

REVIEW

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Thyroid hormone action and liver disease, a complex interplay

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Abstract

Thyroid hormone action is involved in virtually all physiological processes. It is well known that the liver and thyroid are intimately linked, with thyroid hormone playing important roles in *de novo* lipogenesis, beta-oxidation (fatty acid oxidation), cholesterol metabolism, and carbohydrate metabolism. Clinical and mechanistic research studies have shown that thyroid hormone can be involved in chronic liver diseases, including alcohol-associated or NAFLD and HCC. Thyroid hormone action and synthetic thyroid hormone analogs can exert beneficial actions in terms of lowering lipids, preventing chronic liver disease and as liver anticancer agents. More recently, preclinical and clinical studies have indicated that some analogs of thyroid hormone could also play a role in the treatment of liver disease. These synthetic molecules, thyromimetics, can modulate lipid metabolism, particularly in NAFLD/NASH. In this review, we first summarize the thyroid hormone signaling axis in the context of liver biology, then we describe the changes in thyroid hormone signaling in liver disease and how liver diseases affect the thyroid hormone homeostasis, and finally we discuss the use of thyroid hormone-analog for the treatment of liver disease.

Abbreviations: Abcg, ATP-binding cassette subfamily G member; ALD, alcohol-associated liver disease; APOA1, apolipoprotein A1; C3M, matrix metalloproteinase-degraded C3; CDX2, caudal-type homeobox 2; CETP, cholesteryl ester transfer protein; CHREBP, carbohydrate-responsive element-binding protein; CYP7A1, cholesterol 7 α -hydroxylase; DKK, Dickkopf; DNL, *de novo* lipogenesis; ERK, extracellular signal-regulated kinase; FABP, fatty acid-binding protein; FAT/CD36, fatty acid translocase; FDPS, farnesyl diphosphate synthase; FFA, free fatty acid; FOXO1, forkhead box protein O1; fT3, free-T3; fT4, free-T4; GLUT, glucose transporter; HDAC3, histone deacetylase 3; HIF, hypoxia inducible factor; HL, hepatic lipase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; iPLA2 β , calcium-independent membrane phospholipase A2; LDLR, LDL receptor; LPL, lipoprotein lipase; LXR, liver X receptor; MCT, monocarboxylate transporter; NCoR, nuclear receptor co-repressor; NTIS, nonthyroidal illness syndrome; PCAF, P300/CBP-associated factor; PDFF, proton density fat fraction; PDK, pyruvate dehydrogenase kinase; PGC1 α , PPAR γ coactivator 1 α ; PI3K, phosphatidylinositol-3-kinase; PPAR, peroxisome proliferator-activated receptor; PRO-C3, N-terminal type III collagen pro-peptide; rT3, reverse T3; RXR, retinoid X receptor; SHBG, sex hormone-binding globulin; SIRT1, NAD-dependent protein deacetylase sirtuin 1; SMRT, silencing mediator for retinoid or thyroid hormone receptors; SOAT2, sterol O-acyltransferase 2; SRB1, scavenger receptor class B member 1; SRC, steroid receptor coactivator; SREBP, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; T2, 3,5-diiodo-L-thyronine; T3, 3,5,3'-triiodothyronine; T4, 5',3,5,3'-tetraiodothyronine; TBG, thyroid hormone binding globulin; TH, thyroid hormone; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone; TTR, transthyretin; UDP, uracil-diphosphate.

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INTRODUCTION

Thyroid hormone action is involved in virtually all physiological processes and plays a critical role in development, growth, and metabolism.^[1]

In normal physiology, the hypothalamus-pituitary-thyroid axis functions as a classical feedback system. From the hypothalamus, thyrotropin-releasing hormone (TRH) is released to the pituitary portal system promoting the secretion of thyroid-stimulating hormone (thyrotropin or TSH). TSH, in turn, drives the thyroid gland to secrete into circulation 2 hormones derived from the amino acid tyrosine, 5',3,5,3' tetraiodothyronine (thyroxine, T4) and 3,5,3'-triiodothyronine (T3), with T4 being the main product of the thyroid gland.^[2] Notably, while T3 is the active hormone, the majority of T3 derives from the peripheral conversion of T4 into T3.^[3] T4 conversion in peripheral tissues produces the active T3 and reverse T3 (rT3), which is thought to be metabolically inactive.^[4] Additionally, the secretion of leptin from the adipose tissue provides an important modulation of the hypothalamus-pituitary-thyroid axis by stimulating the release of TRH from the hypothalamus.^[5]

T3 is involved in the regulation of several physiological activities, including cellular metabolic rate, cardiovascular and digestive functions, muscle development and activity, brain development, and bone turnover.^[6,7] Owing to the pleiotropy of thyroid hormones (TH) signaling, thyroid disease affects multiple systems including cardiovascular, hepatic function, carbohydrate, and lipid metabolism.^[1]

Hepatic activity and thyroid signaling are closely intertwined. T3 and T4 are essential for regulation of hepatic function, while in turn the liver is involved in metabolism of TH.^[8] Moreover, TH action may play an important role in the pathogenesis of several hepatic disorders, such as alcohol-associated liver disease (ALD) and NASH, which may evolve into cirrhosis and HCC.^[9]

On the other hand, there is evidence that TH action can exert beneficial actions in some liver diseases^[10,11] and several TH analogs have been developed to target liver disease.

The aims of this review are to provide a primer of TH signaling axis in the context of liver biology, to describe the changes in TH homeostasis during liver disease, to describe how liver diseases affect TH homeostasis, and to review the use of TH-analogu directed to the treatment of liver disease.

PRIMER ON THE THYROID HORMONE AXIS

In physiologic states, the thyroid gland produces ~100 mcg of T4 and only 8–10 mcg of T3.^[7]

Extrathyroidal TH conversion is regulated by iodothyronine deiodinases-1, iodothyronine deiodinases-2, iodothyronine deiodinases-3 (D-1, D-2, and D-3, respectively),^[12] which are seleno-enzymes whose expression and activities vary among different tissues. Interestingly, intrathyroidal TH conversion is regulated by D-1 and D-2, accounting for a significant component of the T3 released by the thyroid gland.^[13,14]

These enzymes regulate circulating and intracellular TH levels, thus allowing for a time- and tissue-specific modulation in TH concentration in circulation and in the tissues, ultimately regulating the availability of active hormones for thyroid hormone receptors (TRs) binding.^[15,16]

The deiodinases are responsible for the activation of T4 to T3, inactivation of T4 to rT3, and for the conversion of rT3 and T3 to 3,5-diiodo-L-thyronine (T2), the latter are important steps in the recycling of iodine (Table 1).

D-1 catalyzes inner-ring and outer-ring deiodination, D-2 catalyzes exclusively outer-ring deiodination (activating pathway converting T4 into T3), and D-3 catalyzes only inner-ring mono-deiodination (inactivating pathway). The transcription of both D-1 and D-3 is positively regulated by T3, while thyroid hormone promotes the degradation of D-2.^[17]

Hepatic D-1 has a prominent role in the peripheral metabolism of thyroid hormone by promoting the conversion of the prohormone T4 into its active metabolite T3. Moreover, D-1 is responsible for the disposal of rT3.

TABLE 1 Characteristics of the deiodinase enzymes activation and inactivation of TH, physiological tissue distribution, and changes in activity in relation to thyroid hormone status

Type	D-1	D-2	D-3
Action	T4→T3→T2; T4→rT3→T2; rT3→T2	T4→T3/rT3→T2	T4→rT3; T3→T2; rT3→rT2
Tissue	Liver, kidney, thyroid	Brain, pituitary gland, skeletal muscle, brown Fat	Brain, placenta, skin, fetal tissue, hypoxic tissues
Hypothyroidism	↓ (kidney, liver)	↑	↓
Hyperthyroidism	↑ (thyroid, liver)	↓ (except in the thyroid)	↑

Abbreviations: T2, 3,5-diiodo-L-thyronine; T3, 3,5,3'-triiodothyronine; T4, 5',3,5,3' tetraiodothyronine; rT3, reverse T3; TH, thyroid hormone.

More than 99% of the circulating pool of TH is bound to plasma proteins. The large discrepancy between free and bound components as well as between T4 and T3 concentrations is reflected by the normal reference ranges for free (0.8–1.8 ng/dL) and total (4.9–10.5 mcg/dL) T4 and free (2.3–4.2 pg/mL) and total (76–181 ng/dL) T3.

