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Evaluation of the clinical relevance between thyroid hormones and hepatic lipid metabolism: A comprehensive review

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Abstract
Thyroid hormones have long been recognised to have a significant impact on the production and metabolism of cholesterol and fatty acids in the liver. In fact elevated blood levels of cholesterol and triglycerides along with non-alcoholic fatty liver disease (NAFLD) have been linked to hypothyroidism. The molecular control of hepatic lipid metabolism by thyroid hormones is now well understood because to developments in fields like cell imaging, autophagy and metabolomics. The main aspects of the control of lipogenesis, fatty acid β-oxidation, cholesterol production, and the reverse cholesterol transport system by direct thyroid hormone in both normal and disturbed thyroid hormone states are discussed and summarised in this review. These actions are mediated by thyroid hormone through autophagy, post-translational modifications, and transcription. In light of these advantageous impacts on lipid metabolism, thyroid hormone analogues and mimetics may prove therapeutic in the management of liver-related metabolic disorders, including hypercholesterolaemia and non-alcoholic fatty liver disease.

Keywords: Thyroid hormones, cholesterol and fatty acids, lipid metabolism, non-alcoholic fatty liver disease

Introduction
Thyroid hormones have a crucial role in controlling growth, development and metabolism in animals. Numerous metabolic processes controlled by thyroid hormones involve the anabolism and catabolism of macromolecules such as proteins, lipids and carbohydrates that influence energy balance under various dietary situations. In fact it has long been known that the thyroid hormones T_3 and T_4 directly affect the production and metabolism of fatty acids and cholesterol. Increased levels of LDL cholesterol and HDL cholesterol in the serum might be related with hypothyroidism, whereas their levels are lowered by thyroid hormone therapy and in hyperthyroidism [1]. Similarly hypothyroidism can result in higher blood triglyceride levels while hyperthyroidism causes the opposite effect [1]. Patients with obesity have previously benefited from high-dose T_3 treatment for hypercholesterolaemia and weight reduction [2]. While positive benefits were seen, major cardiac issues and loss of lean body mass prevented T_3 from being developed further as a treatment [2]. Target genes implicated in these homeostasis pathways are transcriptionally regulated which governs much of the effects of thyroid hormones on hepatic lipid homeostasis. However metabolite concentration, cellular energy status and post-translational modifications that take place after thyroid hormone's transcriptional effects can also regulate many of the enzymes, transporters, carrier proteins and cell-signalling proteins involved in hepatic lipid homeostasis [3, 4]. A more thorough understanding of the effects of thyroid hormones on lipids in the liver has been obtained through investigation of cell-signalling and metabolomic alterations in conjunction with transcriptional effects, despite the fact that much is known about lipid synthesis and metabolism at the biochemical and physiological levels. Thyroid hormone receptor (THR) independent effects of thyroid hormones on hepatic lipid metabolism, regulation of cholesterol biosynthesis and clearance, direct thyroid hormone-mediated effects on hepatic lipogenesis and lipid metabolism are all covered in this review. Additionally the potential use of thyroid hormones and thyroid hormone analogues for the treatment of hypercholesterolaemia and non-alcoholic fatty liver disease (NAFLD) is discussed.

There is evidence that thyroid hormone indirectly regulates hepatic lipid metabolism through the central nervous system which may have a significant physiological impact even though our main focus is on the direct effects of thyroid hormone on hepatic lipid metabolism [5, 6].

