Association Between FGF21 and NAFLD in Hypothyroid Patients: Mechanistic and Clinical Insights

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent hepatic disorders worldwide and is increasingly recognized as a multisystem condition strongly influenced by endocrine dysfunction. Among these endocrine factors, hypothyroidism has been consistently associated with metabolic impairment, hepatic steatosis, and elevated cardiovascular risk. Fibroblast growth factor 21 (FGF21), a hepatokine with potent metabolic regulatory effects, has gained attention as a potential mediator linking thyroid dysfunction to NAFLD pathogenesis. Experimental and clinical studies indicate that FGF21 plays a critical role in lipid oxidation, glucose homeostasis, mitochondrial function, and adaptive responses to metabolic stress, suggesting that alterations in FGF21 signaling may be central to the metabolic disturbances observed in hypothyroid patients.

The aim of this review is to synthesize mechanistic and clinical evidence regarding the relationship between FGF21 and NAFLD in individuals with hypothyroidism. More specifically, we examine how thyroid hormone deficiency influences hepatic metabolism; how FGF21 expression and signaling pathways are altered in hypothyroid states; and how these changes intersect with the development and progression of NAFLD. By integrating data from molecular studies, animal models, and clinical cohorts, this review highlights the emerging hypothesis that FGF21 elevation in hypothyroidism may represent a compensatory, yet ultimately insufficient, response to impaired lipid handling and mitochondrial dysfunction. Moreover, a growing body of evidence suggests that FGF21 may serve as a sensitive biomarker for identifying metabolic liver injury in patients with overt or subclinical hypothyroidism, particularly in those with coexisting obesity or insulin resistance.

In conclusion, understanding the interplay between thyroid hormone status, FGF21 physiology, and hepatic lipid metabolism provides valuable insight into the pathogenesis of NAFLD in hypothyroid patients. Elucidating this relationship may facilitate improved risk stratification, early diagnosis, and development of targeted therapeutic strategies—including FGF21 analogs and optimized thyroid hormone replacement approaches. Further research is required to clarify causal pathways, evaluate longitudinal changes in FGF21 during treatment, and determine its clinical utility as a biomarker or therapeutic target in endocrine-related fatty liver disease.

Keywords: *FGF21, NAFLD ,Hypothyroid Patients*

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disorder globally, affecting approximately 25–30% of adults and rising in parallel with the epidemics of obesity and metabolic syndrome [1]. Increasing evidence identifies NAFLD as a multisystem disease profoundly influenced by endocrine dysregulation, including thyroid hormone abnormalities. Thyroid hormones regulate energy expenditure, lipid oxidation, hepatic autophagy, and mitochondrial function; therefore, even mild thyroid dysfunction has measurable metabolic consequences [2]. Epidemiological studies indicate that both overt and subclinical hypothyroidism are associated with higher prevalence and severity of NAFLD, independent of traditional metabolic risk factors [3]. However, the biological mediators linking thyroid dysfunction to hepatic steatosis remain incompletely understood.

Fibroblast growth factor 21 (FGF21), a hepatokine with potent metabolic regulatory properties, has emerged as a potential mechanistic connector between thyroid hormone deficiency and NAFLD. Under physiological conditions, FGF21 enhances fatty acid oxidation, improves insulin sensitivity, and modulates glucose metabolism [4]. Elevated circulating FGF21 levels have been consistently observed in NAFLD, obesity, and type 2 diabetes—often interpreted as a state of "FGF21 resistance" [5]. Importantly, thyroid hormones directly regulate hepatic FGF21 transcription through thyroid hormone receptor–mediated pathways, and hypothyroidism has been linked to altered FGF21 expression in both human and experimental studies [6]. This interplay suggests a complex regulatory axis in which thyroid dysfunction may drive metabolic stress that triggers compensatory FGF21 elevation, potentially contributing to NAFLD progression.

Despite increasing interest in this relationship, significant research gaps remain. It is unclear whether FGF21 elevation in hypothyroidism represents an adaptive hepatic response or indicates impaired FGF21 sensitivity. Additionally, clinical studies evaluating FGF21 as a biomarker for NAFLD in hypothyroid patients are limited by small sample sizes and heterogeneous diagnostic criteria. The aim of this review is to synthesize mechanistic, experimental, and clinical evidence on the association between FGF21 and NAFLD in hypothyroid patients, clarify potential causal pathways, and evaluate the biomarker and therapeutic implications of this endocrine–hepatic interaction.