But it can be rapidly exchanged to the “free” pool for entry into cells. The thyroid hormone-binding proteins comprise thyroid hormone-binding globulin (TBG, also known as SERPINA7), a glycoprotein synthesized in the liver with a half-life of 5 days in plasma.^[18] Hepatic nuclear factor-binding sites hepatocyte nuclear factor (-1, -3) homeobox (- α , - β) determine SERPINA7 transcription in hepatocytes.^[19] TBG has by far the highest affinity for T4, the result of which is that TBG binds 68% of serum T4 and 80% of serum T3.^[20]

Another thyroid hormone-binding protein is transthyretin (TTR, or thyroxine-binding prealbumin), a 55-kDa homo-tetrameric protein comprising 127 amino acids with an extended β -sheet conformation^[21,22] synthesized in liver, with a half-life of 2 days in plasma. The average concentration of TTR in serum is 0.25 mg/mL and corresponds to a maximal binding capacity of approximately 300 μ g T4/dL.^[23] TTR has high affinity but relatively low-binding capacity with respect to TBG so it binds to about 10% of T4 and T3.^[20]

Human serum albumin (HSA) is also a thyroid hormone-binding protein synthesized by the liver. HSA is a 66.5 kD protein composed of 585 amino acids.^[24] After synthesis by hepatocytes, it is rapidly excreted into blood at the rate of about 10–15 g/d. HSA has low-affinity and high-binding capacity for TH and binds the remaining 10%–20% of serum T3 and T4.^[20]

Mutations in TH binding proteins (mostly TBG and HSA) result in significant changes in total thyroid hormone concentrations with minimal changes in their free components.^[25,26]

Thus, thyroid homeostasis is dependent on a close interaction between the thyroid axis and liver synthetic function.

GENOMIC PATHWAYS OF THYROID HORMONE ACTION

T3 and T4 enter cells from the extracellular fluid by diffusion and by means of transmembrane transporters; intracellular T3 binds to TR to exert their biological effects (Figure 1).^[27]

TH action is exerted primarily through nuclear TR, which are members of the superfamily of hormone-responsive nuclear transcription factors.^[15]

T3 binds nuclear TR located on thyroid hormone response elements within promoter regions of genes downstream of TH/nuclear TR^[28] and induces the transcription or repression of target genes.^[1]

The 2 primary isoforms of TR, α and β , are differentially expressed during development and in adult tissue.^[15,29] Alternative splicing from TR α and TR β genes generates TR α 1, TR α 2 isoforms and TR β 1, TR β 2, respectively.^[30]

Human hepatocytes express an equal amount of TR α 1 and TR β 1 isoform, conferring the relative dominance of TR β 1 when compared to other tissues (myocardium, bone, and adipose tissue) where the TR α 1 is more prevalent. The transcriptional effect of TH is exerted by means of formation of homodimers or heterodimers with nuclear receptors, such as retinoid X receptor, other coactivator receptors, like vitamin D receptor, other retinoic acid receptor subtypes and peroxisome proliferator receptor. TR-cognate receptors heterodimers generally function as partner with several transcription factors to regulate target genes modulating the chromatin acetylation or methylation. Lack of ligand causes the binding of corepressors to the transcriptional complex, ultimately inhibiting the transcription of target genes (Figure 1).^[31,32]

NONGENOMIC PATHWAYS OF THYROID HORMONE ACTION

TH can exert their function not only by genomic but also through nongenomic pathways such as integrin α v β 3, which has been identified as a membrane TH receptor that activates both the phosphatidylinositol-3-kinase (PI3K) and extracellular signal-regulated kinase (ERK)-1/2 pathways.^[33] TH binds integrin α v β 3 at 2 sites, S1 and S2, triggering several intracellular pathways and gene transcription (Figure 1).^[34–36]

T4 preferentially binds the α v β 3 S2 site and activates ERK-1/2, which modulates intracellular protein trafficking from the cytoplasm to nucleus and can also induce the sodium proton exchanger (Na⁺/H⁺). The stimulation of the PI3K/Akt/protein kinase B pathway is another nongenomic TH-mediated action. T3 binds exclusively to α v β 3 S1 site, and the T3- α v β 3 S1 and the resulting PI3K activation promotes in turn trafficking of TR α 1 from the cytoplasm to the nucleus. This generates an indirect increase in target gene expression, such as hypoxia inducible factor-1 α . In the cytoplasm, nongenomic T3 signaling rapidly induces the PI3K pathway and initiates downstream gene transcription.

Table 2 describes the molecular pathways and function of genomic and nongenomic TH regulation as discussed by Chi et al.^[37] Of note, it is not clear whether nongenomic T3 signaling plays a clinically relevant role in humans.^[38]

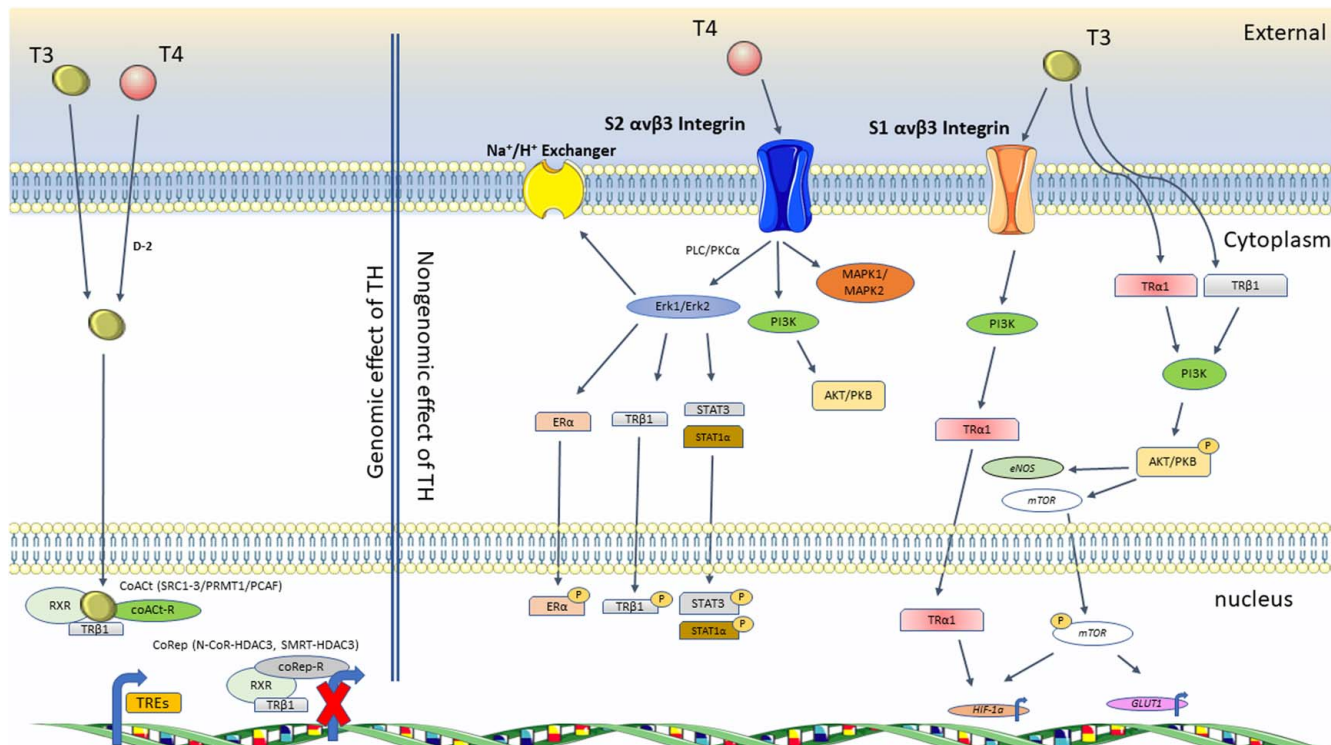


FIGURE 1 Genomic and nongenomic pathways of TH action. Genomic effects of TH (left side of figure). TR dimerizes with other nuclear receptors (in this case RXR) to recruit a set of coactivators forming a mediator-like complex that increase histone acetyltransferase activity (SRCs, PCAF) increasing the transcriptional activity of target genes. In the absence of thyroid hormone, TR/nuclear receptors dimers can recruit corepressors (NCoR, SMRT) with HDAC3 activity, reducing the transcriptional activity of target genes. SRCs and PCAF are histone acetyltransferases and PRMT1 is a histone methyltransferase. Nongenomic effect of TH (left side of figure). TH affect multiple physiological activities by means of interactions with S1 and S2 $\alpha\beta 3$ integrin. The interaction between T4 and S2 $\alpha\beta 3$ integrin, leading to regulation of PI3K, MAPK1/2, and ERK-1/2 by means of PLC and PKC α , promoting phosphorylation of nucleoproteins and modulation of intracellular protein trafficking. ERK-1/2 activity can activate the sodium proton exchanger (Na $^+$ /H $^+$) in the plasma membrane. S1 $\alpha\beta 3$ integrin recognizes T3 and activates the PI3K pathway leading to direct trafficking of TR $\alpha 1$ from the cytoplasm to the nucleus and transcriptional activity of the target gene, HIF-1 α . Furthermore, activation of the PI3K/Akt/PKB pathway can be rapidly stimulated by means of T3 interactions with TR $\beta 1$ or TR $\alpha 1$ and initiates downstream target gene transcription including HIF-1 α and GLUT1. Abbreviations: ERK, extracellular signal-regulated kinase; HDAC3, histone deacetylase 3; HIF, hypoxia inducible factor; NCoR, nuclear receptor co-repressor; PCAF, P300/CBP-associated factor; PI3K, phosphatidylinositol-3-kinase; RXR, retinoid X receptor; SMRT, silencing mediator for retinoid or thyroid hormone receptors; SRCs, steroid receptor coactivator; TH, thyroid hormone; TR, thyroid hormone receptor.

