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Hypothyroidism and Nonalcoholic Fatty Liver Disease: Pathophysiological Associations and Therapeutic Implications

Tomislav Kizivat^{#1,2}, Ivana Maric^{1,2}, Dunja Mudri^{1,2}, Ines Bilic Curcic^{#1,2},
Dragan Primorac^{1,3,4,5,6,7,8} and Martina Smolic^{*1,8}

¹University of Osijek, Faculty of Medicine, Osijek, Croatia; ²University Hospital Osijek, Osijek, Croatia; ³St Catherine Specialty Hospital, Zagreb & Zabok, Croatia; ⁴University of Split School of Medicine, Split, Croatia; ⁵Eberly College of Science, State College, Penn State University, PA, USA; ⁶The Henry C Lee College of Criminal Justice & Forensic Sciences, University of New Haven, West Haven, CT, USA; ⁷University of Rijeka School of Medicine, Rijeka, Croatia; ⁸University of Osijek Faculty of Dental Medicine & Health, Osijek, Croatia

Abstract

Nonalcoholic fatty liver disease (NAFLD) is a complex clinical entity which can be secondary to many other diseases including hypothyroidism, characterized by lowering of thyroid hormones and increased thyroid stimulating hormone (TSH). A lot of emerging data published recently advocates the hypothesis that hypothyroid induced NAFLD could be a separate clinical entity, even suggesting possible treatment options for NAFLD involving substitution therapy for hypothyroidism along with lifestyle modifications. In addition, a whole new field of research is focused on thyromimetics in NAFLD/NASH treatment, currently in phase 3 clinical trials. In this critical review we summarized epidemiological and pathophysiological evidence linking these two clinical entities and described specific treatment options with the accent on promising new agents in NAFLD treatment, specifically thyroid hormone receptor (THR) agonist and its metabolites.

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Introduction

Interest in nonalcoholic fatty liver disease (NAFLD) has been growing rapidly in research and in clinical practice over the last 25 years. Much effort and extensive research in the field have yielded important information on risk factors for devel-

opment and progression of the disease,¹ hepatic and extra-hepatic complications² and on treatment.³ In the last 20 years, NAFLD has become one of the most common liver diseases in the world, encompassing almost 25% of the world's population and including children.⁴

Metabolic syndrome is defined as a cluster of risk factors, including visceral adiposity which increases insulin resistance and predisposes to type 2 diabetes (decreased glucose tolerance), dyslipidemia and hypertension. Each of these factors predicts development of all of the others, thereby clustering them in a metabolic syndrome disorder over time.⁵ Hormonal disbalance, including of sex hormones, growth hormones and thyroid hormones, can also be a predisposing factor for development of metabolic syndrome.^{6–8} NAFLD as a primary disease can follow, coexist or precede metabolic syndrome, but it can also be secondary to other causes.⁹

Some of the secondary causes of NAFLD include viral infections, nutrition, drugs, surgery and some endocrine diseases like primary hypothyroidism, hypogonadism, growth hormone deficiency and polycystic ovary syndrome.⁹ Recently, NAFLD induced by hypothyroidism has been described as a distinct disease entity, due to its strong epidemiological connection and unique pathophysiology; as such, it could serve as a model for identification of new therapeutic options for some cases of primary NAFLD.^{10,11} An additional issue is subclinical hypothyroidism, since it has been reported that one in six patients with NAFLD have concomitant subclinical hypothyroidism, presumably related to carbohydrate metabolism disorders.¹² Surprisingly, Lee and colleagues¹³ reported that in Korean population with hepatic steatosis index of 36 or higher, subclinical hypothyroidism was related to a high risk of NAFLD in males but not in females.

In this critical review, we describe and summarize evidence on epidemiological and pathophysiological associations as well as treatment options for hypothyroid-induced NAFLD. It is important to note that in clinical practice, this association is often not considered by endocrinologists, and moreover gastroenterologists often dismiss underlying thyroid hormone disbalance, leading to NAFLD. Thus, it is necessary to sensitize all specialties involved, in order to adequately address this issue.

