

The thyroid-liver axis in metabolic dysfunction-associated steatotic liver disease: a narrative review

Abstract

Objective: To review the epidemiological and pathophysiological associations between hypothyroidism and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), alongside evaluating novel thyromimetic therapies.

Methods: A concise narrative review of the literature regarding systemic thyroid function, MASLD severity, and liver-directed thyroid hormone receptor-beta (THR-beta) agonists.

Results: Epidemiological data show a significantly higher prevalence of MASLD in populations with both overt and subclinical hypothyroidism, a risk heavily compounded by concurrent metabolic syndrome. Mechanistically, thyroid hormones orchestrate hepatic lipid homeostasis; their localized functional deficiency within the liver (“hepatic hypothyroidism”) actively drives steatogenesis and fibrogenesis. Liver-directed THR-beta agonists demonstrate breakthrough efficacy in resolving metabolic steatohepatitis (MASH) and improving fibrosis.

Conclusion: The bidirectional thyroid-liver axis operates as a pivotal driver of MASLD pathogenesis. Correcting states of hepatic hypothyroidism through targeted THR-beta agonism represents a clinically validated, disease-modifying therapeutic strategy.

Keywords: thyroid-liver, epidemiological, metabolic dysfunction, steatotic liver

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Introduction

The global burden of chronic liver disease has undergone a dramatic epidemiological shift, driven by the rising prevalence of obesity and type 2 diabetes. This syndemic has necessitated a fundamental reclassification of fatty liver disease, transitioning from the exclusion-based “Non-Alcoholic Fatty Liver Disease” (NAFLD) to the affirmative diagnosis of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). MASLD now affects an estimated 30% of the global adult population, presenting a spectrum of pathology that ranges from simple steatosis to Metabolic Dysfunction-Associated Steatohepatitis (MASH), which is characterized by active hepatocellular injury and inflammation with a significant risk of progression to bridging fibrosis (F2–F3), cirrhosis (F4), and hepatocellular carcinoma.

Despite this escalating public health crisis, therapeutic options have historically been limited to lifestyle modifications, which are often difficult to sustain. However, the landscape of hepatology has recently been transformed. In March 2024, the U.S. Food and Drug Administration (FDA) granted accelerated approval to resmetirom, a liver-directed thyroid hormone receptor-beta (THR- β) agonist, marking it as the first pharmaceutical agent approved specifically for the treatment of adults with non-cirrhotic MASH and moderate to advanced liver fibrosis.

This regulatory milestone underscores the critical physiological role of the thyroid-liver axis. The liver is not only a primary target organ for thyroid hormone action but also a central site for its metabolism and transport. Clinical and epidemiological data have long established a bidirectional relationship wherein hypothyroidism—both overt and subclinical—is independently associated with the presence and severity of MASLD.^{1–7} Conversely, the steatotic liver exhibits a state of localized “hepatic hypothyroidism,” characterized by impaired thyroid hormone signaling that perpetuates lipotoxicity and fibrogenesis.^{5–7,9,10}

This narrative review examines the pathophysiological foundations of the thyroid-liver axis, detailing how intrahepatic hypothyroidism drives metabolic dysfunction.^{8–10} We further explore the medicinal chemistry evolution that allowed for the development of liver-selective thyromimetics, overcoming historical cardiovascular safety concerns. Finally, we evaluate the pivotal clinical trials and emerging practice guidance that now position THR- β agonism as a cornerstone in the pharmacological management of at-risk MASH.

Epidemiological evidence: the thyroid–metabolic link

Observational data robustly establish hypothyroidism as a potent, independent risk factor for MASLD. In a highly controlled case-control study by Dalai et al., ultrasonography revealed that 84% of hypothyroid patients exhibited fatty liver changes compared to only 12% in euthyroid controls, with a significant positive correlation between TSH levels and fibrosis scores.¹ Patel et al. similarly determined that fatty liver was present in 59.15% of untreated hypothyroid subjects.²

Even mild thyroid dysfunction plays a critical role. A large-scale analysis by Fan et al. demonstrated that subclinical hypothyroidism (SCH) is significantly associated with advanced hepatic fibrosis and higher FIB-4 scores. This risk is severely compounded by concurrent metabolic syndrome (MetS). Erdogan et al. reported a MetS prevalence of 44% in overt hypothyroid patients and 35% in SCH patients, alongside pronounced insulin resistance. A summary of these and other key epidemiological studies linking thyroid dysfunction to MASLD is provided in Table 1.^{1–6}

Furthermore, simply normalizing systemic TSH with levothyroxine is often insufficient to resolve the hepatic metabolic derangements. Mazo et al. found that among patients with biopsy-confirmed MASLD receiving levothyroxine therapy, 68% still harbored active MASH. Broader meta-analyses consistently confirm these trends, generating pooled odds ratios that indicate an approximately 45%

higher likelihood of MASLD in hypothyroid individuals, alongside a severely pronounced risk for advanced histological severity.