Physiology and Regulation of Fibroblast Growth Factor 21

FGF21 is a hormone-like metabolic regulator primarily secreted by the liver, with additional expression in adipose tissue, pancreas, and skeletal muscle [7]. Unlike classical FGFs, FGF21 functions endocrinologically due to its reduced heparin-binding affinity, permitting systemic endocrine actions through interaction with fibroblast growth factor receptor-1c (FGFR1c) and its co-receptor β-Klotho [8]. It plays crucial roles in glucose uptake, ketogenesis, lipid oxidation, and mitochondrial function, particularly during metabolic stress conditions such as fasting, ketogenic diets, and cold exposure [9]. Its expression is governed by nutrient-responsive transcription factors, chiefly peroxisome proliferator–activated receptor-α (PPARα), which induces FGF21 during fasting, and carbohydrate response element–binding protein (ChREBP), which increases FGF21 under carbohydrate-rich states [10]. These regulatory pathways position FGF21 as an essential mediator linking nutrient status to whole-body energy homeostasis. [7–10]

FGF21 secretion is subject to modulation by multiple endocrine and metabolic factors, underscoring its integration into broader hormonal networks. Thyroid hormones exert direct effects on hepatic FGF21 transcription through thyroid hormone receptor-β (TRβ), demonstrating the sensitivity of FGF21 to thyroid status [11]. Additionally, insulin, glucagon, and growth hormone modify FGF21 expression in context-dependent manners, reflecting its dynamic metabolic role [12]. Circulating FGF21 levels are elevated in metabolic stress disorders such as obesity, insulin resistance, and NAFLD, suggesting a compensatory mechanism aimed at restoring metabolic balance [13]. However, persistently elevated FGF21 may reflect the development of "FGF21 resistance," a state in which target tissues exhibit reduced responsiveness despite high hormone levels, resembling insulin or leptin resistance [14]. This concept highlights the dual importance of FGF21 as both a biomarker and a mechanistic contributor to metabolic dysfunction. [11–14]

Thyroid Hormone Physiology and Metabolic Effects

Thyroid hormones, primarily thyroxine (T4) and the biologically active triiodothyronine (T3), are central regulators of basal metabolic rate, thermogenesis, and macronutrient metabolism. These hormones exert genomic effects through thyroid hormone receptors (TRα and TRβ), influencing transcription of genes involved in mitochondrial biogenesis, oxidative phosphorylation, and lipid oxidation [15]. In the liver, T3 enhances β-oxidation, reduces hepatic triglyceride accumulation, and modulates cholesterol turnover through regulation of LDL receptor expression and sterol metabolism pathways [16]. Additionally, thyroid hormones stimulate hepatic autophagy and lipophagy, processes essential for mobilizing stored lipids and preventing steatosis [17]. Their broad metabolic roles establish them as key determinants of systemic energy homeostasis and hepatic lipid balance, making even subtle alterations in thyroid function clinically relevant. [15–17]

Beyond their direct actions on energy expenditure, thyroid hormones significantly influence glucose metabolism, insulin sensitivity, and lipid handling across multiple tissues. T3 increases glucose utilization by enhancing GLUT4 expression in muscle and adipose tissue, while modulating gluconeogenesis and glycogen turnover in the liver [18]. Thyroid hormone–mediated effects on brown adipose tissue thermogenesis, mediated partly through uncoupling protein-1 (UCP1), further amplify systemic metabolic activity [19]. Disruption of thyroid hormone signaling, as observed in overt and subclinical hypothyroidism, impairs lipid clearance, reduces mitochondrial oxidative capacity, and promotes dyslipidemia—factors that collectively predispose patients to hepatic steatosis and NAFLD [20]. This mechanistic framework underscores the interconnectedness of thyroid endocrine function and metabolic liver disease, providing a biological basis for exploring FGF21 as a mediator of these interactions. [18–20]

