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Review Article

Pathogenesis of hypothyroidism-induced NAFLD: Evidence for a distinct disease entity?

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ABSTRACT

Nonalcoholic fatty liver disease (NAFLD), the most common liver disease worldwide, may be associated with primary hypothyroidism. However, the pathogenesis underlying such an association is complex and not completely understood. Here, we specifically discuss the pathogenic mechanisms potentially involved in hypothyroidism-induced NAFLD. To this end, we summarize the general pathophysiology of thyroid hormones (TH). Next, we analyze the published data from rodent studies by discussing whether hypothyroid rats may develop NAFLD via hyperphagia; whether mitochondria become energetically more efficient; what the overall energy balance is and if diversion of fatty substrates occurs; and the latest advancements in molecular pathogenesis brought about by metabolomics, cell imaging, lipophagy, autophagy and genetically engineered mouse models. Moreover, we discuss the data published regarding humans on the pathogenic role of TH, metabolic syndrome and other risk factors in hypothyroidism-related NAFLD as well as the putative mechanisms underlying the development of NAFLD-related hepatocellular carcinoma in hypothyroidism. In conclusion, although many research questions still remain unanswered, the pathophysiology of hypothyroidism-induced NAFLD makes this a potentially curable and distinct disease entity. However, further studies are needed to better elucidate the underlying mechanisms, and to ascertain whether treatment with either TH or thyromimetic agents improves NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is a common clinicopathologic syndrome resulting from an unbalanced energy homeostasis which is strongly and bi-directionally associated with the metabolic syndrome (MetS) [1,2]. Although the spectrum of NAFLD spans from simple steatosis, nonalcoholic steatohepatitis (NASH) to cirrhosis and hepatocellular carcinoma (HCC) [3], most patients with NAFLD die owing to cardiovascular disease and extrahepatic cancers [4]. Therefore, NAFLD poses a considerable clinical and economic burden on health-care systems worldwide [5,6].

Primary hypothyroidism is an endocrine disease, typically characterized by thyroid hormones (TH) deficiency [7–9]. Overt hypothyroidism is identified by high thyroid-stimulating hormone (TSH) and low free thyroxine concentrations [10]. Hypothyroidism affects up to 2–3% of individuals living in iodine-replete communities [11,12], and can present with systemic symptoms, neuro-psychiatric complaints, or metabolic derangements [7–9].

Although primary hypothyroidism has been associated with NAFLD [13], the pathogenesis of hypothyroidism-induced NAFLD (HIN) is very complex and not completely understood. However, given the clinical importance of HIN from an epidemiological and pharmacological perspective, this narrative review aims at critically discussing the currently available experimental and clinical studies, which may be relevant in further characterizing HIN as a distinct disease entity.

2. Brief overview of epidemiological studies

The epidemiology of HIN has been reviewed elsewhere [13,14]. Overall, the principal original observational studies (Table 1

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Table 1
Principal observational studies pros and contra the NAFLD-hypothyroidism association.