Hepatic lipid metabolism

Thyroid hormone receptors in hepatic lipid metabolism: The THRs are transcription factors that are reliant on ligands and belong to the nuclear hormone receptor family [7]. Two isoforms α (THRα) and β (THRβ) are encoded by the two THR genes, THRA and THRB respectively. Both isoforms are expressed in most tissues; THRβ is mostly expressed in the heart and bone whereas THRβ is primarily expressed in the liver [8, 9]. Because of nucleo-cytoplasmic shuttling, THRs are primarily nuclear, albeit there is a little residual pool of THRs in the cytoplasm [10]. In the absence of a ligand THRs can attach to the thyroid hormone response elements (TREs) of their target genes and repress the transcription of positively regulated genes by enlisting the help of a co-repressor complex that has histone deacetylase activity. Because to conformational changes in the THR resulting from ligand binding co-repressors are released and transcription is activated by recruiting a co-activator complex with histone acetyltransferase activity to the target gene promoter. Thyroid hormones can also control transcription by changing how other transcription factors function [11-13] (e.g., thyroid hormones can activate the forkhead box protein O1 (FOXO1)), modulating cell-signalling cascades through protein-protein interactions (e.g., THRβ can control phosphoinositide 3-kinase (PI3K) [14] or binding to proteins other than THRs (e.g., αvβ3 integrin) [15]. Studies on mice with a dominant negative mutation in Thrb (ThrbPV/PV) initially revealed the significance of THRβ in hepatic lipid metabolism. By the time they are 4-5 months old, these mice have enlarged livers with hepatic steatosis [16]. Increased peroxisome proliferator-activated receptor-γ (PPARγ) signalling and impaired THR-mediated fatty acid β-oxidation are linked to the ThrbPV/PV mice phenotype which results in lipid buildup in the liver [16]. Thyroid hormone and THRβ-specific ligands also lower the level of triglycerides in the liver which is in line with these findings [17, 18]. THRα appears to be involved in lipogenesis since in contrast mice harbouring the dominant negative mutation in the THRα gene locus, ThraPV/PV and THRα-null mice all showed lower liver weights and decreased lipid accumulation [16, 19]. Male mice with a dominant negative Pro398His mutation inserted into the Thra gene locus surprisingly show hepatic steatosis [20], in contrast to the ThraPV/PV-mutant animals. The Pro398His mutant receptor interferes with PPARα binding to its promoter response element, which results in reduced PPARα-mediated transcription of genes encoding proteins involved in fatty acid oxidation [20], which is the cause of this rise in steatosis. Differential recruitment of co-repressors may play a part in the variations in hepatic lipid metabolism between ThraPV/PV and ThrbPV/PV as well as the different THRα mutant and knockout animals. The exact mechanisms behind these differences are unknown. Significant alterations in hepatic lipid production and storage are observed in mice with double and single knockouts of the nuclear receptor co-repressor (NCOR1) and silencing mediator of retinoid acid and THR (SMRT; also known as NCOR2), particularly when NCOR1 is knocked out [21]. Apart from THR, the regulation of hepatic lipid metabolism can also be achieved by other significant regulators of intracellular thyroid hormone levels namely deiodinases [22] and thyroid hormone transporters [23].

Thyroid hormones and hepatic fatty acid uptake: The primary source of lipids for the liver, free fatty acids (FFAs) are produced by lipolysis of dietary fat and fat storage in white adipose tissue when thyroid hormones are stimulated. Protein transporters such as liver fatty acid binding proteins (L-FABPs), fatty acid translocase (FAT; also known as CD36) [24] and fatty acid transporter proteins (FATPs) allow FFAs to enter hepatocytes. According to a 2009 research, THRs [25] may modulate fatty acid transporters. Studies using radiolabelled fatty acid infusion have demonstrated that the presence of thyroid hormones increases the fatty acid uptake from triglyceride-rich lipoproteins in a tissue-specific manner. Specifically, hyperthyroidism has been shown to increase triglyceride-derived fatty acid uptake in oxidative tissues like liver and muscle while hypothyroidism has been shown to increase triglyceride-derived fatty acid uptake in white adipose tissue and decrease its uptake in liver [25]. Additionally in animal models of postnatal hypothyroidism, the levels of hepatic FAT and FABP expression are suppressed [26, 27]. While these findings suggest that thyroid hormones may play a significant role in controlling the liver's intake of free fatty acids, it is still unknown how exactly thyroid hormones affect this process.

Hepatic lipogenesis and triacylglycerol assembly: Exogenous FFAs in the bloodstream or intracellular FFAs produced by glycolysis and lipogenesis from glucose obtained from an excess of food consumption can both contribute to the formation of triglycerides. Known as "de novo lipogenesis," this process of converting glucose to fatty acids is closely controlled by hormones and dietary condition. Many important enzymatic activities, including as elongation and desaturation of fatty acid precursors, fatty acid biosynthesis, triacylglycerol synthesis and VLDL assembly are involved in de novo lipogenesis and the ensuing triacylglycerol synthesis [28]. Since they promote the transcription of several important genes involved in lipogenesis in rodents including fatty acid synthase (Fasn), acetyl-CoA carboxylase alpha (Acc1; also known as Acaca), malic enzyme (Me), and thyroid hormone-responsive Spot14 homologue (Thrsp; also known as Spot14), thyroid hormones are a well-known inducer of hepatic de novo lipogenesis. FFAs can be employed to create and repair cellular components packed into VLDL or stored as fat droplets after being esterified to triacylglycerol after production. Thyroid hormones bind to particular THR [29-32] to influence the expression of several of the genes involved in lipogenesis. Thyroid hormones not only directly regulate the expression of lipogenic genes but they also indirectly regulate the transcriptional regulation of hepatic lipogenesis through their effects on the expression and activities of other transcription factors including liver X receptors (LXRs), carbohydrate-responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein 1C (SREBP1C), all of which are essential for hepatic lipogenesis [33]. By attracting THRs to the promoters of these genes, thyroid hormones directly cause the hepatic cells to express the LXRs [34] and ChREBP [35] genes. There is no known mechanism by which thyroid hormone