THYROID HORMONE ACTION ON LIVER FUNCTION

In the liver, TR β is the predominant TR isoform, and mutations can cause a liver-specific phenotype.^[39–41] Thus, the liver is an ideal target for therapeutic intervention with isoform-specific TH agonists (see the Thyromimetics section).^[42–44]

TH plays a role in hepatic lipid homeostasis and they have direct effects on both cholesterol and fatty acid synthesis and metabolism. It has long been appreciated that the liver is the major metabolic site for cholesterol and triglycerides; TH promotes low-density lipoprotein receptor (LDLR) expression and activity of lipid-lowering liver enzymes, resulting in a reduction in LDL levels.^[45,46]

The expression of apolipoprotein A1, a major component of HDL, is also increased by TH.^[47]

A deeper, mechanistic understanding of the role of TH in hepatic metabolism was made possible thanks to the generation of TR knock-in mouse models. Using a

dominant negative mutation in TR β (Thr β PV/PV) mice, Araki and colleagues established the role of THR β in hepatic lipid metabolism. The authors showed that lack of TR β causes hepatic steatosis and hepatomegaly within a few months from birth. In this Thr β PV/PV mouse model, the decrease in fatty acid oxidation drives the lipid accumulation in the liver. On the other hand, mice expressing the same mutation in TR α (Thr α PV/PV) and TR α -null showed decreased lipogenesis, weight loss, and reduced hepatic accumulation of lipids.^[39] In the next section, we will discuss in more detail how TH is involved in hepatic lipid metabolism and in cholesterol metabolism.

LIPID METABOLISM AND HEPATIC THYROID HORMONE ACTION

TH action modulates the lipolysis of fat stores from white adipose tissue, which generates circulating free

TABLE 2 Summary of the genes/signals regulated by genomic or nongenomic action of TH/THR signal axis. Black arrows represent genes/signals that are upregulated (upward arrow) or downregulated (downward arrow) by TH

	Molecular function	Gene/signal name (↑increase, ↓decrease)
Genomic regulation by TH/TR	Transcriptional coregulator of THR	↑ SP1, p53, Oct-1, GHF-1 ↓ CTCF, LCOR
	Autophagy regulator	↑ DAPK2, Betatrophin
	Cell cycle regulator	↓ UHRF1, STMN1, Mir-214 BC200
	Apoptosis regulator	↑ TRAIL
	Metastatic regulator	↑ BSSP4, LCN2, mir-21 ↓ mir-130b
Nongenomic regulation by TH/TR	Membrane receptor of TH	↑ integrin $\alpha\beta$ 3
	Signal transducer	↑ Src kinase, PI3K/Akt, p-ERK1/2, mTOR/p70S6K, eNOS
	Transcriptional factor	↑ Estrogen receptor, STAT3, HIF1- α , β -catenin
	Metabolic regulator	↑ GLUT1, PFKP, MCT4
	Na-K-ATPase	↓ KCNH2
	Apoptosis regulator	↓ FOXO1, BCL2L11

Abbreviations: FOXO1, forkhead box protein O1; GLUT, glucose transporter; HIF, hypoxia inducible factor; MCT, monocarboxylate transporter; PI3K, phosphatidylinositol-3-kinase; STAT3, signal transducer and activator of transcription 3; TH, thyroid hormone; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone. Adapted from Davis et al.^[47]

fatty acids (FFAs), the major source of lipids for the liver. FFAs can also derive from "de novo" lipogenesis (DNL) and from hydrolysis of dietary triglycerides (Figure 2).^[48]

Most of hepatic lipid homeostasis and some enzymatic carrier proteins, transporter and cell-carrier protein are under control of TH.^[49,50]

TH increases liver uptake of FFAs through a tetrameric plasma membrane protein complex consisting of plasma membrane fatty acid-binding protein, caveolin-1, calcium-independent membrane phospholipase A2, and fatty acid translocase.^[51]

T3 can induce hepatic lipolysis of triacylglycerol stored as lipid droplets which can subsequently be hydrolyzed into FFAs by classical lipase and lipophagy,^[52–55] which involves the engulfment of triacylglycerol stored in the fat droplets by autophagosomes, followed by autophagosomal-lysosomal fusion that delivers the triacylglycerols to lysosomes for degradation and hydrolysis into FFAs.^[54,55]

FFAs are then shuttled into mitochondria where they undergo β -oxidation. The control action exerted by T3 takes place through positive regulation of NAD-dependent protein deacetylase sirtuin 1, forkhead box protein O1,^[50] and by increasing the activity of hormones like FGF21,^[56] various coactivators or nuclear receptors (such as peroxisome proliferator-activated receptor (PPAR)- α 45 and PPAR γ coactivator 1 α (PGC1 α) and target the transcription of genes such as carnitine palmitoyltransferase 1A, acyl-CoA dehydrogenase medium chain, pyruvate dehydrogenase kinase (PDK), isoenzyme 4, and uncoupling protein 2.^[57–61]

TH action increases the number of lipid-laden autophagosomes and lysosomes in a TR-dependent manner both in mice and human hepatocytes.^[62]

De novo lipogenesis involves a number of proteins and enzymes, including sterol regulatory element-binding

protein (SREBP) 1C, thyroid hormone-responsive spot14 homolog, FA synthase, acetyl-CoA carboxylase 1, liver X receptor, carbohydrate-responsive element-binding protein (CHREBP), and malic enzyme, which are upregulated directly and indirectly by T3.^[63–65] After their synthesis, FFAs are typically esterified to triacylglycerol, which can be packaged into VLDL, stored as fat droplets or used to make and/or repair cellular constituents.

TH promotes hepatic cholesterol synthesis (Figure 3) by increasing the expression of 3-hydroxy-3-methylglutaryl-CoA reductase and farnesyl diphosphate synthase.^[66]

Furthermore, TH is involved in the downregulation of gene expression of caudal-type homeobox 2 and sterol O-acyltransferase 2 by means of miR181d, resulting in inhibition of cholesterol ester formation by human hepatocytes.^[67]

Conversely, TH also induces protein and gene expression of apolipoprotein A1, scavenger receptor class B member 1 (SRB1) and sterol regulatory element-binding protein 2 (SREBP2), which then increase LDLR levels to increase cholesterol efflux from peripheral tissues to HDL through the reverse cholesterol transport pathway.^[68,69]

TH increases HDL metabolism by stimulating cholesteryl ester transfer protein activity to accelerate serum cholesterol clearance.^[70]

Cholesterol synthesis, mostly as VLDL, can be stimulated by TH starting with its precursor and acetyl-CoA.^[71]

In addition, the cholesterol uptake from peripheral tissue is indirectly mediated by TH. In fact, TH stimulates the lipoprotein lipase (LPL), which catabolizes the triglycerides-rich lipoproteins, and the hepatic lipase to decrease HDL particle size, resulting in higher