Author, year (Ref)	Study characteristics	Main findings
Studies *in favour* of the association		
Liangpunsakul and Chalasani, 2003 [15]	Cross-sectional case-control study: 174 patients with NASH and 442 matched controls free of liver diseases	Hypothyroidism was independently associated with NASH
Chung et al., 2012 [20]	Cross-sectional study of 4648 adults	Hypothyroidism was independently associated with NAFLD; the severity of hypothyroidism was associated with NAFLD in a dose-dependent manner
Pagadala et al., 2012 [16]	Cross-sectional case-control study: 246 patients with NAFLD and 430 matched healthy controls	Hypothyroidism was independently associated with NAFLD and NASH
Xu et al., 2012 [17]	Longitudinal case-control study: 327 adults with subclinical hypothyroidism and 327 matched euthyroid controls	Subclinical hypothyroidism was independently associated with risk of incident NAFLD
Carulli et al., 2013 [18]	Cross-sectional study of 69 euthyroid patients with NAFLD: 25 with simple steatosis and 44 with NASH	In euthyroid NAFLD patients, high-though-normal TSH values were independently associated with NASH
Pacifico et al., 2013 [22]	Cross-sectional study of 402 consecutive overweight or obese children	Subclinical hypothyroidism was independently associated with NAFLD
Bano et al., 2016 [19]	Longitudinal prospective cohort study of 9419 elderly euthyroid individuals	Both subclinical and overt hypothyroidism were independently associated with risk of developing incident fibrosing NAFLD
Kaltenbach et al., 2017 [23]	Cross-sectional study of 332 overweight or obese children and adolescents	Subclinical hypothyroidism was independently associated with NAFLD
Kim et al., 2018 [21]	Cross-sectional study of 425 individuals with NAFLD	Subclinical hypothyroidism was independently associated with NASH and advanced fibrosis. Both NASH and advanced fibrosis increased in parallel with increasing serum TSH concentrations
Kim et al., 2018 [31]	Cross-sectional study of 7259 adults without thyroid diseases and known causes of chronic liver disease	Subjects with either 'low-normal' thyroid fuction or subclinical hypothyroidism had a higher prevalence of advanced fibrosis than those with strictly-normal thyroid function tests
Studies *against* the association		
Itterman et al., 2012 [24]	Population-based study of 3661 individuals without self-reported history of thyroid or liver diseases	Hypothyroidism was not associated with NAFLD in both sexes. In contrast, serum FT4 levels were inversely associated with NAFLD in both men and women
Zhang et al., 2012 [25]	Cross-sectional study of 1322 euthyroid adults	Subclinical hypothyroidism was not associated with NAFLD
Eshraghian et al., 2013 [26]	Cross-sectional study of 832 consecutive individuals	Neither subclinical nor overt hypothyroidism were associated with NAFLD
Posadas-Romero et al., 2014 [27]	Cross-sectional study of 753 adults	Subclinical hypothyroidism was not associated with NAFLD
Ludwig et al., 2015 [28]	Cross-sectional population-based study of 1276 adults	Neither subclinical nor overt hypothyroidism were associated with NAFLD
Lee et al., 2015 [29]	Longitudinal (retrospective) cohort study of 18,544 NAFLD-free individuals at baseline	Neither subclinical nor overt hypothyroidism were associated with risk of developing incident NAFLD
Lingad-Sayas et al., 2017 [30]	Cross-sectional study of 580 adults	Subclinical hypothyroidism was not associated with NAFLD

[15–31]), as well as the published meta-analyses [13,32–34] have yielded conflicting findings with some observational studies reporting a significant association between NAFLD and overt or subclinical hypothyroidism (or elevated TSH levels, even within the normal range), and with other studies failing to find any significant association between NAFLD and hypothyroidism or normal-high TSH levels. These conflicting findings, which are likely due to the ethnic variability and the variable criteria used for diagnosing NAFLD in such observational studies [13,14], accrue the importance of further addressing HIN under a pathophysiological perspective.

3. Pathophysiology of thyroid hormones

By synthesizing and releasing iodinated TH 3,3′,5,5′-tetraiodo-L-thyronine (T4) and 3,5,3′-triiodo-L-thyronine (T3) into the bloodstream, the thyroid regulates multiple biological activities in the liver, adipose tissue, central nervous, cardiovascular and musculoskeletal systems [12]. By modulating glucose and lipid metabolism, the chief physiological function of TH is to sustain basal energy expenditure. Within the hepatocytes, further to promoting export and oxidation of lipids, TH may stimulate de novo lipogenesis (DNL) [35]; control hepatic insulin sensitivity and suppress hepatic gluconeogenesis [36]. The TH receptor (TR) controls lipid and glucose metabolism both directly, by acting on the expression of multiple genes, and indirectly by acting on a variety of other nuclear receptors, such as peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways [36]. However, a functional interaction may also occur between TH and hormonal stress response. In fact, further to stimulating the expression of uncoupling proteins in mitochondria, TH control both metabolic and energy homeostasis by potentiating the expression of adrenergic receptors and their responsiveness to catecholamines [37]. More specifically, TH may control body weight, thermogenesis, lipolysis and metabolism mainly through the differential tissue distribution of two major TR isoforms: α and β, which exert distinct roles in TH signaling [38]. TRα is preferentially expressed in the brain, white adipose tissue (WAT) and myocardial atria, while brown adipose tissue (BAT) contains both TRα and β [39]. Conversely, TRβ is the predominant receptor isoform in the liver and cardiac ventricles. TRβ agonists, such as sobetirome and eprotirome, may decrease circulating low-density lipoprotein (LDL)-cholesterol levels without increasing heart rate [40]. Other selective TRβ agonists, such as MGL-3196 and VK2809, are currently under investigation in NASH phase 2 clinical trials [3]. Noteworthy, as will also be discussed in greater detail below, preliminary evidence has shown that short-term treatment with MGL-3196 may improve intra-hepatic fat content, serum aminotransferase levels and lipid profile in patients with biopsy-proven non-cirrhotic NASH [41].