regulates SREBP1C in humans. One study found that thyroid hormone negatively regulated Srebp1c transcription in mice through a putative negative thyroid hormone response element (nTRE) [36]; however, another group of researchers found that non-genomic thyroid hormone signaling also upregulates Srebp1c transcription [37]. Thyroid hormone did not result in a net increase in the amounts of triacylglycerol [38] in the mouse hepatic cells despite increasing the expression of genes involved in de novo lipogenesis. The primary cause of this lack of increase is thyroid hormone-induced upregulation of FFA metabolism; however, thyroid hormone-induced downregulation of the essential desaturase enzyme stearoyl-CoA desaturase 1 (SCD1) as seen in humans may also be involved [39]. Although the exact method by which thyroid hormones downregulate SCD1 in people is unknown, it appears to happen in a way that is independent of TRE [39]. Likewise, glycerol-3-phosphate acyltransferase 3 (GPAT3) [40], required for triacylglycerol production in rat hepatocytes has decreased activity in response to thyroid hormones. Additionally, thyroid hormones lower rat liver levels of apolipoprotein B100 (Apo B100), which lowers the synthesis of VLDL and LDL [41]. Triglyceride levels in human serum are normal or slightly lower in hyperthyroidism and normal or higher in range for the condition of hypothyroidism [1, 42]. As evidenced by the fact that levels of HDL are elevated in hypothyroidism due to the reduced activity of cholesteryl ester transfer protein (CETP) and hepatic lipase 1, thyroid hormones also influence the relative quantities of circulating lipoproteins. Thyroid hormones appear to reduce hepatic sphingolipid and phospholipid species production in addition to their effects on neutral lipids and triacylglycerol. A 2005 study shown that thyroid hormones boost the livers of rats' de novo production of sphingolipids [43]. On the other hand, we discovered by metabolomics analysis that thyroid hormone therapy inhibits the hepatic sphingolipid synthesis in rats given a high-fat diet [44]. Moreover the intracellular concentrations of several phospholipid species including cardiolipin [45], phosphatidylcholine and phosphatidylserine can be changed by thyroid hormones.

Lipolysis and hepatic fat oxidation: Thyroid hormones promote lipogenesis but with hyperthyroidism [46], fatty acid metabolism outpaces fatty acid synthesis resulting in a net decrease in total hepatic triglycerides. Thyroid hormones are responsible for the mobilization, breakdown and β-oxidation of fatty acids, which results in an elevated rate of fatty acid metabolism overall. Thyroid hormones particularly boost lipophagy, hepatic lipases and mitochondrial oxidation of fatty acids three of the main mechanisms by which the liver reduces steatosis. Thyroid hormone's catabolic effects on hepatic lipids are mainly caused by free fatty acid (FFA) mobilization from stored triacylglycerol and subsequent β-oxidation. Cytosolic lipases' enzymatic actions influence the release of FFAs from hepatocytes' triacylglycerol stores [47]. Adipose triglyceride lipase (ATGL; also known as PNPLA2) and hepatic lipase are the two main cytosolic lipases in the liver. Thyroid hormone levels have an impact on hepatic lipase expression and activity [48]. Thyroid hormone replacement treatment can restore the decreased hepatic lipase activity linked to hypothyroidism in both humans and animals [49]. It is less evident how thyroid hormones affect the expression and function of ATGL in hepatic cells. Nonetheless, a 2015 research did imply that thyroid hormones promote ATGL recruitment to lipid droplets in order to promote lipolysis [50]. The AZGP1-encoded zinc-α2-glycoprotein promotes lipolysis in humans and causes mice's body fat to decrease [51]. It is noteworthy that hepatic cells express more zinc-α2-glycoprotein when thyroid hormones are present possibly because this activity also contributes to the lipolytic effect of thyroid hormones [52].

Regulation of lipophagy by thyroid hormones: Together with the cytosolic lipases, lysosomal acid lipase/cholesteryl ester hydrolase (LAL) is another important regulator of hepatic triacylglycerol lipolysis [53]. Lipophagy which is an autophagic mechanism is responsible for delivering triacylglycerols to lysosomes [54, 55]. This particular kind of autophagy entails autophagosomes consuming the triacylglycerol that is stored in the fat droplets which is then transferred to lysosomes for hydrolysis and breakdown into free fatty acids (FFAs) via autophagosomal-lysosomal fusion [54, 55]. In both human hepatic cells and mouse liver, thyroid hormones increase the quantity of lipid-laden autophagosomes and lysosomes in a THR-dependent manner [56]. Furthermore, the suppression of autophagy and lipophagy *in vivo* significantly lowers the acylcarnitine flow generated by thyroid hormones and ketogenesis which is the last stage of β-oxidation [56]. While the exact process by which thyroid hormones induce lipophagy remains unclear, it is possible that the activation of β-trophin (C19orf80; ANGPTL8) by thyroid hormones serves as a prerequisite for the enlistment of autophagic apparatus to triacylglycerols that are kept in fat droplets [57]. This observations imply that thyroid hormones also trigger lysosomal biogenesis by suppressing the activity of the mammalian target of rapamycin complex 1 (MTORC1) and triggering the transcriptional activity of transcription factor EB, which is known to regulate lipophagy [58] and regulates the expression of numerous genes encoding proteins involved in autophagy and lysosomal genes. Additionally thyroid hormones stimulate NAD-dependent protein deacetylase sirtuin 1 (SIRT1) to reduce FOXO1 acetylation and phosphorylation. These post-translational changes raise FOXO1's nuclear localization and transcriptional activity, which in turn stimulates the expression of many autophagy-related genes [59].