Keywords: NAFLD; MAFLD; Hypothyroidism; Metabolic syndrome; Thyromimetics.
Abbreviations: HMG-CoA, 3-hydroxy-3-methyl-glutaryl coenzyme A; LDL cholesterol, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ROS, reactive oxygen species; SREBP-1c, sterol regulatory element-binding transcription factor 1c; T1AM, 3-iodothyronamine; T2, 3,5-diiodothyronine; TG, triglyceride; THR, thyroid hormone receptor; TNF- α , tumor necrosis factor- α ; TSH, thyroid stimulating hormone.

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[#]Both authors contributed equally to this manuscript.

***Correspondence to:** Martina Smolic, University of Osijek, Faculty of Medicine, Department of Pharmacology; Faculty of Dental Medicine and Health, Department of Pharmacology and Biochemistry, J. Huttlera 4, 31000 Osijek, Croatia. Tel: +385-31-512-800, Fax: +385-31-512-833, E-mail: martina.smolic@mefos.hr

Epidemiological background

Prevalence of primary hypothyroidism is between 0.3% and 3.7% in the general population of the USA and 0.2 and 5.3% of the European general population. It is defined by biochemical increase of thyroid-stimulating hormone (TSH) and lowering of the thyroid hormones thyroxine and triiodothyronine, as clinical or overt hypothyroidism, and as subclinical hypothyroidism if only TSH is increased and thyroid hormones are in reference interval.¹⁴

Not all observational studies and meta-analyses show connection between hypothyroidism and NAFLD (Table 1). For instance, a recent meta-analysis (published in 2018, with a total of 12 cross-sectional and 3 longitudinal studies that had enrolled 44,140 subjects) has shown that overt hypothyroidism was associated with an increased risk of NAFLD; however, subclinical hypothyroidism was not independently associated with risk of NAFLD.¹⁵ Another meta-analysis published in 2018 also, and including 61,548 patients from 26 studies showed that patients with NAFLD had significantly higher TSH levels than those without NAFLD, independent of thyroid hormones and thereby showing that unclassified hypothyroidism was associated with an increased risk of NAFLD.¹⁶ A cross-sectional study of 425 biopsy-proven NAFLD patients showed that nonalcoholic steatohepatitis (NASH) and advanced fibrosis were independently related to low thyroid function, with risk proportional to the increase of TSH.¹⁷ These findings were confirmed in several other studies.^{18,19} In addition, some specific features of hypothyroidism and NAFLD single it out as a distinct disease entity, especially the reports of the development of hepatocellular carcinoma in patients with hypothyroidism.^{20,21}

On the other hand, there are some studies showing the opposite (Table 1). Escude *et al.*²² in a recent retrospective study involving 10116 subjects showed no significant connections concerning hypothyroidism and NAFLD with respect to controls. In a longitudinal cohort study in South Korea including 18500 subjects with hypothyroidism, both clinical and subclinical, did not find any significant correlation with increased risk of NAFLD.²³

These conflicting results could be in part explained by differences in study design, specific characteristics of investigated populations, differences in definition of hypothyroidism (clinical and subclinical) and NAFLD, and variations in diagnosis of NAFLD. However, if all the above-mentioned studies are taken together, there are indications that hypothyroidism, both clinical and subclinical, could be associated to NAFLD; although, a conclusive proof is still lacking.

Pathophysiological background

NAFLD is a chronic liver disease with the pathohistological manifestations ranging from steatosis to NASH, with an increased risk of progression to cirrhosis and ultimately even to hepatocellular carcinoma.^{24,25} The pathogenesis of NAFLD is complex and certainly multifactorial, including genetic predisposition, metabolic and environmental factors.²⁶ According to the results of previous studies, the key points in the pathogenesis of hypothyroidism-induced NAFLD are metabolic changes, direct action of TSH on the hepatocytes and oxidative stress are summarized in Fig. 1.^{10,27}

Obesity, dyslipidemia and insulin resistance, the main features of metabolic syndrome which are also common in

patients with overt and subclinical hypothyroidism are strongly associated with NAFLD^{9,27,28} (also recently known as metabolic associated fatty liver disease and referred as MAFLD) Moreover, overt and subclinical hypothyroidism is considered to be an independent risk factor for NAFLD.^{18,29} The rising prevalence of obesity during the past decades could be related to the development of NAFLD.³⁰ According to studies, there is an increased prevalence of hypothyroidism in the overweight population compared to the general population.³¹ Furthermore, the incidence of NAFLD directly correlates with body mass index.³²