Local activation of T4 to its biologically active form, T3 by the 5′-deiodinase type 2 (D2) is a key mechanism in the regulation of TH metabolism. D2 is expressed in various tissues, including the hypothalamus, WAT, BAT and skeletal muscles. Moreover, a complex interaction also occurs among D2, TRs, β adrenergic receptors and uncoupling proteins, which play important roles in the development of obesity [42].

The thyroid gland is centrally regulated by both thyrotropin-releasing hormone (TRH) and TSH levels, as well as by leptin and other peptides regulating the appetite. The integration of TH signaling with the adrenergic nervous system occurs in the hypothalamus and peripherally, both in the liver and in adipose tissue [36].

Understanding the mechanisms and interactions of various TH signaling pathways with both glucose/lipid metabolism and energy expenditure will improve our capacity to identify novel therapeutic targets for liver and metabolic diseases [36]. For example, 3,5-diiodo-L-thyronine (T2), which has been initially considered only as a T3 catabolite, may target mitochondria and mimic several effects of T3 on energy metabolism in rat models without those adverse side-effects, which are usually associated with the use of T3 or T4 [43]. Administration of T2 to hypothyroid rats leads to increased fatty acid (FA) oxidation rate; increased downstream respiratory activity; and increased proton leak and decreased oxidative stress [43]. As such, T2 may represent a potential agent for the treatment of selected metabolic conditions [35].

Which pathogenic mechanism(s) account for the association of primary hypothyroidism with NAFLD? To answer this question, we follow a comprehensive approach by discussing experimental studies in rat models (spanning from classical studies of biochemistry to more recent advances in molecular biology); next, we report on those few available data evaluating the pathogenesis of HIN in humans.

4. Experimental studies

4.1. Are hypothyroid rats hyperphagic?

Given the functional link of leptin and other appetite-regulating peptides with thyroid hormones, primary hypothyroidism might promote NAFLD via body weight gain associated with hyperphagia. However, a recent experimental study in high-fat fed rats indicated that surgery-induced hypothyroidism leads to reduced water/food intake and NAFLD via increased secretion of glucagon-like peptide (GLP)-1 [45]. Consistently, in rats treated with methimazole, hypothyroidism-induced hypophagia was associated with alterations in protein expression of neuropeptide Y and pro-opiomelanocortin in the arcuate nucleus, despite the co-existence of central leptin resistance and impairment in leptin signaling cascade [46]. Collectively, therefore, the available experimental evidence suggests that an explanation must be looked for in a more subtle metabolic derangement other than HIN resulting from hyperphagia and weight gain.

4.2. Are mitochondria energetically more efficient in hypothyroid rats?

In animal models, mitochondria have extensively been studied as sub-cellular targets of TH actions owing to their key role in energy homeostasis [47–56]. The general paradigm, emerging from pioneering studies in hypothyroid rats, has identified several changes in the lipidomics of mitochondrial membranes, namely increased linoleic acid and decreased arachidonic acid and Δ 6 and Δ 5 desaturases [47]; increased total cholesterol and cholesterol/phospholipid molar ratio [48]; decreased phosphatidyethanolamine-to-phosphatidylcholine ratio [47] and decreased cardiolipin [55]. Collectively, these lipid changes may decrease the mitochondrial membrane fluidity and depress the activity of membrane-bound carriers, which are key regulators of energy substrate fluxes. Indeed, a lower rate of oxidative phosphorylation; an impaired respiration and efficiency of energy-producing processes; and a reduced lipogenesis will ensue as the result of reduced heart and liver cell metabolism in hypothyroid rats [48]. Several membrane-bound carriers and enzymes, such as the adenine nucleotide translocase [50]; the piruvate carrier [51–53]; the tricarboxylate carrier [54]; the cytochrome oxidase [55,56]; the carnitine translocase [57], and the citrate carrier [47] are all functionally affected by the aforementioned lipidomic changes of mitochondrial membranes.

Interestingly, TH administration to these hypothyroid rats cannot correct the alterations in membrane fatty acyl contents, although it may mimic the effects of unsaturated fatty acyls [58], restore the proton permeability of hepatic mitochondria and thus the respiratory process [59,60]. Similarly, the decreased activity of carnitine-acylcarnitine translocase activity in heart mitochondria is normalized by exogenous cardiolipin, but not by other phospholipids [61].