Effects of thyroid hormones on peroxisomal fat oxidation: Shortening very long-chain fatty acids (>16 carbon atoms) allows mitochondria to further metabolize them and this is one of the main roles of peroxisomal β-oxidation. For many years, scientists have understood that thyroid hormones control the quantity and degree of peroxisomal enzyme expression [60-66]. Nevertheless, it is still unknown how thyroid hormones control the creation and activity of peroxisomes.

Regulation of mitochondrial fatty acid oxidation by thyroid hormones: The primary locations for the metabolism of fatty acids in the liver, mitochondria are also well-known sites for thyroid hormone action [67]. Coordinated signals from the nuclear and mitochondrial genomes [68] are used by thyroid hormones to control mitochondrial biogenesis and function in hepatocytes. Transcription factor A, mitochondrial (mtTFA) axis [68],

nuclear respiratory factor 1 (NRF1), PPARγ co-activator 1α (PGC1α) and transcription factor A are the main targets of thyroid hormone-induced nuclear control of mitochondrial content. It is well recognized that thyroid hormones raise PGC1α protein levels. PGC1α functions as a co-transcriptional regulatory factor inducing mitochondrial biogenesis by activating NRF1 to enhance mtTFA expression [68]. THRs have been found to be localized within mitochondria and to influence transcription from the mitochondrial genome [69], in addition to the PGC1α-NRF1-mtTFA axis. Carnitine O-palmitoyltransferase 1, liver isoform (CPT1-Lα) is the enzyme that limits the rate of mitochondrial β-oxidation. It is driven transcriptionally by thyroid hormones in hepatocytes [70] and inhibited by malonyl-CoA, which is produced by acetyl-CoA carboxylase during the production of fatty acids. In 2013 one study showed that PGC1α activity and CPT1A mRNA expression are regulated by thyroid hormone-mediated SIRT1 activation [71]. Thyroid hormones also control the expression of the CPT1A gene by enhancing PPARα signaling in the hepatic matrix [12]. Notably, PPARα is necessary for the stimulation of fibroblast growth factor 21 (FGF21), a protein that controls the breakdown of fat in the liver, by thyroid hormones [72]. Other mitochondrial enzymes required for fatty acid β-oxidation such as mitochondrial uncoupling protein 2 (UCP2) [75], pyruvate dehydrogenase kinase isoform 4 (PDK4) [74], and medium-chain acyl-CoA dehydrogenase (MCAD) [73] are also expressed more when thyroid hormones are present. Furthermore our group's findings indicates that PGC1α controls mitochondrial β-oxidation and thyroid hormone-induced CPT1-L expression which is regulated by oestrogen-related receptor-α (ERRα; also known as ESRRA). Thyroid hormones not only promote mitochondrial activity and fatty acid β-oxidation but they also facilitate lipophagy by eliminating damaged mitochondria caused by reactive oxygen species (ROS) resulting from elevated oxidative phosphorylation. In 2015 we demonstrated that thyroid hormones preserve the hepatic mitochondria's quality by mitophagy [76], the autophagic elimination of mitochondria. The production of ROS by thyroid hormone-mediated oxidative phosphorylation triggers a signaling cascade that involves Ca^{2+}, calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2), and 5′-AMP-activated protein kinase (AMPK). Serine/threonine-protein kinase ULK1, a crucial mitophagic protein, is activated upon activation of this signaling cascade and translocates into the mitochondria. ULK1 begins mitochondrial clearance [76] and attracts autophagy-related proteins or ATG proteins, which are necessary for the development of nascent autophagosomes. Furthermore, because thyroid hormones stimulate both processes of hepatic mitophagy and mitochondrial biogenesis for this they appear to be related [76, 77]. The preservation of a healthy mitochondrial pool that can withstand enhanced lipid processing brought on by thyroid hormones is ensured by the close relationship between mitochondrial turnover and activity.

