, fatty acid oxidation; FASN, fatty acid synthetase; PDK4, pyruvate dehydrogenase kinase 4; PEP, phosphoenolpyruvate; PEPCK, phosphoenolpyruvate carboxykinase 1; TH, thyroid hormone; UCP2, uncoupling protein 2.

metabolic pathway in the liver that has been implicated in the development of MASLD.[56]

Lipolysis and FAO

FAO is characterized by the oxidation of long-chain FAs to help maintain body temperature and general energy expenditure during fasting (Figure 2, orange arrows).[57] Fatty acids are stored in the body mainly as triacylglycerol. Lipases can hydrolyze triacylglycerol, releasing free FAs from glycerol. Long-chain free FAs are then transferred into the mitochondria, where they can be oxidized. TH stimulates hepatic lipase activity and thus hepatic lipophagy, facilitating triacylglycerol breakdown to free FAs for FAO. Furthermore, TH increases mitochondrial biogenesis and mitophagy, thereby maintaining mitochondrial quality for FAO.[58]

TH regulates FAO through the stimulation of key genes involved in this pathway, including upregulation of the carnitine palmitoyltransferase 1A (*CPT1A*), the rate-limiting enzyme of FAO.[59] TH also increases the levels of *CPT1A* through stimulation of sirtuin 1 (*SIRT1*), peroxisomal proliferator–activated receptor-gamma coactivator-1 alpha (*PGC-1α*), and peroxisome proliferator–activated receptor alpha (*PPARA*).[60,61] In addition, TH plays a role in regulating other mitochondrial enzymes important for oxidative processes such as pyruvate dehydrogenase kinase 4 (*PDK4*), uncoupling protein 2 (*UCP2*), acyl-CoA thioesterase 2, and acyl-CoA oxidase 1.[62–64] T3 is able to promote a reduction of hepatic steatosis associated with stimulation of FAO in a mouse model of fatty liver and mild hepatitis.[25] In a different dietary mouse model of MASH, TH treatment decreased hepatic triglycerides, increased β-oxidation of FA, and reduced lipotoxicity, oxidative stress, hepatic inflammation, and fibrosis. In addition, in cultured hepatic cells, TH increased FAO under basal and lipotoxic conditions.[65] In summary, TH acts in multiple ways to facilitate FAO — from maintaining mitochondrial quality to facilitating hepatic lipases and increasing transcription of key enzymes associated with FAO.

Cholesterol regulation

Cholesterol is essential for many cellular functions, such as cell membrane structure, cell permeability, vitamin D synthesis and hormone production, and bile acid formation.[66] Cholesterol is insoluble in water, and it needs to be transported in the plasma by lipoproteins, which are complex molecules composed of lipids (cholesterol, triglycerides, and phospholipids) and proteins (apolipoproteins and enzymes). Lipoproteins are classified as chylomicrons, VLDL, IDL, LDL, and HDL.[67]

Cholesterol levels are primarily regulated by the liver through the stimulation of HMG-CoA reductase, an enzyme that is the rate-limiting step in cholesterol biosynthesis. TH has been shown to stimulate HMG-CoA reductase activity in multiple studies (Figure 3B).[68,69] Furthermore, key genes that promote HMG-CoA reductase expression are activated by T3. Cholesterol is also regulated by hepatic low-density lipoprotein receptors (LDL-Rs), which increase the uptake of cholesterol from the blood. TH acts to increase LDL-R expression in part through direct recruitment of the THR to the LDL-R promoter and, second, through the activation of sterol regulatory element-binding protein 2 (*SREBP2*), which increases LDL-R transcription (Figure 3A).[70,71] Cholesterol can be eliminated from the body after being secreted into the biliary system and excreted as bile acids.[66,67] TH induces cholesterol 7 alpha-hydroxylase (*CYP7A1*), the rate-limiting enzyme that converts cholesterol into bile acids, in animal and human cell lines (Figure 3C).[69] Lastly, TH regulates reverse cholesterol transport, where cholesterol is transported from peripheral tissues by HDL to the liver for excretion. This is in part through TH regulation of apolipoprotein A1 (ApoA1), which enables cholesterol efflux from tissues through the ATP-binding cassette transporter A1.[69]

Although many studies on the mechanisms of TH and its role in cholesterol metabolism are based on animal models, it has long been known that TH is a key regulator of serum cholesterol in humans and that this is an inverse correlation.[72,73] Clinically, even mild reductions in TH correlate with hyperlipidemia with elevations in serum total cholesterol, LDL, and ApoB.[73–77] Hyperthyroidism, on the other hand, is associated with a reduction in cholesterol levels. Dyslipidemia is also observed in patients with resistance to thyroid hormone β, where TH cannot interact with the THR. Patients often present with higher levels of total cholesterol, triglycerides, LDL-C, and increased hepatic lipid content compared to unaffected individuals.[78,79]