Differently from hyperthyroidism, which mimics feeding an unbalanced high-carbohydrate, fat-free diet [62], overt hypothyroidism in rats is not associated with increased hepatic lipogenesis, but lipogenesis mostly occurs in the skin, bone, and muscles [63]. Lipogenesis involves fluxes of metabolites across mitochondrial membranes, requiring cooperation between multiple mitochondrial and cytoplasmic enzymes [64]. TH may modulate the liver's contribution to total lipogenesis in rats to a substantial extent. Hypothyroidism is associated with significant decreases in basic metabolic rate, oxygen consumption, and oxidation of glucose, FAs and aminoacids [65,66] as well as with decreased FA synthase activity [67]. It has been demonstrated experimentally that the liver's contribution to total lipogenesis (accounting for ~35% in hyperthyroid rats) drops to as little as ~5% in hypothyroid rats [68].

In hypothyroidism, altered lipidomics may also exert some systemic effects. For example, ceramides (i.e., the second messenger in the sphingomyelin signaling pathway) decrease in the liver as a result of reduced rate of sphingomyelin hydrolysis [69]. Decreased hepatic ceramides account for hypothyroidism in rats, leading to increased cell proliferation and decreased cell differentiation and apoptosis, all of which result from a low-grade proinflammatory state [69].

Collectively, the aforementioned experimental evidence supports the existence of an altered fluidity of mitochondrial membranes, which may induce decreased total and resting energy expenditure, impaired hepatic lipogenesis and systemic low-grade inflammation. Therefore, it is plausible to assume that in HIN there is an alteration in systemic (extra-hepatic) energetic homeostasis.

4.3. Overall energy balance and fatty substrate diversion

Rats with methimazole-induced hypothyroidism exhibit a hypo-metabolic phenotype, featuring decreased total and resting energy expenditure as well as decreased glucose oxidation [70]. In these hypothyroid rats, triglyceride-derived FA uptake is increased in WAT in association with increased lipoprotein lipase (LPL) activity, but unaffected in the muscle and the heart, and decreased in the liver [70]. LPL, by hydrolyzing triglycerides in circulating triglyceride-rich lipoprotein particles, serves as a metabolic 'gatekeeper', by regulating tissue-specific FA uptake and directing substrates to tissues according to the body's metabolic status [71–73].

Yao did not observe any increased hepatic fat content in hypothyroid mice, although the liver was enlarged [74]. He also found that hypothyroidism decreased saturated fatty acid (SFA) content, while TH treatment restored the level of SFA. In agreement with this finding, the authors found that the expression of both acetyl-CoA carboxylase 1 and FA synthase (i.e., the rate-limit enzymes for DNL) decreased in hypothyroid mice, while increased after TH treatment. Again, they found that the ratio of C18:1n-9/C18:0 and C16:1n-7/C16:0 was decreased by TH treatment, suggesting that the activity of stearoyl-CoA desaturase-1 was suppressed [74]. This finding suggests that TH may suppress hepatic

fat accumulation by reducing FA desaturation via decreased activity of stearoyl-CoA desaturase-1, the main enzyme responsible for the conversion of SFA to monounsaturated FAs [75,76]. Additionally, hepatic glycogen content was substantially influenced by TH status, which was associated with increased glycogen synthase expression. Thus, the increased hepatic glycogen storage might explain hepatomegaly of these hypothyroid mice [74]. Collectively, these experimental findings support the notion that, in hypothyroid mice, DNL suppression could divert the surplus dietary carbohydrate to glycogen synthesis rather than storing as lipids, accounting for increased amounts of hepatic glycogen in front of declining hepatic steatosis [74].

Although it is different from NAFLD in humans, the mouse models of methimazole-induced hypothyroidism suggest that HIN may not entirely be attributed to decreased TH signaling in the liver with a consequent decrease in lipid utilization [74]. Based on the above findings, Ferrandino et al. [77] hypothesized that systemic (extra-hepatic) mechanisms might also contribute to HIN. To identify such mechanisms, these authors generated an experimental model of mildly hypothyroid mice which, although their hepatic TH signaling and lipid utilization were normal, developed multiple features of MetS, such as expanded and inflamed adipose tissue, impaired pancreatic insulin secretion, hepatic insulin resistance (IR) and NAFLD [77]. In contrast, severely hypothyroid mice showed down-regulation of TH signaling in their livers and profound suppression of adipose tissue lipolysis, which decreased delivery of FAs to the liver. The resulting lack of substrates for triglyceride esterification protected severely hypothyroid mice against NAFLD [77]. Therefore, in these animal models, NAFLD developed when TH levels were mildly reduced, but, paradoxically, not when they were severely reduced, thus confirming that the pathogenesis of HIN is both intra- and extra-hepatic [77]. Collectively, therefore, these experimental data in animals underline the need to investigate the pathogenesis of human HIN in a more integral fashion [77].