Table 1 Key epidemiological studies linking thyroid dysfunction and MASLD

Study	Study design	Key findings
Dalai et al. ¹	Case-control	84% prevalence of fatty liver in hypothyroid patients vs. 12% in controls.
Patel et al. ²	Cross-sectional	Fatty liver detected in 59.15% of untreated hypothyroid subjects.
Fan et al. ³	Retrospective cohort	Subclinical hypothyroidism associated with advanced fibrosis and higher FIB-4 scores.
Erdogan et al. ⁴	Cross-sectional	Metabolic syndrome prevalence of 44% in overt and 35% in subclinical hypothyroidism.
Mantovani et al. ⁶	Meta-analysis	Primary hypothyroidism associated with ~45% higher likelihood of MASLD and advanced histological severity.

Pathophysiology of the thyroid–liver axis

The metabolic effects of thyroid hormones are executed through highly conserved genomic pathways mediated by nuclear thyroid hormone receptors (TRs). While TR-alpha1 predominantly regulates cardiac effects, TR-beta1 is the dominant receptor subtype within the hepatic parenchyma. Triiodothyronine (T3) binding induces an allosteric shift that recruits vital co-activators, such as PGC-1alpha, to drive the transcription of essential metabolic gene cassettes.

Thyroid hormone acts as the master switch orchestrating hepatic lipid clearance. T3 heavily upregulates Carnitine Palmitoyl transferase 1A, accelerating mitochondrial beta-oxidation. Furthermore, T3 is an absolute requisite for “lipophagy”—the selective autophagic degradation of intracellular lipid droplets. The molecular pathways orchestrating these processes, including genomic action and lipophagic control, are illustrated in Figure 1.

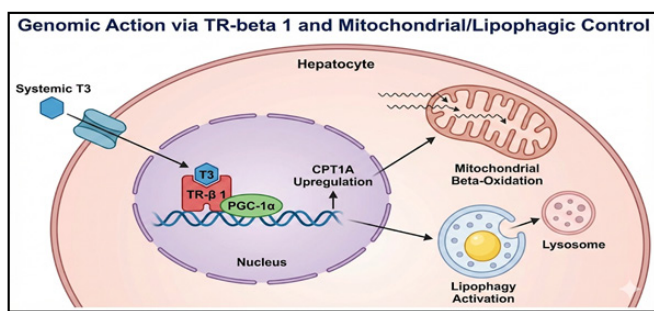


Figure 1 Molecular pathways of the thyroid–liver axis.

Crucially, systemic circulating hormone levels do not perfectly reflect the intrahepatic state. In active MASH, chronic lipotoxicity and pro-inflammatory cytokines potently suppress hepatic deiodinase 1 (D1) enzymatic activity, starving the hepatocytes of active T3. This precipitates a localized state of “hepatic hypothyroidism.” Without functional TR-beta engagement, autophagic machinery stalls, and beta-oxidation collapses, fueling a vicious, self-amplifying cycle of massive steatogenesis and progressive fibrogenesis.

Recent mechanistic insights have clarified that hepatic hypothyroidism in MASLD is not merely a consequence of systemic hormone levels but a localized tissue-specific defect. Under conditions of metabolic stress, the liver exhibits an altered expression of deiodinases—specifically, a downregulation of Type 1 Deiodinase (DIO1) and an upregulation of Type 3 Deiodinase (DIO3). DIO3 actively inactivates T4 and T3 into reverse T3 (rT3) and T2, effectively starving the hepatocyte of active hormone even when serum TSH is normal. Furthermore, the expression of crucial thyroid hormone transporters like MCT8 is suppressed in fibrotic livers, creating a “double hit” where hormone entry is blocked and intracellular inactivation is accelerated. This localized hypothyroid state directly promotes lipogenesis via the SREBP-1c pathway and impairs mitochondrial beta-oxidation. These pathophysiological mechanisms are depicted in Figure 2.