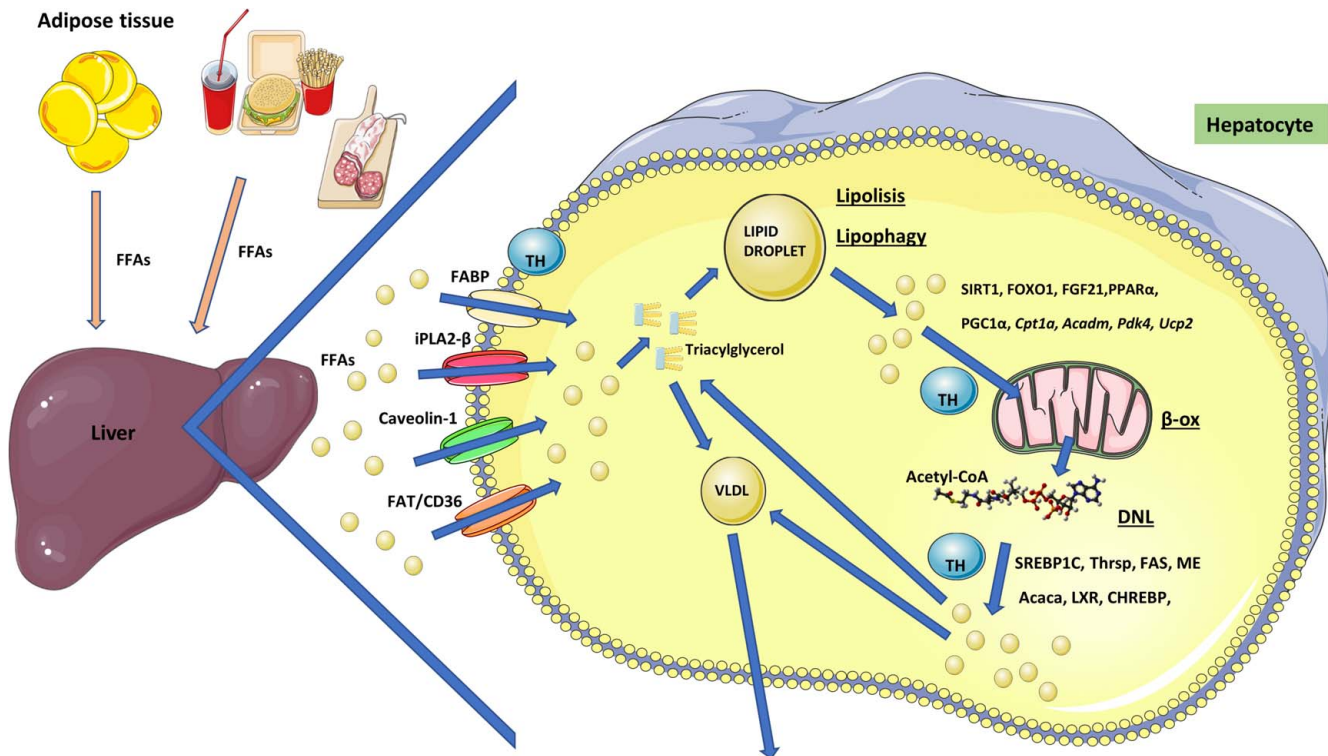


FIGURE 2 Hepatic FFAs metabolism and TH effect in hepatocytes. Thyroid hormone stimulates lipolysis from fat stores in white adipose tissue and from dietary fat sources to generate FFAs that enter the hepatic cells by means of protein transporters such as fatty acid-binding protein (FABP), calcium-independent phospholipase A2 Beta (iPLA2- β), caveolin-1, and fatty acid transporter (FAT/CD36). FFAs are typically esterified to triacylglycerol and subsequently packaged into VLDL for export or stored as intracellular lipid droplets. Triacylglycerol stored as lipid droplets can also be hydrolyzed back to FFAs by means of classic lipases and lipophagy by regulating transcription factors (SIRT1, FOXO1), various coactivators or nuclear receptors such as (PPAR α , FGF21, and PGC1 α) and target the transcription of genes such as *Cpt1a*, *Acadm*, *Pdk4*, and *Ucp2*. Thyroid hormone induces DNL by means of the transcription of several key lipogenic genes such as *Acaca*, *Fas*, *Me*, and *Thrsp*. In addition, thyroid hormone indirectly controls the transcriptional regulation of hepatic DNL by regulating the expression and activities of other transcription factors such as SREBP1C, LXRs, and ChREBP. Abbreviations: CHREBP, carbohydrate-responsive element-binding protein; DNL, *de novo* lipogenesis; FABP, fatty acid-binding protein; FAT/CD36, fatty acid translocase; FFA, free fatty acid; FOXO1, forkhead box protein O1; LXR, liver X receptor; PGC1 α , PPAR γ co-activator 1 α ; PPAR, peroxisome proliferator-activated receptor; SREBP, sterol regulatory element-binding protein; SIRT1, NAD-dependent protein deacetylase sirtuin 1; TH, thyroid hormone.

relative levels of lipid-poor apolipoprotein A1 in HDL that facilitates the cholesterol uptake.^[72,73] The cholesterol 7 α -hydroxylase expression, which converts cholesterol into bile acids in the reverse cholesterol transport pathway, is increased by TH.^[46,74]

In addition, TH increases the efflux of bile acids in both the liver and intestines, which are the last steps of the reverse cholesterol transport pathway, by stimulating ATP-binding cassette subfamily G member 5 and 8 gene transcription.^[75]

THYROID HORMONE ACTION ON HEPATIC CARBOHYDRATE METABOLISM

The liver plays a unique role in carbohydrate metabolism owing to its ability to both store and release glucose to minimize changes in serum glucose concentration between fed and fasted states. In healthy individuals,

the intake of a mixed meal results in modest hyperglycemia, accompanied by substantial storage of glycogen in the liver. In response to ingestion of glucose or a mixed meal and the resulting hyperinsulinemia and hyperglycemia, the fasting liver shifts from net output to net uptake of glucose.^[76]

Glucose enters the hepatocyte by means of the insulin-independent glucose transporter-2 and is phosphorylated by hexokinase isoenzymes to glucose 6-phosphate, which may follow several metabolic pathways; during the postprandial period, most glucose 6-phosphate is used to synthesize glycogen by means of the formation of glucose 1-phosphate and uracil-diphosphate (UDP)-glucose. Minor amounts of UDP-glucose are used to form UDP-glucuronate and UDP-galactose, which are donors of monosaccharide units used in glycosylation. A second pathway of glucose 6-phosphate metabolism is the formation of fructose 6-phosphate, which may either start the hexosamine pathway to produce UDP-N-acetylglucosamine or follow the glycolytic pathway to generate

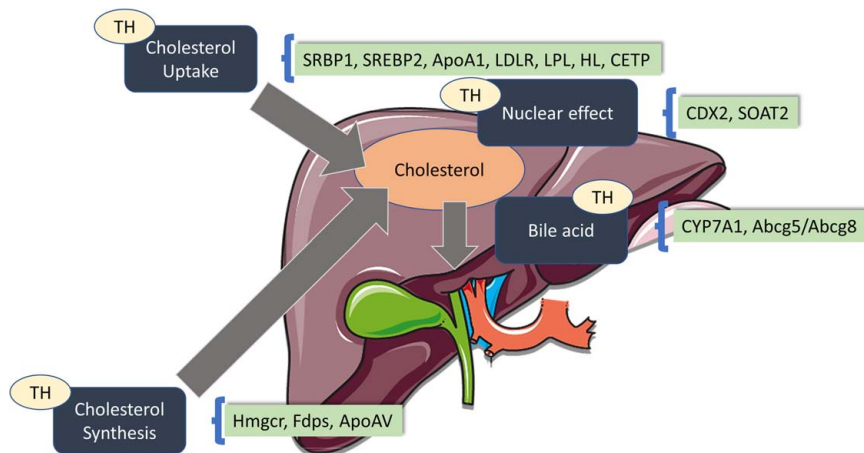


FIGURE 3 TH effect on cholesterol metabolism. TH increases the expression of HMGCR and FDPS to promote hepatic cholesterol synthesis. TH is involved also in the cholesterol uptake from peripheral tissue inducing the gene and protein expression of SRBP1, SREBP2, Apo A1, LDLR, CETP, LDLR, LPL, and HL. TH is also involved in the reverse cholesterol transport pathway increasing expression of CYP7A1. Furthermore, TH increases the efflux of bile by stimulating Abcg5/Abcg8 gene transcription. Additionally, TH can negatively modulate cholesterol ester formation by means of CDX2 and SOAT2. Abbreviations: Abcg, ATP-binding cassette subfamily G member; APOA1, apolipoprotein A1; CDX2, caudal-type homeobox 2; CETP, cholesteryl ester transfer protein; CYP7A1, cholesterol 7 α -hydroxylase; FDPS, farnesyl diphosphate synthase; HL, hepatic lipase; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; LDLR, LDL receptor; LPL, lipoprotein lipase; ; SOAT2, sterol O-acyltransferase 2; SRB1, scavenger receptor class B member 1; SREBP, sterol regulatory element-binding protein; TH, thyroid hormone.

pyruvate and then acetyl-CoA. Acetyl-CoA may enter the tricarboxylic acid cycle to be oxidized or may be exported to the cytosol to synthesize fatty acids when excess glucose is present within the hepatocyte. Finally, glucose 6-phosphate may produce NADPH and ribose 5-phosphate through the pentose phosphate pathway. In addition to metabolizing carbohydrates, the liver produces glucose to be released in circulation from glycogen breakdown, or by means of *de novo* synthesis using primarily lactate and alanine (gluconeogenesis), including the hexosamine pathway, the pentose phosphate pathway, and oxidative routes. Excess glucose is used to synthesize fatty acids in the liver. This unique ability of the human liver to store and release glucose is crucial to endure periods of fasting.^[77]