Cholesterol biosynthesis and clearance

The body needs baseline serum cholesterol levels to satisfy its regular needs for cellular synthesis and thyroid hormones assist in maintaining these levels. By promoting cholesterol production, export (Mostly as VLDL and LDL), reverse transport from peripheral tissues, hepatic reuptake via LDL receptors (LDLRs) and conversion into bile acids in the liver, thyroid hormones control blood cholesterol levels [78]. Thyroid hormones stimulate the expression of farnesyl pyrophosphate synthetase (Fdps) and hydroxymethylglutaryl-CoA reductase (Hmgcr) in rats to encourage the liver's production of cholesterol [79]. Additionally, scavenger receptor class B member 1 (SRB1) and Apo A1 gene and protein expression are substantially induced by thyroid hormones increasing cholesterol efflux from peripheral organs to HDL in the reverse cholesterol transport pathway [80, 81]. Moreover thyroid hormones can boost CETP activity [82] to raise HDL metabolism. Hepatic LDLRs are stimulated to improve cholesterol clearance which is the main mechanism by which thyroid hormones lower blood cholesterol levels in rats [81]. SREBP2 which is transcriptionally controlled by thyroid hormones [83] in both humans and rats also controls LDLR. Moreover thyroid hormones have the ability to upregulate the transcription of LDLR-related protein 1 (LRP1), a lipoprotein implicated in the clearance of VLDL [84] and chylomicron remnants in both mice and humans. Thyroid hormones lower the expression of Apo B protein, the main apolipoprotein in LDL and increase the expression of rat cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme that converts cholesterol into bile acids in the reverse cholesterol transport pathway in the liver in order to further lower serum levels of LDL cholesterol [85, 86]. Furthermore thyroid hormones can directly and independently of their effects on LXRs [87] stimulate the transcription of the mouse ATP-binding cassette subfamily G member (Abcg5/Abcg8) complex gene, which in turn promotes the excretion of bile acids in the liver and intestines, the final stages of the reverse cholesterol transport pathway. Lastly thyroid hormones may employ microRNAs (miRNAs) to control blood cholesterol levels in addition to transcriptionally regulating genes implicated in bile secretion, reverse cholesterol transport and cholesterol synthesis [88]. As a result human miR181d is expressed in response to thyroid hormones and this in turn reduces the production of CDX2 a transcription factor that activates sterol O-acyltransferase 2 (SOAT2). The preferred form of cholesterol in low-density lipoproteins (LDLs) cholesterol esters [89] is created by the conversion of cholesterol to SOAT2. This example of thyroid hormones using miRNAs suggests that thyroid hormones may decrease blood cholesterol levels through a mechanism other than TRE-mediated action.

Non-transcriptional effects

The transcriptional control of target genes by THRs binding to TREs and the recruitment of co-activators to enhance RNA polymerase binding to the basal transcriptional protein complex was formerly thought to be the only mechanism of action of thyroid hormones. Interestingly T_3 and T_4 have biological effects without the need for THRs to bind to DNA or even for THRs to exist [90, 91]. Consequently T_3 uses a non-genomic method to activate the serine/threonine-protein kinase (AKT) signaling pathway PI3K-RACα92. T_3's control over FASN expression has been linked to this signaling pathway. The fact that PI3K and extracellular signal-regulated kinase 1 (ERK1) inhibitors block T_3-mediated stimulation of FASN expression further implies the existence of other non-transcriptional mechanisms that regulate hepatic lipogenesis by thyroid hormones [32].

Thyroid hormones can also control the metabolism of hepatic lipids by triggering the Ca^{2+}-AMPK and cAMP-protein kinase A (PKA) pathways [93-95]. Apart from T_3 and T_4, the capacity of 3, 5-diiodothyronine, a derivative of thyroid hormone to control hepatic lipid metabolism through non-THR-mediated signaling has been well investigated [96]. Research conducted both *in vivo* and *in vitro* demonstrates that 3, 5-diiodothyronine suppresses the lipogenic pathways and promotes fatty acid oxidation in hepatocytes [97-103]. Interestingly 3, 5-diiodothyronine directly stimulates SIRT1, which causes PGC1α to be deacetylated and its transcriptional activity to be activated. These results in the induction of the genes needed for fatty acid oxidation [104]. In order to promote lipid mobilization from fat droplets 3, 5-diiodothyronine also modifies the activity and location of hepatic lipases [50]. Furthermore 3, 5-diiodothyronine improves lipid metabolism in a rat model of familial hypercholesterolemia by lowering blood levels of LDL cholesterol through an LDLR-independent mechanism [86]. As of right now there is no proof that reverse T_3 controls transcription through nuclear THRs or affects metabolism cell signaling or any other non-transcriptional processes.

TSH and hepatic lipid metabolism

While a drop in thyroid hormone levels in the blood is assumed to be the cause of hypothyroidism-associated enhanced hepatosteatosis, investigations have shown that high serum levels of TSH also bind to TSH receptors in the liver to control lipid metabolism. Studies on *in vivo* rodents demonstrate that hepatocytes express TSH receptors which are activated by TSH to cause hepatosteatosis via SREBP1C [105]. Moreover TSH inhibits hepatic bile acid production through the SREBP2-hepatocyte nuclear factor 4α (HNF4α)-CYP7A1 signaling pathway [106]. Furthermore via raising AMPK-mediated phosphorylation of HMGCR to block HMGCR function, TSH suppresses the synthesis of cholesterol [107]. Taken together these results lend credence to the idea that TSH can control hepatic lipid and cholesterol homeostasis. Nevertheless because TSH is concurrently reduced in the serum *in vivo* research verifying TSH's direct action, separate from thyroid hormone is highly ambiguous.