4.4. Major advances in molecular pathogenesis of hypothyroidism-induced NAFLD

Significant discoveries in metabolomics, cell imaging, lipophagy, autophagy and genetically engineered mouse models have recently contributed to promoting our understanding of the TH- and TRH-mediated molecular regulation of hepatic lipid metabolism [78,79].

Lipidomic signature is key to the risk of NASH progression or resolution [80]. A consistent line of research has identified T3 as a factor protecting from lipotoxic compounds, such as ceramides and diacylglycerol, which derive from excess intracellular palmitate [81]. Further to its action mediated by increased expression of mRNA and enzymatic activity of hepatic lipases [82], T3 promotes FA catabolism through hepatic lipophagy (namely autophagy of FAs in hepatocytes) to traffic lipids to lysosomes [83,84] and stimulate FA β-oxidation [84]. Furthermore, autophagy may promote cell survival during starvation and upon challenge by either inflammatory or pro-apoptotic injuries [82,85]. Sirtuin-1 (SIRT1) is required for TH-mediated autophagy [86].

Viability of hepatocytes and pancreatic beta cells critically depends on the organisms' capacity to prevent the degeneration of mitochondria via normal mitophagy [81]. In this regard, confocal microscopy studies showed that T3 increased both mitophagy and mitochondrial biogenesis mediated by PGC1a [81,86]. Importantly, liver-tissue specific hypothyroidism may be a feature of NAFLD, as supported by the finding that hepatic T3 concentrations (rather than those of T4 and rT3) are decreased in rats developing NAFLD after a 12-week methionine- and choline-deficient diet [81].

Finally, Yan et al., by leveraging a genetically engineered mouse model knock-out for TSH receptor, documented a novel extra-thyroid role of TSH in regulating triglyceride metabolism via decreased AMPK and increased activity of hepatic SREP-1c through the cAMP/PKA/PPAR-alpha pathway [79].

Collectively, these innovative experimental studies offer new insights into the potential molecular mechanisms and subcellular/molecular targets for HIN, providing strong rationale for using TH and/or thyromimetic agents to treat liver and metabolic disorders [78].

5. Hypothyroidism-induced NAFLD in humans: putative pathogenic mechanisms

Similarly to what has been observed in animal models, the pathogenesis of HIN in humans is based mainly on extra-hepatic factors [74,77], which include the MetS and its individual features, as schematically illustrated in Fig. 1.

5.1. Metabolic syndrome

Hypothyroid individuals often exhibit the typical features of MetS [86–88], and even slightly elevated serum TSH levels (with normal FT4 levels) may be associated with an increased prevalence of MetS [89,90]. The finding that MetS features are partly reversible after levothyroxine replacement therapy further supports the existence of a cause-and-effect relationship [89,90].

MetS represents a gamut of heterogeneous metabolic disorders among which obesity, dysglycemia and dyslipidemia may also be influenced by hypothyroidism [7,91].

Obesity appears to abrogate the hepatic effects of T3. Experimentally, the expression of a subset of genes, regulating RNA metabolism, protein degradation, and energy metabolism, was inversely associated with hepatic fat content in both humans and mice, whose obesity had been induced by high-fat diets; however, T3 injection acutely increased the expression of such genes in the livers of chow-fed mice, but not in high fat-fed mice, suggesting that obesity may impair the regulation of T3 on these genes [92].

Properly conducted levothyroxine replacement therapy in hypothyroidism will usually lead to an improvement of obesity [91]. Conversely, whether pharmacological correction of hypothyroidism also results in decreased blood pressure is presently unknown. In fact, one study suggested the existence of complex pathophysiological mechanisms at the basis of the association between hypothyroidism and hypertension owing to increased arterial resistance and stiffness [93]. However, overt hypothyroidism may have a modest effect on hypertension, whereas subclinical hypothyroidism does not [94].

Hypothyroidism is also often associated with atherogenic dyslipidemia, featuring hypertriglyceridemia [95–97]; raised LDL-cholesterol and VLDL-cholesterol [27,96,98–100]; low HDL-cholesterol [95,101]; and elevated apoB lipoproteins [96]. The mechanisms underlying this association are incompletely understood and the finding that atherogenic dyslipidemia is observed also in subclinical hypothyroidism [102] raises the possibility that high serum TSH levels might directly promote dyslipidemia in these individuals. Moreover, hypothyroidism may worsen NAFLD-associated atherogenic dyslipidemia [16], which may also be exacerbated by smoking and IR [103].