Centrally, TH action increases hepatic glucose production and reduces insulin sensitivity through a sympathetic pathway connecting the paraventricular hypothalamus to the liver and through glucagon hormone signaling.^[78]

In the liver, T3 positively modulates genes involved in glycogenolysis and gluconeogenesis.^[79] Increased deacetylation and activation of the master gluconeogenic transcription factor forkhead box protein O1 by NAD-dependent protein deacetylase sirtuin 1 is also stimulated by T3 leading to increase in gluconeogenesis.^[50] Indeed, 2 key enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxylase 1 and glucose-6-phosphatase are modulated by T3 in the liver.^[80,81] TH positively regulates PDK4 expression^[82] promoting gluconeogenesis. Moreover, TR β and CCAAT enhancer binding protein regulate the phosphoenolpyruvate carboxylase, which is an enzyme critical for glucose homeostasis.^[80]

Apart from regulating gluconeogenic gene transcription, increased alanine transport and inhibition of insulin signaling may also contribute to TH-induced hepatic glucose production. Ultimately, TH action results in an increase in hepatic gluconeogenesis and hepatic insulin resistance.

ROLE OF LIVER IN THE NONTHYROIDAL ILLNESS SYNDROME

Nonthyroidal illness syndrome (NTIS) also referred as “euthyroid sick syndrome” can be defined as any acute or chronic inflammatory condition not originating in the thyroid causing a perturbation in the serum concentrations of TH and TSH. NTIS is characterized by a low serum concentration of T3, normal or in some case reduced T4 serum concentration, and an increased serum concentration of rT3^[83] with normal or low TSH concentration. The pathophysiology of NTIS involves several organs, including the liver,^[84] where a variety of changes in deiodinases, TH transporters, and TR action have been observed.

With respect to the deiodinases, a healthy liver predominantly expresses D-1, with very low expression of D-3. The low serum concentration of T3 during NTIS has been ascribed to reduced activity of D-1, which is responsible for conversion of T4 to T3.^[85–87] Inflammatory states inhibit D-1 transcription causing a decrease in circulating T3 and accumulation of rT3, which are the hallmark of NTIS.^[6] Liver D-3 is differentially regulated during illness: acute inflammation in mice results in decreased D-3 levels^[85] but prolonged critical illness, and hypoxia both in patients and in rabbits, increase D-3.^[87,88]

Furthermore, a report indicated that serum from patients with NTIS inhibits T4 uptake, mediated in part by increased bilirubin and nonesterified fatty acids, which also inhibit T4 to T3 conversion.^[89] In systemically ill patients, nonesterified fatty acids levels rise in parallel with the severity of the illness.^[83]

During acute illness, the concentration of serum binding protein and the affinity of TH binding to transport proteins are altered. TBG levels may be increased while serum levels of TTR and albumin are decreased, especially during prolonged illness, resulting in a decrement of total T3 serum level.^[90]

Reduced expression of TRH in the hypothalamus appears to play a key role in the prolonged phase of critical illness, although the processes that trigger this upstream disturbance are somewhat unclear; a paradoxical increase in hypothalamic D2 activity leads to the suppression of TSH secretion.^[91]

Interestingly, TH transport in the human liver is differentially affected during illness: *MCT8* expression increases in prolonged critical illness compared to acute illness.^[4] This means that patients with the lowest T3 serum show the highest upregulation of *MCT8* mRNA. The positive correlation in patients between *MCT8* mRNA and low tissue T3 levels could suggest that the upregulated *MCT8* represents a compensatory mechanism to increase T3 levels in tissues while the circulating T3 concentrations are low.^[92]

Furthermore, hepatic *TR α* and *TR β* mRNA expression is differentially affected during illness, depending on severity and duration. In rodents during acute illness but not in chronic illness, liver *TR α* and *TR β* expression decrease.^[85,93] In contrast, biopsy studies performed in patients with chronic liver disease prior to liver transplantation indicated that *TR α* and *TR β* mRNA expression are increased in association with low serum T3 and T4 levels.^[94] However, in patients with a variety of chronic liver diseases, hepatic *TR α 1*, *TR α 2*, and *TR β 1* and T3-target gene expression were unchanged despite reduced serum TH levels.^[31]

The differential regulation of TH transporters, deiodinases, and THR expression in acute and chronic states of disease supports the concept that there is altered hepatic TH metabolism during NTIS. The clinical importance of NTIS is still not clear because this phenomenon may protect against the catabolic state associated with the underlying condition or represent a maladaptive response leading to a decreased delivery of TH to target tissues.

ALD AND THYROID HORMONE HOMEOSTASIS

Alcohol is one of the world's largest modifiable risk factors for disease and disability, affecting almost all organs and systems.^[95] Alcohol is metabolized by the

liver, which is the primary site of damage, and its abuse is the primary cause of several diseases, such as fatty liver, alcohol-associated hepatitis, and cirrhosis.^[9,16] In hepatocytes, cellular levels of TH are closely associated with ALD.^[96]

The hepatic dysfunction due to alcohol, in turn, affects thyroid function including hormone levels and gland size. In fact, a significant reduction in thyroid gland volume has been reported in patients with ALD.^[97–99] Alcohol causes a moderate suppression of serum T4 levels with more significant suppression of T3 levels in heavy drinkers. In addition, individuals with dependence to alcohol may present with features of NTIS,^[100,101] which correlates with the severity of liver dysfunction and mortality risk.^[102–104]

Papineni and colleagues conducted a prospective cohort study for 1 year on a group of 70 males aged 30–80 years with alcohol use disorder who had a regular alcohol intake of more than 60–80 g/d for the past 10 years. The authors investigated whether TH levels could be used as markers of ALD and assessed the changes in thyroid hormone levels with treatment and concluded that TH levels, particularly free-T3 (fT3) and free-T4 (fT4), should be evaluated in patients with chronic ALD. Additionally, the authors suggest that assessing free TH levels during the withdrawal and abstinent periods is important because decreased hormone levels may be associated with increase withdrawal symptoms and craving for alcohol.^[105]

Alcohol-induced liver steatosis is a highly prevalent liver pathology.^[106] The effects of TH on this condition have been partially studied in animal models, and preliminary observations suggested that a decrease in TH action, presumably by reducing cell metabolic rate and oxidative stress, may ameliorate necrosis and hypoxia in the liver.^[107,108]

Clinically, propylthiouracil, a thiourea-derivate antithyroid medication was tested in clinical trials in alcohol-associated hepatitis and cirrhosis to mitigate the presumed negative effects of excess of TH in the liver.^[109] Of note, propylthiouracil use is associated with hepatotoxicity particularly in the pediatric population, and it carries a FDA “black box.”^[110]

NAFLD AND THYROID HORMONE AXIS

Chronic liver disease is a major public health problem worldwide, estimated to affect up to one-third of the US population^[111] often in association with obesity and/or type 2 diabetes mellitus.^[112]

NAFLD is initiated by lipid accumulation in hepatocytes,^[113,114] which leads to a spectrum of liver dysfunction ranging from excess lipid storage (hepato-steatosis) to progressive NASH, that in turn increases the risk for cirrhosis and HCC.^[115] NAFLD is considered the hepatic

phenotype of the metabolic syndrome, associated with insulin resistance or established type 2 diabetes mellitus, increased visceral adiposity, overweight/obesity, dyslipidemia, and arterial hypertension^[116] and is associated with increased risk of cardiovascular, hepatic, and metabolic diseases. In the United States, NAFLD is recognized as one of the leading causes of chronic liver disease in adults^[117] and children,^[118] and has an estimated prevalence of 20%–40% in western countries.^[119]

As discussed, TH exerts important effects on hepatic lipid metabolism. In hypothyroid states, centrilobular hepatocytes have increased steatosis.^[120,121] These studies support the role of the thyroid axis in the development and progression of NAFLD, which often occurs in association with endocrine disorders.^[122,123]

Hypothyroidism has been proposed as a contributory mechanism in the pathophysiology of NAFLD,^[1,124] but to date, no human studies showed an association between circulating TH and histological features of NAFLD despite TH are crucial in the regulation of many hepatic metabolic processes^[125–128] and the transcription of several lipogenic genes, whose expression are altered in NAFLD.^[5,129]

While TH action in hepatocytes promotes a decrease in cholesterol and triglyceride levels, patients with NAFLD show elevated cholesterol, LDL, and triglycerides levels.^[130,131]