Metabolic diseases of the liver

Thyroid hormone effects on hypercholesterolaemia

We have known that human thyroid hormone status and LDL cholesterol levels are inversely correlated since the early 1950s [108]. Additionally people with hypothyroidism see improvements in their lipoprotein and lipid profiles when they take thyroid hormone supplements [109]. Early research on the thyroxine enantiomer dextrothyroxine and levothyroxine had encouraging results in lowering serum levels of low-density lipoprotein (LDL) cholesterol; however these trials were stopped because to substantial side effects including damage to the heart, bones, and muscles [110-112]. However these investigations yielded encouraging findings that prompted the creation of thyroid hormone mimetics that are selective for liver and THR isoforms as potential lipid-lowering agents [113, 114]. In 1986, 3, 3-dibromo-3′-pyridazinone-1-thyronine (L-94901), the first liver-selective thyromimetic was identified. In hypothyroid rats this chemical lowers cholesterol without negatively affecting the heart [115]. In a similar vein three more compounds (CGH-509A, CGS-23425, and T-0681) have demonstrated effectiveness in reducing serum levels of LDL cholesterol [116, 117]; yet, there hasn't been a concerted effort to develop these compounds for clinical application.

Table 1: Thyroid hormone analogues and mimetics and their biological effects

Thyroid hormone analogues and mimetics	Biological effects	Species	References
L-94901	Lowers cholesterol	Mouse	[115]
CGH-509A	Lowers cholesterol	Rat	[117]
CGS-23425	Lowers cholesterol	Rat	[117]
T-0681	Lowers cholesterol	Mouse	[116]
DITPA	Lowers cholesterol	Human	[118]
GC-1 (sobetirome)	Lowers cholesterol, triglyceride, blood glucose, adipose tissue and atherosclerosis	Mouse	[119-121]
KB-141	Lowers cholesterol, triglyceride, adipose tissue and blood glucose	Monkey, rat and mouse	[122]
KB2115 (eprotirome)	Lowers cholesterol and triglyceride	Human	[123]
MGL-3196	Lowers cholesterol and triglyceride	Human	[124]
MB07811	Lowers cholesterol, triglyceride and blood glucose	Human	[126]
3,5-Diiodothyronine	Lowers blood glucose and triglyceride and improves hepatic insulin resistance	Rat	[44, 103]

The first THR-selective thyromimetic that shows a somewhat greater affinity for THRβ than THRβ is 2, 5-Diiodothyropropionic acid (DITPA). DITPA treatment was shown to moderately lower blood levels of total cholesterol and LDL cholesterol in individuals with congestive heart failure during a 6-month clinical study [118]. As a member of the first generation of highly focused THRβ agonists, GC-1 sometimes referred to as sobetirome, lowers blood levels of triglycerides and cholesterol in obese animal models [119]. A 2-week GC-1 therapy regimen decreased blood levels of LDL cholesterol in healthy subjects by as much as 41% in a phase I study [120]. Moreover GC-1 lowers the amount of cholesterol in plaques that form on the walls of the aorta arteries in animals lacking apolipoprotein E (APOE) [121]. Another thyromimetic that is specific to THRβ, KB-141 also lowers cholesterol plasma levels in rats and primates mostly via activating the reverse cholesterol pathway [122]. Phase III studies with the THRβ-specific analogue KB2 [115], also called eprotirome have shown comparable benefits on cholesterol plasma levels making it the first thyroid hormone mimic intended for the treatment of dyslipidemia. In individuals with hypercholesterolemia, eprotirome further lowers LDL cholesterol, triglycerides and lipoprotein levels when combined with statin therapy [123]. MGL-3196 is a different THRβ-specific thyromimetic that is presently undergoing a phase I trial [124] to treat hypercholesterolemia. Liver-selective prodrugs and their metabolites that bind to THR with a high affinity constitute another class of thyromimetics. Some of these substances are activated by hepatic CYP450 enzymes producing the short-lived active

metabolites. As a result the majority of this family of thyromimetics' thyromimetic effects is limited to the liver minimizing negative effects on non-hepatic organs. In rabbits, dogs, and monkeys [125], one such medication MB07811 is useful in lowering blood levels of LDL cholesterol and total cholesterol. A phase Ib clinical study [126] that supported the drug's safety was followed up by a phase II trial [127]. While most mild hypothyroidism patients show little to no abnormalities in blood triglyceride and VLDL1 levels, hypertriglyceridemia is a condition that some severe hypothyroidism patients experience. Thyroid hormone mimics can reduce hypertriglyceridemia, a known risk factor for atherosclerosis that is independent of LDL cholesterol levels in a manner similar to how levothyroxine replacement treats hypothyroidism. GC-1 lowers blood triglyceride levels in hypothyroid and normal animals by >50-60% [128]. In a similar vein KB-141 and MB07811 both significantly lower blood triglyceride levels in both normal and obese mice [17, 129].