Pathophysiology of Hypothyroidism and Metabolic Dysfunction

Hypothyroidism leads to widespread metabolic impairment due to decreased thyroid hormone availability, resulting in reduced basal metabolic rate, diminished mitochondrial activity, and impaired lipid mobilization. Lower T3 and T4 levels reduce expression of genes controlling oxidative phosphorylation, fatty acid oxidation, and thermogenesis, thereby promoting lipid accumulation in hepatic and adipose tissues [21]. Additionally, hypothyroidism decreases lipoprotein lipase (LPL) activity and hepatic LDL receptor expression, contributing to hypertriglyceridemia and elevated LDL cholesterol levels [22]. These abnormalities create a metabolically unfavorable environment characterized by increased oxidative stress and impaired lipid clearance, which predispose affected individuals to the development of hepatic steatosis. [21–22]

The metabolic dysfunction of hypothyroidism extends beyond lipid abnormalities to encompass glucose metabolism, insulin sensitivity, and adipokine regulation. Hypothyroid states are associated with increased insulin resistance, partly due to reduced GLUT4-mediated glucose uptake in skeletal muscle and altered hepatic glucose production [23]. In addition, inflammatory signaling is amplified through increased secretion of cytokines such as TNF-α and IL-6, further impairing insulin signaling pathways [24]. Adipokine imbalance—including decreased adiponectin and increased leptin—compounds these metabolic effects by altering hepatic lipid handling and promoting steatogenic pathways [25]. Collectively, the metabolic and inflammatory alterations of hypothyroidism form a pathophysiological substrate highly conducive to the onset and progression of NAFLD. [23–25]

Overview of Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of hepatic conditions characterized by excessive fat accumulation in hepatocytes in the absence of significant alcohol intake or secondary causes of liver disease. It ranges from simple steatosis to non-alcoholic steatohepatitis (NASH), which can progress to fibrosis, cirrhosis, and hepatocellular carcinoma [26]. NAFLD is strongly associated with components of metabolic syndrome—including obesity, insulin resistance, dyslipidemia, and type 2 diabetes—highlighting its nature as a multisystem metabolic disorder rather than a liver-limited condition [27]. The pathogenesis involves multiple parallel insults such as lipid overload, oxidative stress, endoplasmic reticulum dysfunction, mitochondrial impairment, and inflammatory cytokine

activation [28]. These processes create a cycle of hepatocellular injury and impaired lipid homeostasis that promotes disease progression and systemic complications. [26–28]

The increasing global prevalence of NAFLD has positioned it as a major public health concern, with estimates suggesting that up to 30% of the adult population is affected, rising to over 70% among individuals with obesity or diabetes [29]. The disease is often asymptomatic in early stages, leading to delayed diagnosis and increased risk of progression to advanced fibrosis. Non-invasive tools, such as transient elastography and serum fibrosis biomarkers, have improved risk stratification, although liver biopsy remains the diagnostic gold standard for differentiating simple steatosis from NASH [30]. Importantly, recent evidence indicates that endocrine disorders—including hypothyroidism—play a significant role in modulating susceptibility to NAFLD, independent of traditional metabolic risk factors [31]. This association underscores the importance of evaluating hormonal and metabolic regulators, such as FGF21, that may contribute to hepatic lipid dysregulation in endocrine-related NAFLD. [29–31]

Epidemiological Links Between Hypothyroidism and NAFLD

A growing body of epidemiological evidence supports a significant association between hypothyroidism—both overt and subclinical—and the development of NAFLD. Large population-based cohort studies have demonstrated that individuals with higher thyroid-stimulating hormone (TSH) levels, even within the upper-normal range, have a greater prevalence of hepatic steatosis and increased risk of NASH [32]. Cross-sectional analyses from diverse populations, including the Rotterdam Study and NHANES cohorts, consistently show that hypothyroidism contributes independently to NAFLD risk after adjusting for age, BMI, diabetes, dyslipidemia, and other metabolic factors [33]. Furthermore, elevated TSH has been linked to increased hepatic fat content assessed by imaging modalities such as ultrasound and MRI-PDFF, suggesting a dose–response relationship between thyroid dysfunction severity and hepatic steatosis burden [34]. These findings underscore the importance of thyroid status as a determinant of liver fat accumulation across varying degrees of metabolic health. [32–34]