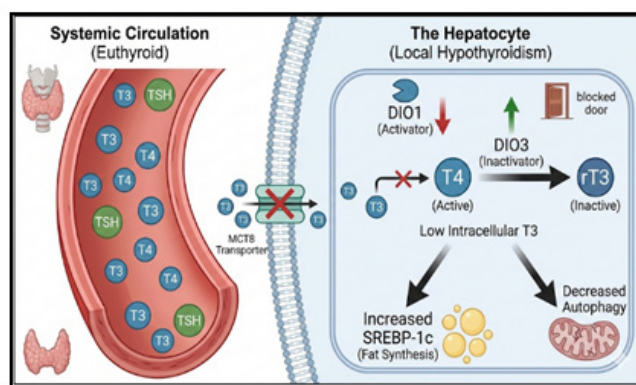


Figure 2 The Paradox of Systemic Euthyroidism and Local Hepatic Hypothyroidism in MASLD.

Evolution of thyromimetics

TR-alpha vs. TR-beta: The cardiac safety barrier

The therapeutic potential of thyroid hormones in metabolic disease has historically been limited by a narrow therapeutic index, primarily dictated by the differential tissue distribution of thyroid hormone receptor (TR) isoforms. The physiological actions of T3 are mediated by two major receptor classes encoded by separate genes: TR-alpha (TRα) and TR-beta (TRβ). Crucially, these receptors are not uniformly distributed. TR-alpha1 is the dominant isoform expressed in the myocardium, where it governs heart rate (chronotropy) and contractility (inotropy), as well as in the brain and skeletal tissue. Conversely, TR-beta1 is the predominant isoform in the liver, accounting for approximately 80% of hepatic TR activity, where it orchestrates cholesterol clearance, bile acid synthesis, and mitochondrial fatty acid oxidation.

This anatomical dichotomy creates a “cardiac trap” for non-selective thyroid hormone therapy. While systemic administration of T3 or T4 can effectively lower intrahepatic lipids and improve metabolic profiles, the doses required to achieve these hepatic benefits inevitably activate cardiac TR-alpha receptors. This results in thyrotoxic side effects, including tachycardia, arrhythmias, muscle wasting, and accelerated bone resorption. Consequently, simple hormone supplementation is unviable for MASLD treatment, as the risk of inducing iatrogenic hyperthyroidism outweighs the metabolic benefits.

The objective of modern thyromimetics (thyroid hormone analogs) is to decouple these effects through two primary mechanisms:

- a) **Isoform selectivity:** Designing ligands with a higher binding affinity for TR-beta over TR-alpha.
- b) **Tissue selectivity (hepatoselectivity):** Engineering compounds that are specifically taken up by organic anion transporting polypeptides (OATPs) expressed on hepatocytes, thereby concentrating the drug in the liver while minimizing systemic exposure to the heart and bone.

Chemical evolution

The development of liver-directed thyromimetics has historically been hindered by the ubiquity of TR-alpha receptors in the myocardium, where agonism precipitates tachycardia, arrhythmias, and bone loss. Early generation analogs like GC-1 (sobetirome)

achieved partial liver selectivity but failed to translate into robust clinical safety margins. The breakthrough in modern thyromimetics lies in “hepatoselection”—a dual mechanism involving not only high affinity for the TR-beta isoform (predominant in the liver) but also specific chemical modifications that mandate uptake by liver-specific OATP transporters. This restricts the drug’s biodistribution almost exclusively to the hepatocyte, shielding the heart and bone from off-target activation.

These advances laid the groundwork for the development of resmetirom and VK2809, which embody the principles of both isoform selectivity and hepatoselective delivery.^{9,11–14} The trajectory of this medicinal chemistry evolution is summarized schematically in Figure 3.