Effects of thyroid hormones in Nonalcoholic Fatty Liver Disease (NAFLD)

With a prevalence of 30% or more among people in both industrialized and developing nations NAFLD is a worldwide epidemic [130]. As a hepatic manifestation of the metabolic syndrome non-alcoholic fatty liver disease (NAFLD) is linked to the emergence of additional metabolic risk factors including hyperlipidemia, coronary artery disease, and type 2 diabetes mellitus [131]. The term non-alcoholic steatohepatitis (NASH) refers to a group of liver diseases that include hepatosteatosis, an excessive buildup of lipids in the hepatocytes that is initially benign but progresses to a more advanced stage with inflammation. NASH eventually leads to fibrosis, which is accompanied by increased inflammation, apoptosis and liver tissue scarring (Cirrhosis) [132]. Hepatocellular carcinoma is another condition that NAFLD patients are more likely to develop [133]. NAFLD is becoming the most prevalent reason for liver transplants in the US due of its long-term complications [133]. Numerous global epidemiological studies demonstrate a negative correlation between serum thyroid hormone levels and the prevalence of non-alcoholic Failed Family Disease (NAFLD) [134, 135]. In a cross-sectional study of 878 elderly Chinese euthyroid individuals, serum-free T_4 levels were considerably lower in Asian patients with NAFLD than in control patients (11.12±1.43 pmol/l versus 11.58±1.47 pmol/l; $p< 0.001$) [136]. Another investigation found a strong concentration-dependent relationship between NAFLD and subclinical hypothyroidism even when the levels were within the upper-normal range of TSH [137]. The substantial clinical association between NAFLD and overt hypothyroidism is confirmed by the fact that overt hypothyroidism is a risk factor that is even more strongly related to NAFLD and independent of other established metabolic risk factors [137, 138]. Children with obesity and elevated TSH [139] had more severe hepatosteatosis than obese children with normal TSH [139] in pediatric populations. Notably two studies conducted in 2014 and 2016 show an inverse relationship between blood levels of free T_3 & free T_4 and the free T_3: free T_4 ratio. Additionally TSH levels are linked to NAFLD in the general population even in those who fall within the reference range for adults with euthyroid conditions [140, 141]. Apart from the adverse impacts of reduced thyroid hormone levels in the blood on hepatic lipid homeostasis it is plausible that elevated thyroid hormone levels in and of them might facilitate the onset of non-alcoholic fatty liver disease (NAFLD) by inducing lipogenesis in the liver [105]. Furthermore individuals with NAFLD [142-144] may have lower intrahepatic thyroid hormone concentrations and thyroid hormone signaling in their livers. Studies conducted over the past three decades indicate that intracellular fatty acids reduce thyroid hormone activity (THR activity), however the sources of such resistance to thyroid hormone action in the liver remain unclear. Furthermore, there is a strong correlation between blood thyroid hormone levels and the levels of type 1 iodothyronine deiodinase (DIO1), the enzyme that changes T_4 into T_3 in the liver. Thus by lowering the conversion of T_4 to T_3 reduced DIO1 expression and activity may cause intrahepatic hypothyroidism. Notably, individuals with advanced NASH [146] have been observed to have lower serum T_3 and higher reverse T_3. Additional mechanisms that may influence thyroid hormone signaling in non-alcoholic fatty liver disease (NAFLD) include decreased intrahepatic concentrations of thyroid hormone transporters, thyroid hormone (THR) and nuclear co-activators of THR. Notably, hepatosteatosis in NAFLD can be decreased by exogenous thyroid hormones, thyroid hormone analogs and a new glucagon-thyroid hormone hybrid molecule [147, 148]. Reduced intrahepatic concentrations of thyroid hormones may be present in just a portion of NAFLD patients due to the multitude of variables, including food, endocrine state and gene polymorphisms that contribute to the disease's development. Additional research on blood indicators of thyroid hormone impact on hepatic function such as ferritin, cholesterol, acylcarnitines and sex hormone-binding globulin may yield useful instruments to assess intrahepatic thyroid hormone status [149, 150]. Thyroid hormone analogues have shown promise in lowering lipid buildup in animal models of non-alcoholic fatty liver disease (NAFLD) in a number of preclinical investigations. A synthetic derivative of thyroid hormone GC-1 binds to THRβ1 with the same affinity as T_3 and preferentially in an isoform-specific manner. Like T_3 GC-1 keeps rats fed a diet that causes NASH from going into hepatosteatosis and even reverses it. In these same animals GC-1 also reduces blood triglyceride levels, liver weight and the liver weight: body weight ratio. Since GC-1 medication reduces the rise in blood levels of aspartate transaminase (AST) and alanine transaminase (ALT), it also reduces lipoperoxidation and liver damage in addition to hepatic lipid accumulation [148]. According to these results, GC-1 if it meets the necessary safety criteria is a great thyromimetic for the treatment of non-alcoholic fatty liver disease. Rats and mice with hepatic steatosis can benefit from MB07811, an oral THRβ-specific agonist that acts on the liver [17]. By raising mitochondrial respiration rates, hepatic β-oxidation and the expression of genes related to β-oxidation, MB07811 lowers hepatic triglycerides. Rats with NAFLD can also benefit from the thyromimetic KB2 [115, 151]. Furthermore, individuals on statins had a decrease in blood cholesterol levels after 12 weeks of KB2 medication indicating that KB2 is a safe long-term treatment since the study's authors did not report any cardiac or bone toxicity [123]. Regretfully, despite these positive outcomes, KB2's clinical studies were stopped because a concurrent 12-month dosage study in dogs revealed detrimental effects on cartilage [152]. These results