Additional studies indicate that hypothyroidism not only increases NAFLD prevalence but may also influence disease severity and progression. Evidence from Asian, European, and Middle Eastern cohorts shows that patients with overt or subclinical hypothyroidism exhibit higher rates of advanced fibrosis and more pronounced steatotic changes compared with euthyroid individuals [35]. The association persists across different diagnostic approaches—including liver biopsy studies, which confirm increased lobular inflammation and ballooning in hypothyroid patients—suggesting true pathophysiological relevance beyond confounding metabolic factors [36]. Moreover, thyroid hormone replacement therapy has been associated with reduced hepatic fat content and improved metabolic markers in several observational studies, further supporting a causal link [37]. Collectively, epidemiological data consistently demonstrate that hypothyroidism is an independent and clinically meaningful risk factor for NAFLD development and disease progression, justifying deeper mechanistic exploration of mediators such as FGF21. [35–37]

FGF21 Expression and Role in Liver Steatosis

FGF21 is predominantly produced by hepatocytes and is markedly induced under conditions of metabolic stress that challenge hepatic lipid homeostasis, such as fasting, ketogenic diets, obesity, and high-fat feeding [7,9]. In experimental models, hepatic Fgf21 expression is upregulated in response to increased fatty acid flux via PPARα activation, promoting transcriptional programs that enhance β-oxidation and ketogenesis while reducing triglyceride accumulation in the liver [10,38]. FGF21 also modulates lipoprotein metabolism and improves systemic insulin sensitivity, thereby indirectly lowering hepatic steatosis by reducing peripheral lipolysis and decreasing delivery of free fatty acids to the liver [4,39]. These actions collectively position FGF21 as a critical hepatokine that defends against lipid overload and steatotic injury, especially in settings of nutritional imbalance. [4,7,9,10,38,39]

Paradoxically, clinical and experimental studies have consistently shown that circulating FGF21 levels are elevated in patients with NAFLD and NASH, where hepatic fat accumulation and metabolic injury are already established [13,40]. Higher FGF21 concentrations correlate with histological severity of steatosis, inflammation, and fibrosis, suggesting that FGF21 is induced as a compensatory response to

hepatocellular stress and lipotoxicity [40,41]. However, the persistence of steatosis despite high FGF21 levels has led to the concept of "FGF21 resistance," in which target tissues—such as adipose tissue and liver—exhibit diminished responsiveness due to downregulation of β-Klotho or alterations in FGFR signaling [14,38]. This impaired signaling may blunt the protective metabolic actions of FGF21, allowing progression from simple steatosis to NASH and fibrosis. Understanding this dual pattern—protective in physiology yet insufficient in chronic disease—is essential when considering how FGF21 behaves in hypothyroid states complicated by NAFLD. [38,40,41]

Alterations of FGF21 Levels in Hypothyroid Patients

Several clinical studies have investigated circulating FGF21 concentrations in patients with thyroid dysfunction, revealing that hypothyroidism is frequently accompanied by significant alterations in FGF21 levels. In overt hypothyroidism, serum FGF21 is often elevated compared with euthyroid controls, a finding interpreted as a compensatory response to the profound dysregulation of lipid and energy metabolism in these patients [42]. Experimental work has demonstrated that thyroid hormone directly regulates hepatic Fgf21 transcription via TRβ, and hypothyroid states alter this axis, leading to complex patterns of FGF21 expression that may depend on disease severity and concomitant metabolic stressors such as obesity or insulin resistance [11,43]. Some cohorts have shown a positive correlation between TSH levels and circulating FGF21, suggesting that more pronounced thyroid failure is associated with stronger FGF21 induction, while free T3 and T4 levels tend to correlate negatively with FGF21 [42,43]. These observations support the concept that thyroid hormone deficiency perturbs FGF21 homeostasis as part of a broader adaptive response to metabolic stress. [11,42,43]