Little is known regarding the association, if any, of hypothyroidism with T2D [104,105]. However, if we admit that hypothyroidism may induce IR, we could also anticipate an increased risk of incident T2D. Further research on this topic is eagerly awaited, although studies on the natural history of untreated overt hypothyroidism in humans would be, of course, unethical.

Interestingly, one study reported that the significant association between hypothyroidism and NAFLD persisted after adjustment for

coexisting metabolic risk factors [20], supporting the notion that hypothyroidism might contribute to NAFLD development, irrespective of obesity and MetS.

IR and increased oxidative stress, which are not included among the diagnostic criteria of MetS, are nevertheless key determinants of its pathogenesis [106]. IR has closely been associated with overt/subclinical hypothyroidism; and the observed improvement in systemic IR after levothyroxine replacement therapy strongly suggests a cause-and-effect association [107–113]. Individuals with hypothyroidism are also prone to increased oxidative stress [114,115], secondary to mitochondrial dysfunction [16] [i.e. a pathogenic feature of both hypothyroidism and NASH [116,117]], which may partly be explained by an altered cardiolipin metabolism [118,119].

5.2. Other factors

5.2.1. TSH

Several observational studies showed that elevated serum TSH levels were significantly associated with the presence and severity of NAFLD [13,18,21–23,34]. However, the criteria used for diagnosing subclinical or overt hypothyroidism were heterogeneous across such published studies. Mechanistically, increased serum TSH levels may directly promote hepatic steatogenesis, mainly via an up-regulation of SREBP-1c activity triggered by stimulation of TSH receptors, located in hepatocyte cell membranes [79] (Fig. 1). This finding further supports the view that multiple, not mutually exclusive, pathogenic mechanisms are probably involved in human HIN.