Carbohydrate metabolism

Carbohydrate metabolism and TH are closely interconnected, and the liver plays a key role in maintaining serum glucose levels during feeding and fasting periods. Peripherally, TH acts on skeletal muscle, the pancreas, the liver, and adipose tissue to regulate glucose metabolism.[80] Centrally, the paraventricular hypothalamus, under the control of TH, can regulate glucose synthesis and insulin sensitivity through a sympathetic pathway to the liver.[81,82] TH increases hepatic glucose production through actions on critical transcription factors and enzymes involved in gluconeogenesis (Figure 2, green arrows). Key gluconeogenic enzymes that are positively regulated by TH include phosphoenolpyruvate carboxykinase 1 (*PCK1*) and glucose-6-phosphatase.[83,84] These genes are in

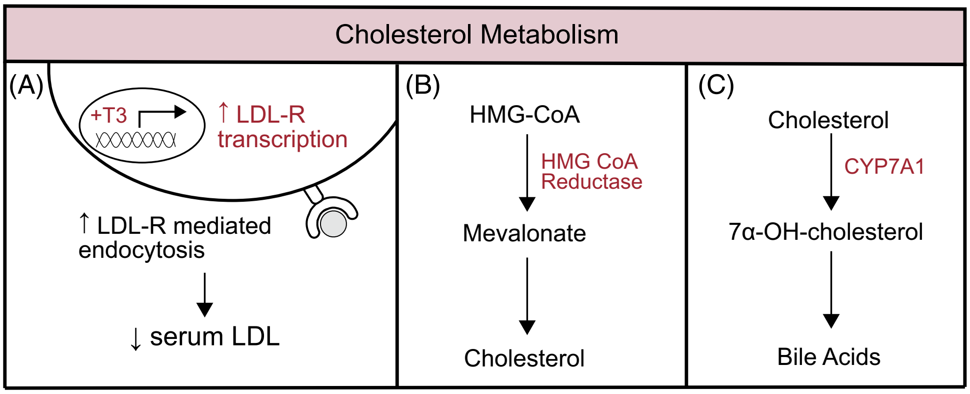

FIGURE 3 TH and cholesterol metabolism. Key areas of TH on cholesterol metabolism are in red. (A) TH acts to increase transcription of the LDL-R, which increases LDL-R–mediated endocytosis and lowers serum cholesterol. (B) HMG-CoA reductase catalyzes the rate-limiting step in cholesterol synthesis and is activated, ultimately increasing cholesterol synthesis. (C) Cholesterol is broken down into bile acids for excretion. CYP7A1 is the rate-limiting enzyme of this process that catalyzes the conversion of cholesterol to 7-alpha-hydroxy cholesterol, and its activity is increased by TH. Abbreviation: LDL-R, low-density lipoprotein receptor.

part activated by forkhead transcription factor (FoxO1), a critical transcription factor whose deacetylation and activation are mediated by TH.[85] Further, TH increases pyruvate dehydrogenase kinase isoenzyme 4 (PDK4) expression to promote gluconeogenesis.[62] PDK4 regulates the pyruvate dehydrogenase complex, acts as a critical regulator of glucose metabolism, and has been implicated in the development of MASH.[86,87] On the other hand, TH has also been shown to increase pathways and genes associated with glycogenolysis and gluconeogenesis, including glucose-6-phosphatase (*G6pc*), an enzyme that plays a role in both pathways and phosphoenol pyruvate kinase (*Pepck)* (Figure 2, green arrows).[83–85,88]

TH also contributes to hepatic and systemic insulin sensitivity, and altered TH levels and impaired TH action can lead to insulin resistance, altered hepatic glucose production, and the development of metabolic disorders, including MASLD and type 2 diabetes.[88–90] This is in part through the modulation of inflammatory pathways that are associated with insulin resistance.[91–94] In addition, hepatic THRβ is required for the stimulation of glucagon-like peptide 1 production as the treatment of hypothyroid mice with T3 is accompanied by an increase in glucagon-like peptide 1 levels. This increase in glucagon-like peptide 1 leads to the glucose-lowering effects of TH and is lost in the absence of hepatic THRβ .[95] Clinically, patients with hyperthyroidism have elevated levels of basal hepatic glucose production and higher rates of gluconeogenesis.[96] On the contrary, hypothyroidism is associated with reduction of hepatic gluconeogenesis.[97]