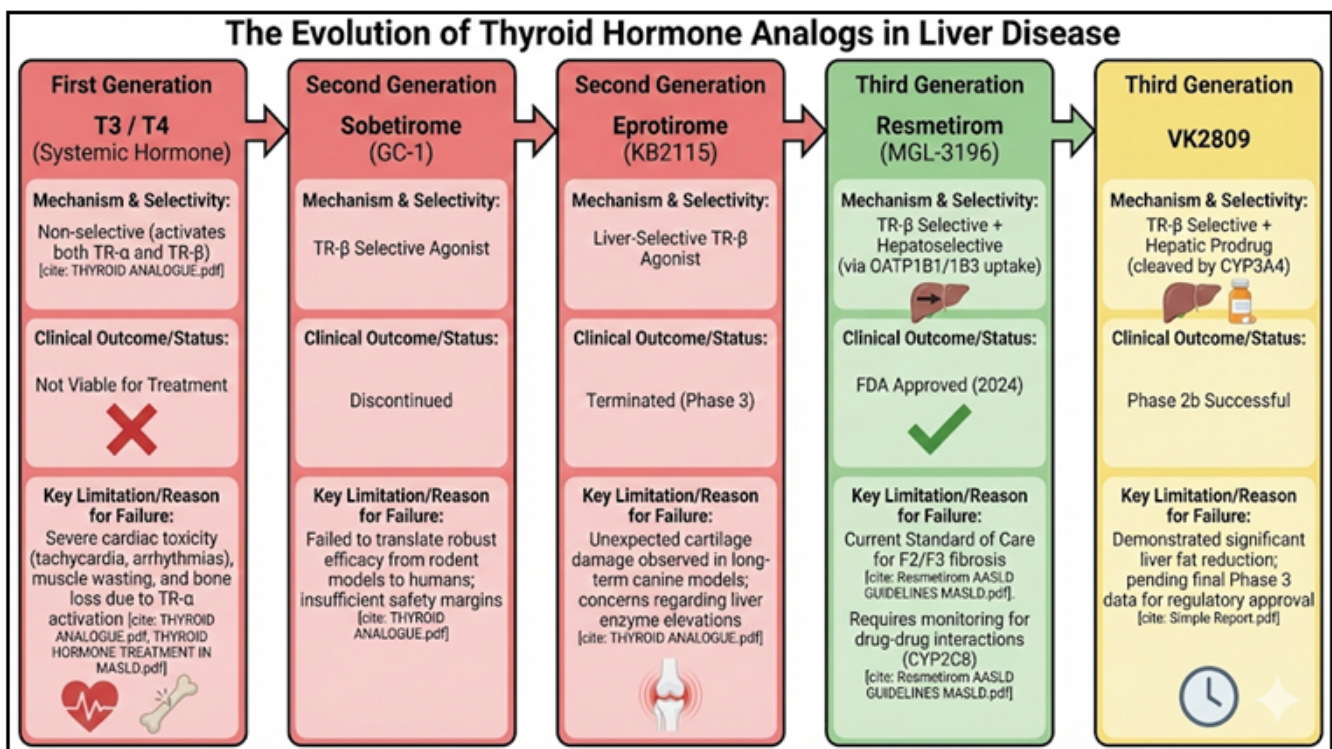


Figure 3 The evolution of thyroid hormone analogs in liver disease.

Clinical efficacy of novel thyromimetics

Resmetirom (MAESTRO Trials)

The clinical validation of selective THR-β agonism was established in the pivotal Phase 3 MAESTRO-NASH trial. In this study, resmetirom (80 mg and 100 mg) demonstrated statistical superiority over placebo in achieving the dual primary endpoints of MASH resolution without worsening of fibrosis and fibrosis improvement (by at least one stage) without worsening of MASH. Specifically, MASH resolution was achieved in up to 29.9% of patients on the 100 mg dose compared to 9.7% for placebo, while 25.9% achieved fibrosis improvement. Crucially, resmetirom also significantly reduced key secondary biomarkers, including LDL cholesterol, apolipoprotein B,

and triglycerides, reflecting its systemic metabolic efficacy beyond the liver.

VK2809 (VOYAGE Trial)

VK2809 represents a distinct class of thyromimetics utilizing a “prodrug” mechanism, requiring cleavage by liver-specific CYP3A4 isozymes to release the active agonist. In the Phase 2b VOYAGE study, VK2809 achieved robust reductions in liver fat content, with patients experiencing relative reductions ranging from 37% to 55% at week 52. The agent also demonstrated significant rates of MASH resolution, highlighting the potential for this class to drive histological reversal. The key histologic and clinical efficacy outcomes from these pivotal resmetirom and VK2809 trials are summarized in Table 2.