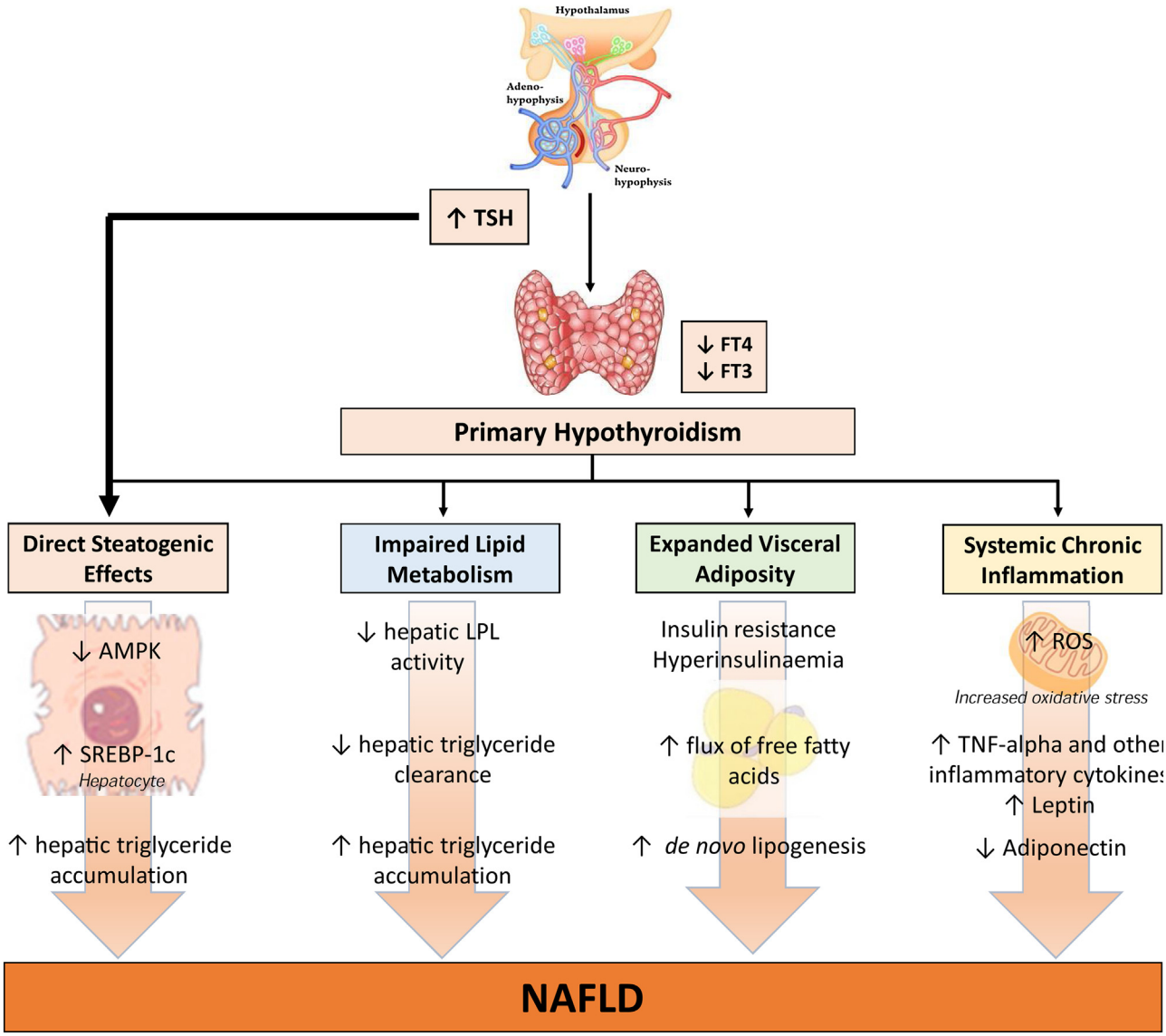

Fig. 1. Possible pathogenic mechanisms linking primary hypothyroidism to the development and progression of NAFLD.
This cartoon highlights the duality of pathogenic mechanisms potentially involved in hypothyroidism-induced NAFLD. The MetS plays a key role in mediating the link between hypothyroidism and NAFLD via decreased concentrations of serum thyroid hormones. However, a more direct pathogenic pathway can also occur owing to the agonism exerted, independent of thyroid hormone concentrations, by increasing serum thyroid stimulating hormone (TSH) levels directly stimulating TSH receptors on the hepatocyte cell membranes, which may contribute to the development of NAFLD via a more direct route involving AMPK, cAMP, PKA and PPARα. Although not mutually exclusive, these two different pathogenic pathways (mediated by reduced thyroid hormones or, directly, by increased TSH levels) pave the way to different therapeutic strategies (agonism of thyroid hormone receptors as opposed to antagonism of TSH receptors).

5.2.2. Sex hormones

Younger men are more likely to develop NAFLD than age-matched women; post-menopausal women, however, are no longer protected from NAFLD [120]. Also hypothyroidism is a sexually dimorphic condition, affecting women more than men [16,121–123]. The finding that the association between hypothyroidism and NAFLD occurred more frequently in women, though its statistical significance was lost after adjusting for waist circumference [24], further highlights the possible pathogenic role of abdominal visceral fat accumulation [i.e., a typical feature of men and post-menopausal women [120]] in the link between hypothyroidism and risk of NAFLD development and progression.

5.2.3. Fibroblast growth factor-21

The emerging evidence suggesting that in hypothyroidism serum levels of FGF-21 are raised [124] is intriguing, given that FGF-21 may play a role in NASH development [125,126]. However, further larger studies are needed to confirm these findings.

5.3. Evidence from randomized controlled trials in NAFLD

Further evidence of a possible causal association between primary hypothyroidism and NAFLD comes from the findings of three recent small clinical trials performed in patients with NAFLD.

In a post-hoc analysis of an open-label, randomized controlled trial designed to assess the effects of levothyroxine replacement therapy on plasma lipid profile in patients with subclinical hypothyroidism (n = 366 elderly Chinese individuals), the authors found that compared with patients treated with placebo, a 15-month treatment with levothyroxine resulted in a marked improvement in serum liver enzymes and NAFLD on ultrasonography both in patients with significant subclinical hypothyroidism (i.e., defined as a serum TSH level ≥10 mIU/L) and in those with mild subclinical hypothyroidism (i.e., TSH of 4.2–10 mIU/L) and coexisting dyslipidemia [127].

In a phase 2b, single arm, multicenter trial, involving 20 euthyroid men with NAFLD and stable T2D (performed in six hospitals in Singapore), the authors examined whether a 16-week, low-dose levothyroxine therapy significantly decreased intrahepatic lipid content as measured by proton magnetic resonance spectroscopy. Notably, this trial showed that low-dose levothyroxine administration (titrated for reaching a serum TSH level of 0.34–1.7 mIU/L before a 16-week maintenance phase) was associated with a significant decrease in intrahepatic triglyceride content by ~12% relative to baseline (absolute change, −2%; 95%CI, −3 to 0; p = .046), despite small or negligible decreases in body weight, body fat composition (abdominal visceral and subcutaneous adipose tissue), IR and plasma lipid profile [44].