At the transcriptional level, many of the genes whose expression is altered in NAFLD^[132] such as genes regulating lipid synthesis (eg, *acetyl-CoA carboxylase 1*, *fatty acid synthase*, *diacylglycerol o-acyltransferase*) and mitochondrial β -oxidation (eg, *long-chain acyl-CoA dehydrogenase*, *hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha*, *UCP2*, *acyl-CoA oxidase*) are upregulated,^[133] potentially as a secondary compensatory mechanism to respond to the increased flow of substrate due to calorie overload. Of interest, these genes are positively regulated by TH as well.^[132] Furthermore, altered expression and activation of proinflammatory genes (eg *IL-1 receptor* family and genes regulating fibrotic responses (*TGF beta-1*, *FGFR2 receptor 2*) that may contribute to the development of NASH are also under the control of TH.^[134,135]

These observations have provided the rationale for therapeutic interventions with TH in preclinical models of NAFLD,^[136] as well a small clinical trial which showed that low-dose levothyroxine (synthetic T4) administration resulted in a significant reduction in hepatic fat content from baseline.^[137]

Observational and meta-analysis data linked TH and NAFLD. Several studies have investigated the association between either subclinical (ie, elevated TSH with normal TH levels) or overt hypothyroidism (elevated TSH with subnormal TH levels) and NAFLD. Data are conflicting: some studies indicated that hypothyroidism, mainly subclinical, was common, occurring in ~25% of

the individuals with imaging-defined or biopsy-proven NAFLD,^[9] other studies, however, failed to identify a significant association between hypothyroidism and NAFLD.^[138] In a large population-based cohort study conducted on 3144 euthyroid subjects, Chen et al^[139] found positive associations of ft3 levels and ft3/ft4 ratios with NAFLD in euthyroid women but not in euthyroid men.

In addition, a study conducted in children with obesity and NAFLD showed that adolescents with hepatic steatosis had elevated values for ft3/ft4 ratio. This finding is consistent with peripheral conversion of T4 to T3 due to increased deiodinase activity as a compensatory mechanism to increase energy expenditure to prevent excessive fat accumulation.^[140] Conversely, it is also possible that the shift to the right of the thyroid axis is driven by the adiposity resulting in elevated leptin levels, which in turn stimulate the hypothalamic release of TRH ultimately stimulating the thyroid axis.^[141] A significant positive relationship between TSH levels and hepatic steatosis, independent of age, sex, and stage of puberty was also observed in euthyroid severely obese children and adolescents. Higher TSH levels were associated with a greater degree of fatty infiltration, emphasizing the possible significance of subclinical hypothyroidism as a predictor of metabolic comorbidity.^[142] Collectively, the human data do not demonstrate whether the changes in circulating TH observed in NAFLD are causative or rather the consequence of obesity, which is associated *per se* with NAFLD.

The axiom that hypothyroidism is associated with fatty liver has been partly challenged by recent mouse model data. Experimental observations indicate that mice develop NAFLD when TH levels are mildly reduced but, counterintuitively, not when there is a severe reduction of TH levels. The disease process of hypothyroidism-induced NAFLD therefore appears to involve both intrahepatic and extrahepatic factors, with important differences between mild (subclinical) and severe hypothyroidism.^[143] Future mechanistic and clinical studies are needed clarify this emerging concept.

HEPATIC CANCER AND THYROID HORMONE SIGNALING

HCC is the fifth-most common form of cancer worldwide and one of the most prevalent causes of tumor-related mortality.^[144] HCC is linked to high mortality rates, and the majority (80%–90%) develop from cirrhotic livers.^[145]

Two case-control studies suggested that hypothyroidism represents a risk factor for HCC.

In the first study, Hassan et al^[146] observed an increased association between hypothyroidism and HCC in women,

independent of established HCC risk factors; in the second study, Reddy et al^[147] observed that hypothyroidism was more prevalent in patients with HCC of unknown etiology.

Furthermore, several studies indicate that disruption of TH signaling is involved in the development of HCC (Figure 4).^[146–148] Other studies have shown that mutated or truncated forms of TR α and TR β are expressed at high frequencies in human HCC (Figure 4).^[149,150] In rat models of HCC, T3/TR was shown to suppress the carcinogenic process. Intriguingly, *in vivo* studies showed that a short treatment with T3 accelerated the regression of chemically induced hepatic preneoplastic lesions in rats subjected to the resistant-hepatocyte (R-H) model of hepatocarcinogenesis.^[151] The authors observed that only 50% of the rats exposed to repeated cycles of T3 developed HCC, with no sign of lung metastases.^[152] An anti-pneoplastic effect of T3 was also observed in the choline-devoid methionine-deficient nutritional model.^[153] Interestingly, T3 has also been recognized as a strong inducer of hepatocyte proliferation in rats and mice.^[154,155] The potent mitogenic effect of T3 was demonstrated not only for intact liver, but also during the regenerative response in rodents after 70% partial or 90% subtotal hepatectomy.^[156,157] Hepatic mitogenic effects of TH were shown also in the absence of activation of other transcription factors, such as *activator protein 1*, *NF- κ B*, or *signal transducer and activator of transcription 3*, while *c-fos*,

c-jun, or *c-myc* proto-oncogenes and cyclin D1 mRNA and protein levels were increased.^[155]

Collectively, these results suggest a possible protective effect of T3 against malignant transformation in conditions characterized by an impaired regenerative ability (such as aged livers) or when a rapid growth stimulation of the liver is required.^[158,159] On the other hand, Chen et al^[160] have shown that T3/TR signaling upregulates members of the urokinase plasminogen activator system, which increases hepatoma cell metastasis. Among them, urokinase plasminogen activator is highly expressed in multiple types of malignancies, including liver, lung, colon, stomach, breast, and ovarian cancers.^[161] It is important to note that low levels of PGC1 α , whose transcription is positively regulated by TH signaling, were associated with poor prognosis in HCC (Figure 4). Moreover, PGC1 α suppressed metastasis of HCC cells by inhibiting the Warburg effect by means of the Wnt/ β -catenin/PDK1 axis, in a PPAR γ -dependent manner (Figure 4). Collectively, the data indicate that TH-mediated PGC1 α may act as a candidate therapeutic target for patients with HCC.^[162] Moreover, *in vitro* and *in vivo* models indicate that the activation of PPAR γ can inhibit HCC cell proliferation and tumor growth by inducing cell cycle arrest and apoptosis by means of the regulation of a panel of downstream effector molecules, such as p18, p21, p27, p53, and caspase-3/7 and caspase-8, respectively (Figure 4).^[163] β -catenin expression in HCC is correlated with poor