Importantly, FGF21 alterations in hypothyroidism appear to be at least partially reversible with appropriate thyroid hormone replacement. Studies evaluating patients before and after levothyroxine therapy have documented reductions in FGF21 levels parallel to improvements in lipid profiles, body weight, and insulin sensitivity, indicating that normalization of thyroid status alleviates the metabolic stimuli driving FGF21 elevation [42,44]. However, not all patients demonstrate complete normalization of FGF21, particularly those with persistent obesity or metabolic syndrome, suggesting that non-thyroidal factors such as adiposity, hepatic fat content, and systemic inflammation continue to modulate FGF21 secretion [44]. These findings imply that hypothyroidism acts as a key but not exclusive determinant of FGF21 dysregulation, and that FGF21 responses in hypothyroid patients must be interpreted within the broader context of their metabolic phenotype. This has direct relevance when assessing the relationship between FGF21 and NAFLD in this population, where both thyroid dysfunction and hepatic steatosis may independently drive FGF21 upregulation. [42–44]

Mechanistic Pathways Connecting FGF21, Thyroid Dysfunction, and NAFLD

The mechanistic interplay between thyroid dysfunction, FGF21 signaling, and NAFLD centers on the shared disruption of hepatic lipid metabolism, mitochondrial activity, and endocrine regulation. Thyroid hormone deficiency reduces hepatic β-oxidation, impairs mitochondrial oxidative phosphorylation, and promotes lipid storage, creating a metabolic environment that induces FGF21 expression as a compensatory hepatokine response [11,21,45]. FGF21 is upregulated through PPARα-dependent pathways activated during lipid overload and metabolic stress—both prominent features of hypothyroidism and NAFLD [10,38,45]. Additionally, impaired thyroid hormone signaling decreases autophagy and lipophagy, further contributing to hepatic lipid accumulation and generating cellular stress that stimulates FGF21 release [17,46]. These metabolic alterations place FGF21 at a central point in the adaptive response to hypothyroidism, attempting to restore lipid balance but often insufficient in the presence of persistent hepatic steatosis. [10,11,17,38,45,46]

A second mechanistic link arises from the concept of **FGF21 resistance**, which mirrors the patterns of hormonal resistance observed in hypothyroid-related metabolic dysfunction. Chronic lipid excess and inflammation in NAFLD reduce β-Klotho expression, impair FGFR1c signaling, and diminish tissue responsiveness to FGF21, thereby blunting its protective metabolic actions [14,41,47]. Hypothyroidism may exacerbate this state by increasing oxidative stress, promoting adipose dysfunction, and altering adipokine secretion—each of which interferes with FGF21 receptor signaling pathways [24,25,47].

Furthermore, shared downstream pathways such as AMPK, SIRT1, and PPARα are dysregulated in both hypothyroidism and NAFLD, reducing the efficacy of FGF21-induced metabolic improvements [45,48]. This convergence of impaired thyroid hormone action, elevated yet ineffective FGF21, and progressive hepatic fat accumulation illustrates a pathogenic cycle in which endocrine and hepatic dysfunction reinforce one another, promoting NAFLD progression in hypothyroid individuals. [45,47,48]

Clinical Evidence for the Association Between FGF21 and NAFLD in Hypothyroidism

Clinical studies demonstrate that hypothyroid patients with NAFLD exhibit significantly higher circulating FGF21 levels compared with hypothyroid individuals without hepatic steatosis, suggesting an additive metabolic stress that amplifies FGF21 expression [49]. In cohorts assessing thyroid function, hepatic fat content, and FGF21 simultaneously, serum FGF21 positively correlated with TSH levels and hepatic steatosis grades on ultrasound or MRI-PDFF, while inversely correlating with free T3 and T4 levels [42,50]. These associations support a mechanistic model in which worsening thyroid dysfunction promotes hepatic lipid overload, thereby stimulating FGF21 secretion. Importantly, FGF21 elevation in hypothyroid NAFLD patients often exceeds that seen in euthyroid NAFLD individuals, underscoring the synergistic metabolic impairment driven by thyroid hormone deficiency [50,51]. These findings highlight the potential of FGF21 as a metabolic indicator reflecting the combined burden of endocrine dysfunction and hepatic fat accumulation. [42,49–51]