Lipophagy

Autophagy is a self-degradative process in which cytosolic components are degraded within the lysosome. This process is essential for cellular maintenance. The most common type of autophagy is macro-autophagy, in which a phagophore expands and engulfs the cytosolic components to become an autophagosome. Autophagosomes fuse with lysosomes, organelles containing digestive enzymes. This generates an autolysosome where lysosomal digestive enzymes break cellular components down and release them into the cytoplasm.[98] Autophagy dysregulation is associated with hepatic disorders, including MASLD, as the breakdown of lipids can also occur by a type of autophagy called lipophagy. In this process, the lipids are broken into free FA, and the lipid droplets are engulfed by autophagosomes and lysed by the digestive enzymes in lysosomes. Therefore, hepatic lipophagy could serve as a preventive mechanism against MASLD.[99,100]

TH plays an important role in lipid metabolism by regulating autophagy. In both in vitro and in vivo models, T3 stimulates hepatic lipophagy, controlling the mobilization of lipids in hepatocytes.[101] In the context of autophagy, lysosomal functions have been investigated, and it was suggested that T3 can regulate the hydrolytic enzymes and/or the transporter proteins. T3 also increases liver lysosomal activity by upregulating lysosomal genes and increasing lysosome-associated membrane protein stability, which constitutes ~50% of all proteins found in lysosome membranes.[102]

TH agonists and the liver

Systemic TH administration therapy to address MASLD is not indicated due to its adverse cardiac, muscle, and bone effects mediated mainly by THRA.[103,104] Because of this, a more selective approach targeting only *THRβ* is ideal to avoid these negative side effects. Several *THRβ* agonists with potential therapeutic applications have been identified and are currently in clinical development to treat liver and metabolic diseases (Table 1).

In 1998, a THRβ-selective agonist compound GC-1 (sobetirome) was first reported. GC-1 has been extensively studied in animal models, reaching a phase 1 clinical trial. Its beneficial effects, such as lipid-lowering, have been reviewed by Columbano and colleagues.[103,105] Recently, it was shown that GC-1 upregulated *CPT1A* transcription in human hepatocyte-derived huh-7 cell lines, indicating its ability to stimulate hepatic beta-oxidation.[103,106] Despite the efficacy of GC-1 improving lipid profiles without significant adverse side effects in clinical trials, it has not been studied further for use in treatment of hyperlipidemia for unclear reasons.[107]

Resmetirom (MGL-3196) was recently approved for the treatment of nonalcoholic steatosis with liver fibrosis.[21] The data collected supported its efficacy and safety to be used as a therapeutic approach in adults with MASH. Harrison and colleagues conducted a phase III trial in adults with NASH and fibrosis who received resmetirom once daily at a dose of 80 mg, 100 mg, or placebo for 52 weeks: 25.9% of the patients receiving 80 mg of resmetirom and 29.9% of the patients receiving 100 mg had MASH resolution compared to 9.7% in the placebo group. Patients treated with both doses also showed an improvement in fibrosis by at least 1 stage. Diarrhea and nausea were the side effects most frequently observed in the resmetirom groups.[21] (ClinicalTrials.gov Identifier: NCT03900429). Further studies are ongoing (ClinicalTrials.gov identifier: NCT04951219 and NCT05500222).

Studies using animal models have also demonstrated the effects of resmetirom on decreasing hepatic steatosis and lipid levels. In a MASH mouse model induced by a diet high in fat, fructose, and cholesterol for 34 weeks and treated with resmetirom for 8 weeks saw improvements in MASLD activity score with reduction in liver weight, hepatic steatosis, plasma alanine aminotransferase activity, liver and plasma cholesterol, and blood glucose.[108] Rats fed with high-fat diet for 14 days and submitted to a single dose (5 mg/kg) of the drug had a reduction in total and LDL cholesterol.[106] Taken together, the data from human trials and from animal studies support the use of resmetirom as a potent therapeutic agent to improve MASLD and MASH.

KB-141 (3,5-dichloro-4-(4-hydroxy-3-isopro-pylphenoxy) phenylacetic acid) is another THRβ-selective agonist with clinical relevance, as it has been shown to reduce cholesterol in rats whose diet was supplemented with cholesterol and cholic acid.[109] Besides the promising results found, KB-141 has not been investigated in human trials.[110]

Eprotirome (KB2115) is a TH analog that has a higher affinity for the THRβ isoform.[103] Studies in humans using this agonist have shown very promising results, lowering LDL-C and stimulating bile acid synthesis with no cardiac harm after 14 days of treatment.[111] A phase III trial was conducted to investigate the effects of eprotirome in patients with familial hypercholesterolemia at 2 different