imply that thyroid hormone analogs have side effects beyond those associated with heart and bone. Before starting clinical trials for different medicines, researchers must carefully check for side effects in preclinical research. A 2016 study revealed the creation of a hybrid molecule that lowers hepatosteatosis in NAFLD without having a negative impact on the heart or bones. This compound combines thyroid hormone and glucagon [147]. Because this chemical targets a particular tissue while the other hormone has intracellular action it has created an interesting new avenue for synthetic bi-hormonal treatment of metabolic disorders. The thyroid hormone metabolite 3,5-diiodothyronine is also capable of lowering hepatosteatosis and hepatic insulin resistance indicating that it is a promising option for the treatment of non-alcoholic fatty liver disease (NAFLD), especially as it does not appear to have the systemic side effects of T_3 and T_4 [44]. Interestingly, compared to 7.2% of individuals with normal liver function, 15% of patients with NASH had hypothyroidism [153]. According to a 2012 research, individuals with NASH were more likely to have hypothyroidism than people with NAFLD who did not have NASH and hypothyroidism also raised the risk of NASH [154]. A further investigation revealed that those who were subclinically hypothyroid as well as those who were hypothyroid had higher rates of NASH and advanced fibrosis [155]. These data imply that in addition to hepatosteatosis, hypothyroidism and subclinical hypothyroidism also raise the risk of NASH [142]. Despite the fact that these data point to a possible protective benefit of thyroid hormones against NASH, no interventional research on humans or animals have shown those thyroid hormones or their analogues may stop or reverse the development of NASH. In humans, a higher risk of hepatocellular carcinoma has been linked to decreased thyroid hormone levels [156]. Thyroid hormones have also been demonstrated to have anti-neoplastic properties in liver cancers [157]. Individuals with NASH are at risk for developing hepatocellular carcinoma and a high frequency of THR mutations has been seen in these individuals [158]. According to the dominant theory, THRs function as tumour suppressors by promoting TGFβ signaling, cyclin-dependent kinase 2 (CDK2), cyclin E, and WNT signalling. Cell cycle arrest at the G1 phase is believed to result from the activation or inhibition of various signaling pathways [159]. Thus, it is proposed that the presence of mutant THRs blocks the suppressive action of thyroid hormones. Thyroid hormones may not be able to prevent hepatocellular carcinoma in animals or individuals with NASH and fibrosis, according to research that conclusively shows this.

Discussion and Conclusion

Thyroid hormones and THRs play a crucial role in preserving proper hepatic lipid homeostasis and this understanding has grown with advances in our knowledge of the cellular and molecular mechanisms of fatty acid and cholesterol generation and metabolism. We now possess a deeper, more mechanistic understanding of the lipid derangements that can arise in hypothyroidism and hyperthyroidism. Some regulatory points in the signaling pathways that govern serum and liver triglyceride and cholesterol levels may be influenced by thyroid hormones; as a result, they may be suitable targets for thyroid hormone analogs or other medications. Furthermore, the hypothalamic-pituitary-thyroid axis' adequacy is characterized by blood levels of free T_3 & free T_4 and TSH; however, these values may not precisely represent intrahepatic thyroid hormone levels, which can be lowered in NAFLD patients' livers. Recent research indicates that bi-hormonal thyroid hormone analogs or analogues specific for THRβ or THRβ in the liver may be useful as treatments for metabolic diseases such NAFLD and hypercholesterolemia. While basic scientists and clinicians have long been interested in the effects of thyroid hormones on the metabolism of fatty acids and cholesterol in the liver, the new insights into these areas provided in this review offer more compelling reasons and treatment options for hepatic metabolic disorders that can be treated with thyroid hormone or thyromimetic drugs.

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