Table 2 Pivotal clinical trials of liver-directed THR-beta agonists

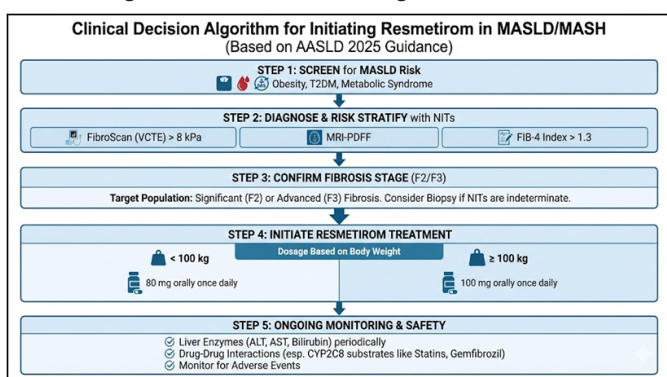
Trial name	Drug (dose)	Study phase	MASH resolution	Fibrosis improvement (\geq I Stage)
MAESTRO-NASH	Resmetirom (80 mg)	Phase 3	25.9% (vs 9.7% placebo)	24.2% (vs 14.2% placebo)
MAESTRO-NASH	Resmetirom (100 mg)	Phase 3	29.9% (vs 9.7% placebo)	25.9% (vs 14.2% placebo)
VOYAGE	VK2809 (combined)	Phase 2b	68.6% (vs 29.3% placebo)	51.1% (vs 34.1% placebo)

With the FDA approval of resmetirom, the 2025 AASLD guidance has integrated thymomimetics into the standard of care for non-cirrhotic MASH with moderate to advanced fibrosis (F2–F3). The guidance emphasizes that resmetirom is not a replacement for lifestyle modification but an adjunct for “at-risk” MASH patients. Crucially, the guidelines suggest that non-invasive tests (NITs) like VCTE (FibroScan) or MRI-PDFF may be sufficient for initiation in many cases, reducing the barrier of liver biopsy. Clinicians are advised to monitor for potential drug-drug interactions, particularly with agents metabolized by CYP2C8, as resmetirom inhibition of CYP2C8 may necessitate dose adjustments.

Guideline-based management

Patient Selection

The 2025 AASLD Practice Guidance recommends resmetirom for adult patients with clinically significant fibrosis (stages F2 to F3) confirmed by biopsy or non-invasive tests (NITs). While the FDA label does not strictly contraindicate use in F1 (mild fibrosis) or compensated cirrhosis (F4), the guidance prioritizes treatment for those with moderate-to-advanced fibrosis where the risk of progression is highest. Clinicians are advised to utilize NITs such as VCTE (FibroScan) or MRI-PDFF to stratify risk and identify candidates, reserving biopsy for indeterminate cases. This risk-stratification and treatment algorithm is summarized in Figure 4.

**Figure 4** Clinical Decision Algorithm for Initiating Resmetirom in MASLD/MASH.

Monitoring and drug–drug interactions

Given resmetirom’s metabolism via CYP2C8, clinicians must be vigilant regarding drug-drug interactions. The guidance specifically warns against concurrent use with strong CYP2C8 inhibitors (e.g., gemfibrozil) due to the risk of increased resmetirom exposure. Conversely, resmetirom itself inhibits CYP2C8 and OATP1B1/1B3, necessitating dose adjustments for concomitant statins (specifically simvastatin, pravastatin, and atorvastatin) to prevent statin-induced myopathy.

Safety and future directions

Bone health and the HPT axis

While liver-selective agonists minimize cardiac toxicity, the suppression of the hypothalamic–pituitary–thyroid (HPT) axis remains a theoretical concern. Chronic activation of the negative feedback loop can lower TSH and free T4 levels, which could impact bone turnover markers. Although Phase 3 data for resmetirom showed no adverse signals for bone mineral density or fracture risk over 52 weeks, long-term pharmacovigilance is required to ensure skeletal safety in post-menopausal populations.

Combination therapies

The future of MASH treatment likely lies in combination strategies. While THR- β agonists excel at resolving lipotoxicity and fibrosis directly, they produce only modest weight loss compared to GLP-1 receptor agonists (e.g., semaglutide, tirzepatide). Combining the potent weight-loss and insulin-sensitizing effects of GLP-1s with the direct anti-fibrotic and lipid-lowering actions of thymomimetics offers a synergistic approach. This strategy aims to target multiple pathogenic pathways simultaneously—systemic metabolic dysfunction and local hepatic fibrogenesis—to maximize histological reversal.

Conclusion

The bidirectional thyroid-liver axis is an indispensable physiological node in MASLD pathogenesis.^{1–10} The clinical translation of highly selective, liver-directed THR-beta agonists successfully short-circuits the deadly cycle of hepatic hypothyroidism.^{5–10,13,14} By safely restoring autophagic turnover and enforcing mitochondrial biogenesis, thymomimetics represent a profound paradigm shift, transitioning MASLD management into an era of proactive, structural disease modification.^{9–14}

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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