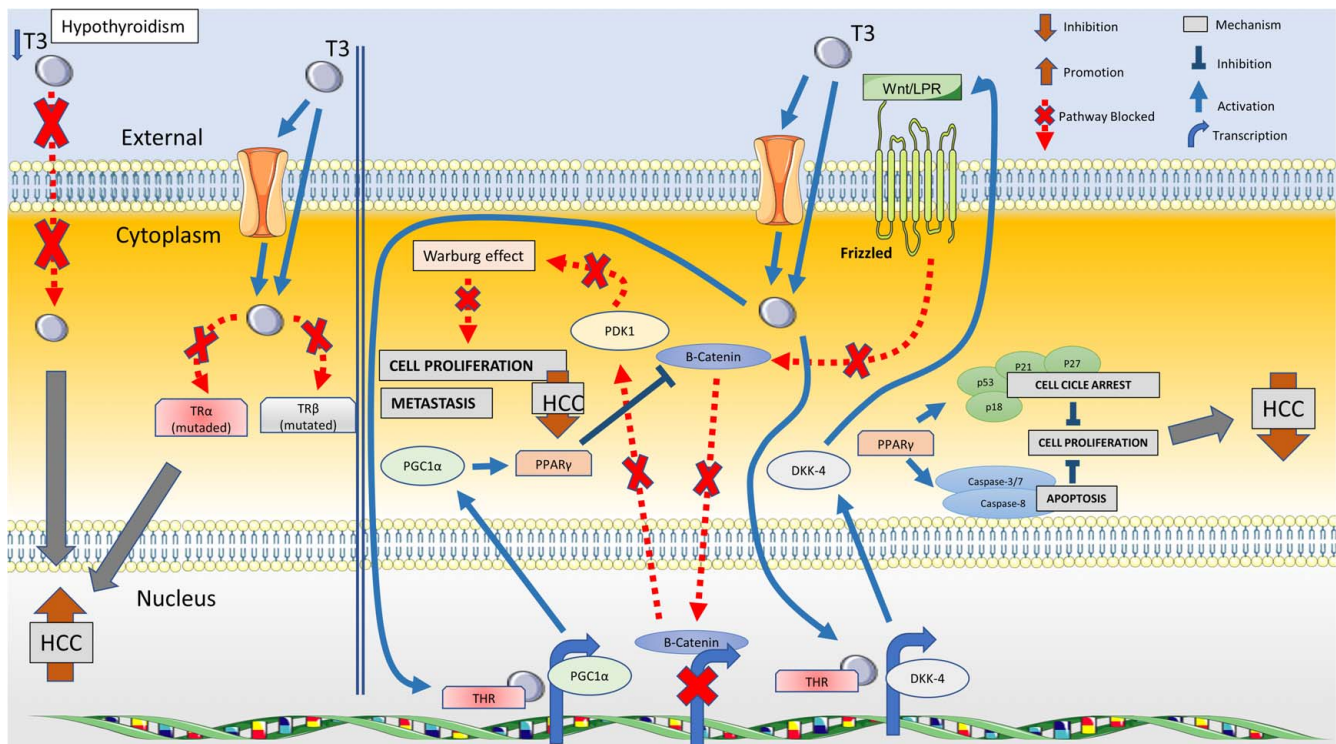


FIGURE 4 TH action promotes differentiation and inhibits neoplastic proliferation in hepatocytes, while hypothyroidism and somatic mutations in the TR α and TR β genes are involved in HCC progression. TH action is also involved in HCC inhibition by means of Wnt/ β -catenin/PDK1/PGC1 α or Wnt/ β -catenin/DKK-4 pathway. TH signaling indirectly activates PPAR γ , that is also involved in HCC inhibition by means of cell cycle arrest and apoptosis. Abbreviations: DKK, Dickkopf; PDK, pyruvate dehydrogenase kinase; PGC1 α , PPAR γ co-activator 1 α ; PPAR, peroxisome proliferator-activated receptor; TH, thyroid hormone; TR, thyroid hormone receptor.

prognosis^[164,165] but TH can suppress the Wnt/ β -catenin pathway by means of Dickkopf-4 induction, leading to inhibition of hepatoma cell proliferation and metastasizing (Figure 4).^[166] Conversely, the proteolytic enzyme cathepsin H is induced in TR-expressing hepatoma cells on T3 treatment and its upregulation results in increased cell migration and activation of matrix metalloproteinase or ERK activation.^[163]

In aggregate, TH signaling in the liver has a mostly protective effect against neoplastic transformation and progression.

THYROID HORMONE AND THYROID HORMONE ANALOGS IN NAFLD AND HCC

The development of TH analog compounds started in the 1980s when 2 compounds, L-94901 and CG-23425, were shown to reduce cholesterol levels in rats without unfavorable effects on the heart.^[167]

In the late 1980s and early 1990s, crystallography studies provided new information on TR structure and function. The crystal structure of the ligand-binding pocket of the TR α and TR β revealed that they varied only in 1 amino acid residue (Asn331, TR β , Ser277, and TR α) and that the selectivity originated from this difference.^[167–169] These discoveries allowed to improve the design of TR-targeting drugs, in particular for TR β 1-selective thymomimetics, and a number of different ligands were subsequently developed: (3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)-phenoxy) acetic acid (GC-1) known as sobetirome, 3-[(3,5-dibromo-4-(4-hydroxy-3-(1-methylethyl)-phenoxy)-phenyl)-amino-3-oxopropanoic acid] known as eprotirome, KB2115, (3,5-dimethyl-4-(4'-hydroxy-3'-isopropylbenzyl)phenoxy] methylphosphonic acid known as MB07344/VK2809, and 2-[3,5-Dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yl)oxy]phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile, also known as MGL-3196 and resmetirom.

TH could be useful in the treatment of hyperlipidemia and NAFLD. However, supraphysiologic TH levels trigger significant end-organ side effects, such as sarcopenia, osteoporosis, cardiac arrhythmia, and heart failure.^[170] Conversely, some TH derivatives may exert beneficial actions without considerable side effects.^[10,11,170]

As discussed, TH and thymomimetics regulate lipid parameters through numerous associated pathways, such as bile acid synthesis, reverse cholesterol transport, and cholesterol reabsorption by means of LDL receptors.^[167]

THYROMIMETICS

Sobetirome. Sobetirome, developed in 1998, was the first synthetic TR β agonist.^[171] It accumulates predominantly in the liver and binds all major TR β isoforms with similar

affinity to T3 binding preferentially to TR β relative to TR α , and was initially studied as a lipid-lowering compound able to stimulate hepatic pathways with minimal side effects due to its hepatic tropism.^[172] Sobetirome binds selectively to TR β 1 with half maximal EC₅₀ of 0.16 vs. 0.58 μ M for TR α 1,^[173] exhibiting gene-specific actions relative to the native TH form.^[6] Sobetirome (48 nmol/kg) reduces HDL cholesterol and VLDL triglyceride levels in euthyroid mice, reduces HDL cholesterol and triglyceride levels, increases hepatic HDL receptors and stimulates bile acid synthesis in hypercholesterolemic mice.^[174]

In the choline-methionine deficient diet rats, a model of NAFLD, sobetirome prevented and reverted choline-methionine deficient-induced fat accumulation, ameliorated steatohepatitis and promoted regression to pre-existing fat accumulation without significant side effects on heart rate. Sobetirome ameliorated hepatic steatosis also in other animal experimental models, such as obese/obese mice and western diet-fed LDLR $-/-$ mice.^[141]

In rats and mice, sobetirome also replicates the T3 effects as a powerful inducer of hepatocyte proliferation,^[175,176] thus sobetirome might be beneficial in the area of hepatic regenerative medicine. Indeed, preclinical studies demonstrated that mice pretreated with sobetirome showed a significant increase in hepatocyte proliferation following partial hepatectomy.^[177] Sobetirome exerts therapeutic effects on HCC. T3 or sobetirome administration in rats treated with diethylnitrosamine combined with a choline-deficient diet dramatically reduced the preneoplastic lesions caused by diethylnitrosamine.^[178–180]

Eprotirome. Eprotirome is another TR β liver-selective agonist. Eprotirome prevented hepatic steatosis development and significantly lowered serum total and LDL cholesterol.^[141,181,182] Rats treated with eprotirome had increased hepatocyte proliferation with no evidence of significant liver toxicity.^[183] Eprotirome appeared to be more liver-specific than sobetirome and did not cause myocardial off-target effects.^[181,182] At present, no data regarding the effect of eprotirome on HCC development/progression are available.

MB07344/VK2809. The active compound MB07344/VK2809, derived from hepatic enzymatic cleavage of MB07811/VK2809, has been characterized as a liver-selective TR β agonist. MB07344 displays around 12-fold selectivity for TR β over TR α and approximately half of the affinity of T3.^[171,174] MB07811/VK2809 treatment for 2 weeks in high-fat diet exposed or diabetic obese animals significantly decreased cholesterol and both serum and hepatic triglycerides without effects on body weight, glycemia, and the thyroid hormone axis, while showing an acceptable side effect profile.^[130]

MB07811/VK2809 is a promising drug for the treatment of metabolic disorders, including NASH. In a rodent model of diet-induced NASH, VK2809 caused a significant reduction in plasma and liver lipids, as well

as improvements in liver fibrosis. In animal models of hypercholesterolemia, VK2809 demonstrated a promising reduction in plasma cholesterol with minimal effect on the thyroid hormone.^[184]

MB07811 markedly reduced hepatic steatosis, plasma FFAs, and triglycerides in several experimental models of NAFLD, such as Zucker diabetic fatty rats, obese/obese mice, and diet-induced obese mice.^[184] Importantly, after treatment with MB07811, no sign of liver fibrosis or other histological liver damage was observed.

Resmetirom. Resmetirom is a highly selective TR β agonist with an EC₅₀ value of 0.21 μ M and it is 28-fold selective for TR β (EC₅₀ = 0.21 μ M) over TR α (EC₅₀ = 3.74 μ M).^[171] Resmetirom showed a very positive myocardial safety profile in rats and was efficacious in a preclinical model at doses that showed no impact on the central thyroid axis. In studies conducted in healthy volunteers, resmetirom administered orally once daily at 50 mg or higher dose for 2 weeks exhibited an excellent safety profile and decreased LDL cholesterol and triglycerides.^[171]

In diet-induced obese mice treated at human-equivalent doses, resmetirom reversed and prevented progression of lipid accumulation, inflammatory, and fibrotic markers of NASH without the adverse effects of T3. In humans, 60% reduction in triglycerides was observed for doses ranging from 50 to 200 mg, in the absence of drug-related adverse events.^[185]

CLINICAL USE OF THYROMIMETICS

Eprotirome phase 3 clinical trial was undertaken to compare eprotirome (at the daily doses of 50 and 100 μ g) versus placebo in 236 patients with familial hypercholesterolemia. The trial was interrupted because of a significant increase in liver enzymes in 4 patients and the contemporary report of cartilage side effects in

animals.^[186] Conversely, after achieving excellent results in experimental models, clinical trials have been started with resmetirom and MB07811/VK2809, and the initial reports are extremely encouraging.^[187,188]

NAFLD/NASH. Thyromimetic compounds (Table 3) actions are mediated in the liver by TR β and have been proven to be beneficial in dyslipidemia and NAFLD.^[141,190,191]

To date, 4 different compounds have been employed in clinical trials, originally studied for their ability to reduce LDL cholesterol, in particular sobetirome and eprotirome, however, in recent years, TR β agonists have been considered for NAFLD/NASH treatment in particular, MB07344/VK2809, and resmetirom.