Longitudinal data further support the interaction between thyroid status, FGF21, and NAFLD outcomes. Studies evaluating levothyroxine therapy in hypothyroid patients show reductions in hepatic steatosis parallel to improvements in FGF21 levels, suggesting that restoration of euthyroidism mitigates the metabolic triggers of both NAFLD and FGF21 overproduction [44,52]. Additionally, research in subclinical hypothyroidism indicates that even mild thyroid impairment produces measurable increases in FGF21, particularly in individuals with coexisting NAFLD or metabolic syndrome, reinforcing the sensitivity of FGF21 to early thyroid-related metabolic stress [53]. The consistency of these findings across diverse populations and diagnostic modalities strengthens the hypothesis that FGF21 serves as a key biomarker and potential mediator linking hypothyroidism with NAFLD progression. Together, clinical evidence supports a robust association between thyroid dysfunction, FGF21 dysregulation, and hepatic steatosis, providing a compelling rationale for integrating FGF21 assessment into metabolic evaluation of hypothyroid patients. [44,49–53]

Diagnostic and Biomarker Potential of FGF21 in NAFLD

FGF21 has emerged as a promising biomarker for detecting metabolic liver injury, including NAFLD, due to its strong association with hepatic fat content and steatohepatitis severity. Several studies have demonstrated that circulating FGF21 levels are significantly higher in patients with NAFLD compared with healthy controls, and correlate positively with liver fat measured by imaging or histology [40,54]. In biopsy-proven NAFLD cohorts, serum FGF21 rises with increasing grades of steatosis and necroinflammation, suggesting that it reflects not only lipid accumulation but also hepatocellular stress [40,55]. Receiver operating characteristic (ROC) analyses indicate that FGF21 may have moderate diagnostic performance for identifying NAFLD or NASH, particularly when combined with other clinical variables such as BMI, ALT, and markers of insulin resistance [54,55]. These data support the role of FGF21 as a sensitive, though not entirely specific, indicator of metabolic liver injury in clinical practice. [40,54,55]

In hypothyroid patients, the biomarker value of FGF21 must be interpreted within the context of concomitant endocrine and metabolic disturbances. Evidence suggests that FGF21 concentrations are higher in hypothyroid individuals with NAFLD than in those without hepatic steatosis, and that FGF21 levels track with both TSH and indices of liver fat, indicating that it integrates signals from thyroid dysfunction and hepatic metabolic stress [42,49,50]. This dual sensitivity positions FGF21 as a potential tool for early identification of NAFLD in hypothyroid populations, especially in patients with subclinical disease who might otherwise be missed by routine liver enzyme testing. However, FGF21 is also elevated in obesity, diabetes, and generalized insulin resistance, limiting its specificity when used in isolation [13,41,54]. Therefore, its most rational use may be as part of a composite biomarker panel or

risk score incorporating thyroid function, metabolic parameters, and non-invasive liver assessment to refine NAFLD risk stratification in hypothyroid patients. [50-54]

Conclusion

The relationship between hypothyroidism, FGF21 dysregulation, and non-alcoholic fatty liver disease represents a significant intersection of endocrine and metabolic pathology. Across physiological, mechanistic, and clinical domains, thyroid hormone deficiency impairs hepatic lipid oxidation, disrupts mitochondrial function, and promotes adipose tissue dysfunction. These disturbances create a metabolic environment that both elevates FGF21 secretion and simultaneously blunts its biological effectiveness through emerging patterns of FGF21 resistance. Although FGF21 is induced as part of an adaptive response to metabolic stress, its sustained elevation in hypothyroid patients with NAFLD reflects a failure to restore metabolic homeostasis.

Current evidence strongly supports the concept that FGF21 acts not only as a biomarker of metabolic derangement but also as an active participant in the pathophysiology linking hypothyroidism to hepatic steatosis. Thyroid hormone replacement can partially normalize FGF21 levels and improve hepatic fat content, implying that modulation of this hepatokine is integral to restoring metabolic balance. However, because FGF21 is influenced by multiple metabolic factors—including obesity, insulin resistance, and systemic inflammation—its diagnostic utility must be interpreted within a broader clinical framework.

The integration of FGF21 measurement into metabolic evaluation may enhance early detection of NAFLD in hypothyroid patients, identify individuals at higher risk of progression, and potentially guide targeted therapeutic interventions. Future research should prioritize longitudinal studies to clarify the causality between FGF21 changes and NAFLD improvement during thyroid hormone replacement, explore mechanisms of FGF21 resistance, and evaluate emerging FGF21 analogs as therapeutic options. A deeper understanding of these interconnected pathways may ultimately support more precise, endocrine-informed strategies for preventing and managing NAFLD in patients with thyroid dysfunction.

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