TABLE 1 Summary of TH agonist's effects on the liver

Phase	Agonist	Outcomes	Adverse events	Reference
III	MGL-3196 (Resmetirom)	Patients with MASH presented a significant reduction of hepatic and serum triacylglyceride and serum LDL-C	Gastrointestinal (diarrhea and nausea)	[21]
IIb in progress	MB07811 (VK2809)	Reduction of LDL-C and hepatic lipid content in patients with primary hypercholesterolemia and fatty liver disease	No serious adverse side being reported	[40]
Terminated during phase III	KB2115 (eprotirome)	Patients with hypercholesterolemia presented a reduction in LDL-C levels	Potential to induce liver injury; cartilage damage in dogs	[112]
Terminated after phase I	GC-1 (sobetirome)	Cholesterol-lowering effects: LDL-C reduced by up to 41%	None reported (well tolerated by patients)	[105]
Preclinical testing	TG68	Reduction of liver weight, serum transaminases, circulating triglycerides, neutral fat accumulation, and ameliorated liver injury in a high-fat diet mouse model. Strong reduction of MASH in a very short time exposure (2–3 wk)	Lack of toxicity in extrahepatic organs/tissues such as heart and kidney	[115]

Abbreviation: MASH, metabolic dysfunction–associated steatohepatitis.

doses (50 and 100 μg); the trial was planned to last between 52 and 76 weeks. However, it was terminated after 6 weeks due to parallel studies in dogs showing cartilage damage caused by eprotirome administration. During the 6 weeks of treatment, eprotirome decreased the levels of LDL-C and triglycerides[112] (ClinicalTrials.gov identifier: NCT01410383).

VK2809 (formerly known as MB07811) is a prodrug that undergoes first-pass hepatic extraction and requires cytochrome P450 cleavage to generate the negatively charged THRβ agonist VK2809A. In an obese mouse model induced by diet, MB07811 decreased cholesterol and both serum and hepatic triglycerides.[40] The deficiency of glucose-6-phosphatase, an enzyme that catalyzes the final step of gluconeogenesis and glycogenolysis, leads to the accumulation of glucose-6phosphate (*G6pc*), which increases the levels of glycogen and triglycerides in the liver. Studies conducted in G6pc-deficient mice treated with VK2809 for 4 days showed that the THRβ agonist decreased the levels of triglycerides through restoration of autophagy, mitochondrial biogenesis, and β-oxidation of FA.[113] A phase II trial was conducted for VK2809, showing that it is a promising candidate for the treatment of MASH due to its beneficial effects on decreasing LDL-C and hepatic lipid content in patients with primary hypercholesterolemia and MASLD compared to placebo patients in a 12-week treatment. Its use has been demonstrated to be safe and well tolerated with no serious adverse effects reported (ClinicalTrials.gov identifier: NCT02927184). Currently, VK2809 is being investigated in a phase IIb trial (ClinicalTrials.gov identifier: NCT4173065).

Recently, a novel halogen-free THRβ-selective agonist IS25 and its prodrug TG68, using GC-1 as a scaffold compound, was reported.[114,115] In vitro analysis revealed that both IS25 and TG68 have minimal to no toxicity and decrease total lipid accumulation into lipid droplets with an effect comparable, or even higher, than equimolar doses of T3. In vivo studies showed that the hepato-specificity of both compounds increased hepatocyte proliferation similar to T3.[114] Studies conducted in a high-fat diet–induced MASH mouse model showed that administration of TG68 for 3 weeks reduced hepatic lipid accumulation and markers of liver injury with no adverse effects in the kidney and heart, and its efficacy was comparable to that of MGL-3196. This compound is an attractive candidate for the treatment of MASLD-MASH and it may be sufficiently safe for use in humans. However, further clinical studies are required to confirm these results.[115]

The use of THR agonists represent a continued area of study for treatment of liver metabolic diseases, such as MASLD and MASH. Currently, resmetirom is approved for use, and TG68 is a THRβ-selective agonist that is a promising drug candidate. However, it is critical to better understand the pathways these agonists are activating as TH acts at multiple levels in the liver and in contrasting ways.

CONCLUSIONS

It has long been known that TH regulates several liver metabolic pathways that are critical for maintaining hepatic homeostasis. Although the mechanisms by which TH acts are becoming clearer, the contrasting actions of TH on lipid metabolism, carbohydrate metabolism, and insulin sensitivity indicate that further studies are required. Numerous TH agonists have been studied for the treatment of liver disease, and resmetirom (MGL-3196) is currently approved for the treatment of certain hepatic disorders. However, different agonists have different side effects and outcomes. Thus, a better understanding of the role of TH on metabolic pathways of the liver will allow for greater insight into the mechanism by which TH analogs work and potentially provide new avenues for targeted therapy of MASLD (Table 1).

AUTHOR CONTRIBUTIONS

Lorraine Soares De Oliveira and Megan J. Ritter contributed to the conception and design, data interpretation in reviewed studies, drafting and revising of the article, and final approval of the version to be published.

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CONFLICTS OF INTEREST

The authors have no conflicts to report.

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