Finally, an ongoing 36-week multicenter randomized, double-blind, placebo-controlled phase 2 trial in adult patients with biopsy-proven NASH evaluates the efficacy of MGL-3196 (i.e. a selective TRβ agonist) in reducing hepatic steatosis as assessed by magnetic resonance imaging proton density fat fraction. Preliminary findings of 116 patients with NASH revealed that after 12 weeks of treatment the primary study endpoint of a relative reduction in proton density fat fraction was reached. This reduction in hepatic fat content in patients randomly treated with MGL-3196 was achieved without significant changes in body weight, but with significant decreases in serum lipids and aminotransferase levels [41].

We believe that, collectively, the results of these recent randomized controlled trials provide a strong rationale for further investigation, development, and testing of TH and/or TH analogs for long-term treatment of patients with NAFLD.

6. Pathogenic mechanisms underlying the development of NAFLD-related hepatocellular carcinoma in hypothyroidism

6.1. Epidemiology of HCC

Owing to the decline of viral causes of this primary liver cancer, NAFLD-related HCC is an ever-increasing cause for liver transplantation and mortality worldwide [128–135].

Compared to HCC due to viral etiology, NAFLD-related HCC pathogenic pathways are less characterized; the population at risk is poorly identifiable; the predisposing condition has higher prevalence rates in the general population; and its occurrence in non-cirrhotic livers is higher [133,134]. Collectively, these features have so far hampered effective screening programs and management protocols to apply to NAFLD-related HCC, thus contributing to increased mortality of these patients [130,133,136–141]. Further research in this area is therefore a major clinical priority.

6.2. Pathogenesis of HCC in hypothyroidism

Some studies have suggested that hypothyroid patients are at high risk of developing incident HCC [137,138] which is mediated by NAFLD. In their seminal case-control study of 160 HCC patients, Reddy et al. found that patients with 'cryptogenic' HCC were more likely to have a history of hypothyroidism as compared to HCC patients with HCV or alcoholic liver disease [137]. A subsequent case-control study enrolling 420 patients with HCC compared to 1104 healthy controls showed that hypothyroidism and HCC were significantly associated among hepatitis virus-negative, non-drinker, non-diabetic, non-smoker and non-obese individuals. Moreover, an increased risk of HCC was also found in diabetic women and in patients with chronic HCV infection, but not in those with hyperthyroidism [138].

A reduced TH signaling in the liver harboring pre-neoplastic liver lesions [142]; long-standing hypothyroidism; decreased sex hormone binding globulin (SHBG), together with increased lipid peroxidation, IR/hyperinsulinemia, increased insulin-like growth factor-1 levels, systemic chronic inflammation, DNA damage and obesity could play a pathogenic role in the development of NAFLD-related HCC in primary hypothyroidism [138]. Further confirming the clinical potential of these topics, the interaction of TH with its receptor(s) may act as a tumor suppressor in HCC cell lines via the regulation of miR-214 [143].

However, given the complex and multi-step cancerogenesis leading to HCC [144,145], more research is warranted to discover specific pathogenic mechanism(s) linking primary hypothyroidism with NAFLD-related HCC.

7. Conclusions

The inconsistent findings across the published observational studies raise the possibility that in primary hypothyroidism NAFLD is triggered by variable pathogenic (both intra- and extra-hepatic) mechanisms based on individual predisposition. The coexistence of MetS features with increased serum TSH levels does not necessarily entail hypothyroidism as the cause of NAFLD in all patients.

While keeping such limitations in mind, in this review we have highlighted that the theory supporting a causal association between primary hypothyroidism and NAFLD may have a strong biological rationale and important clinical and pharmacological implications.

We believe that, based on its unique etiology and increasingly recognized bio-molecular pathophysiology, hypothyroidism-induced NAFLD is a distinct disease entity. At variance with primary NAFLD, hypothyroidism-induced NAFLD has the potential for being

curable with thyroid hormone replacement therapy. Althoughthis conclusion remains to be definitely proven in larger randomized controlled trials, the possibility to use some of the biological actions of TH and their non-toxic derivatives remains a fascinating perspective for the treatment of NAFLD and its most dreadful complications.

Conflict of interest

None declared.

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