Sobetirome completed phase 1 clinical trials in 2008 and demonstrated lipid-lowering effects with both single and multiple dosing^[192] with no phase II trials being planned due to the reported elevation of liver enzymes.

Eprotirome progressed to phase 3 clinical trial but was terminated due to unexpected side effects in animal studies.^[193] Four clinical trials were conducted between 2008 and 2012 (identifier: NCT00677248, NCT00776321, NCT00593047, and NCT01410383).

In 2021, Younossi and colleagues studied 125 patients with NASH, of whom 84 were treated with 80 mg/d with resmetirom and 41 with placebo for 36. Compared to placebo, resmetirom-treated patients showed significant improvement of health-related quality of life.^[194]

In a randomized, double-blind, placebo control in phase 2 clinical trial (NCT02912260), resmetirom was studied in 116 patients with NASH (fibrosis stages 1–3). Seventy-eight patients received 80 mg of resmetirom 38 patients were treated with placebo for 36 weeks.^[187] Patients treated with resmetirom (n = 78) showed a relative reduction of hepatic fat at week 12 and week 36. Biopsy performed at 36 weeks showed that histological markers of inflammation were reduced. Adverse events

TABLE 3 Thyromimetic compounds in clinical trials

Compound	NCT number	Sponsor	Condition	Status	Phase
<i>Sobetirome</i>		QuatRX	Hypercholesterolemia	Complete	1
<i>Eprotirome</i>	NCT00677248	Karo Bio AB	Hypercholesterolemia	Complete	2
	NCT00776321	Karo Bio AB	Primary hypercholesterolemia	Complete	2
	NCT00593047	Karo Bio AB	Dyslipidemia	Complete	2
	NCT01410383	Karo Bio AB	Heterozygous familial hypercholesterolemia	Complete	3
VK2809	NTC04173065	Viking Therapeutics, Inc.	NASH	Active	2
	NCT02927184	Viking Therapeutics, Inc.	Hyperlipidemia/NAFLD	Complete	2
<i>Resmetirom</i>	NCT04197479	Madrigal Pharmaceuticals, Inc.	NAFLD	Active	3
	NCT02912260	Madrigal Pharmaceuticals, Inc.	NASH	Active	2
	NCT03900429	Madrigal Pharmaceuticals, Inc.	NASH	Active ^a	3
	NCT04951219	Madrigal Pharmaceuticals, Inc.	NAFLD	Active	3
	NCT04643795	Madrigal Pharmaceuticals, Inc.	Hepatic impairment/NASH/cirrhosis	Active	1

^aResults reported in abstract form.^[189]

were mostly mild or moderate and were balanced between groups, except for a higher incidence of transient mild diarrhea and nausea in the resmetirom-treated group.

MAESTRO-NAFLD-1 (NCT04197479), a 52-week phase 3 “real-life NASH study” that enrolls patients based on NASH diagnosis using noninvasive assessments is currently ongoing.

An explorative 36-week active treatment open-label extension study was conducted in 31 consenting patients with NASH (14 treated with placebo and 17 treated with 80 or 100 mg resmetirom orally per day).^[195] At the end of the open-label extension study after 36 weeks, patients treated with resmetirom had improvements in proton density fat fraction, reduction of lipoprotein (LDL cholesterol, ApoB, triglycerides, and ApoC3), reduction of liver enzymes, and increased sex hormone-binding globulin from baseline. However, given the small number of patients treated with 100 mg compared with 80 mg, no statistical comparison was possible between the 2 doses. The ratio N-terminal type III collagen pro-peptide and matrix metalloproteinase-degraded C3 indicated an overall decrease in fibrosis. Resmetirom was well tolerated, without serious adverse events.

Based on these results, a resmetirom phase 3 clinical trial “MAESTRO-NASH” (NCT03900429) was designed. Patients with NASH and stage F2 or F3 fibrosis are currently recruited for a 52-week double-blind, 3-arm placebo-controlled trial with resmetirom 80 mg, 100 mg daily, or placebo. Endpoints of the study are resolution of NASH, or significant reduction of fibrosis on liver biopsy. The results of this study, presented very recently in abstract form, indicate that resmetirom treatment 80 mg, and 100 mg compared to placebo resulted in highly significant increase in NASH resolution 26%, 30% vs. 10%, and reduction in NAFLD activity score 24%, 26% versus 14%, respectively. Moreover, resmetirom treatment 80 mg, and 100 mg compared to placebo resulted in significant decrease in LDL cholesterol -12%, -16% versus 1%. Resmetirom

was well tolerated with only significant increase in diarrhea and nausea.^[189]

Currently, (Table 4), 5 resmetirom clinical trials are ongoing, all in active recruitment state (ClinicalTrials.gov identifier: NCT02912260, NCT04197479, NCT03900429, NCT04951219, and NCT04643795). Long-term and postapproval surveillance studies will be necessary to confirm safety and assure absence of off-target effects.

VK2809 was tested in a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial for safety, tolerability, and efficacy (NCT02927184). In this study, 337 patients with NAFLD and liver fat content $\geq 8\%$ were assigned to 3 different doses of VK2809 or placebo for 12 weeks. Safety was also assessed at 16 weeks (4 wk following completion of the treatment with active compound). Following 12 weeks of therapy, patients treated with VK2809 experienced statistically significant reductions in liver fat content relative to placebo. These effects were maintained at the week-16 assessment. VK2809 was well tolerated in this study and no serious adverse events were reported in any cohort, and overall excellent side effect profile. These data indicate that a 12-week treatment with low-dose (1.0, 2.5, or 5.0 mg) VK2809 produced significant and robust improvements in liver fat content in patients with NAFLD that were similar to the high dose (10 mg) every other day.^[196,197]

Currently, VK2809 has progressed to phase 2 clinical trial in patients with primary hypercholesterolemia and NAFLD (ClinicalTrials.gov identifier: NCT04173065).

A therapeutic strategy based on thyromimetic use, either as single agents or in combination with other drugs, may be effective for the treatment of liver diseases, as NAFLD and NASH are currently devoid of any effective treatment. Future data from thyromimetic clinical trials will provide more clarity on their safety and their possible clinical indications.

Liver is one of the major target tissues of TH action and TH levels are closely correlated with

TABLE 4 Thyromimetic compounds in clinical trials (↑ increase, ↓ decrease)

	Results	No. patients (treated vs. placebo)	Type of treatment
NCT02912260	↓ Hepatic fat ↓ Inflammation markers	116 (78 vs. 38)	80 mg daily OL
	↑ PDFF ↓ Lipoprotein (LDL-C, ApoB, ApoCIII, tryglicerides) ↓ Liver enzyme (ALT, AST, GGT) ↑ SHBG ↑ Fibrosis (↑ collagen markers ↑ Pro-C3 and ↓ C3M)	31 (17 vs. 14)	80 or 100 mg daily OL
NCT04197479	Current enrolling data not available		
NCT03900429	Current enrolling data not available		
NCT04951219	Current enrolling data not available		
NCT04643795	Current enrolling data not available		

Abbreviations: C3M, matrix metalloproteinase-degraded C3; PDFF, proton density fat fraction; PRO-C3, N-terminal type III collagen pro-peptide; SHBG, sex hormone-binding globulin.

liver-associated diseases with a spectrum ranging from hepatic steatosis to HCC. There is a complex interplay between the thyroid axis and the liver, and the role of TH in the pathogenesis of liver diseases has been established. Conversely, liver disorders may affect TH levels, and at the present time, it is not clear whether they are adaptive or maladaptive. In this review, we have discussed the growing complexity of TH signaling in the liver and highlighted the potential benefits associated with TH-based therapeutic strategies for liver-related diseases as well as recent encouraging results from clinical trials on the use of thyromimetics for the treatment of liver disease, especially NASH.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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