Thyroid hormones have a significant role in hepatic lipid metabolism; acting through the thyroid hormone β receptors, they can lead to hepatic fat accumulation and stimulate hepatic lipogenesis.³³ Also, thyroid hormones modify lipid accumulation in the liver, affecting leptin and adiponectin; cytokines that also have significance in the pathogenesis of hepatic steatosis.^{19,34} Leptin stimulates beta-oxidation and suppresses lipogenesis,³⁵ while an inverse correlation has been found in many studies to exist between adiponectin, triglyceride (TG), and low-density lipoprotein (LDL)-cholesterol.³⁶⁻³⁸ Previous studies have shown that not only thyroid hormones but also thyroid hormone derivatives provide an important contribution to hepatic lipid metabolism. According to results in *in vitro* studies, thyroid hormone derivative 3,5-diiodo-L-thyronine (T2) lowers excess fat in cultured hepatocytes.^{39,40}

The important effect of thyroid hormone derivatives, such as reduction of lipid accumulation and stimulation of lipid oxidation, is also supported by the results of *in vivo* studies.^{41,42} In the studies of the direct effects of thyroid hormone on hepatic lipid metabolism, it has been found that the intrahepatic thyroid hormone concentration could be decreased in those patients with NAFLD.^{43,44} In addition, hypothyroidism is associated with impaired glucose and insulin metabolism, a major risk factor for NAFLD.⁴⁵ Insulin resistance leads to decreased responsiveness of glucose uptake in muscle and fat tissues, and to insulin, further affecting the lipid profile.⁴⁶⁻⁴⁸ It is considered that leptin and certain adipocytokines [e.g., tumor necrosis factor (TNF)- α and interleukin-1] play a significant role in hypothyroidism and insulin resistance, affecting the development and progression of NAFLD.^{10,27,43}

Mechanisms linking NASH and hypothyroidism are relatively clear, but whether they can be applied to subclinical hypothyroidism remains an open question. A recently published study investigating miRNA alterations and proteome profiles in a subclinical hypothyroidism mouse model identified several different miRNA-protein regulatory modules potentially associated with hepatic lipid metabolism, contributing to the growing body of evidence connecting thyroid hormones and NAFLD.⁴⁹

Although, seemingly, the main reason for steatohepatitis in patients with hypothyroidism is a decrease in thyroid hormone levels, elevated TSH, regardless of thyroid hormone levels, could also affect the development of NAFLD.⁴³ Through binding to the TSH receptor on the cell membrane of hepatocytes, elevated serum TSH causes liver TG accumulation via hepatic sterol regulatory element-binding transcription factor 1 (SREBP-1c) up-regulation, subsequently causing steatosis.^{10,27,50} Furthermore, TSH stimulates hepatic gluconeogenesis and causes hypercholesterolemia by decreasing hepatic 3-hydroxy-3-methyl-glutaryl coenzyme A (commonly referred to as

Table 1. Studies of NAFLD and hypothyroidism

Reference	Study design	Method for hypothyroidism diagnosis	Method for NAFLD/HCC diagnosis	Main results
15	Meta-analysis of 12 cross-sectional and 3 longitudinal studies with 44,140 included subjects (adults, children and adolescents)	Previous history of hypothyroidism on levothyroxine replacement therapy or found abnormal thyroid function tests	Imaging techniques (mainly ultrasound, computed tomography, or liver biopsy)	Hypothyroidism is significantly associated with an increased risk of NAFLD and severity of the disease
16	Systematic review and meta-analysis included 26 studies with 61,548 subjects (60,319 adults and 1229 children and adolescents)	Abnormal thyroid function parameters, hypothyroidism on replacement levothyroxine therapy	Ultrasound, liver biopsy, FLI or MRS	Elevated TSH may be a risk factor for the development of NAFLD/NASH, independent of thyroid hormones status
17	Cross-sectional study with 425 subjects >18 years	Subclinical hypothyroidism defined as TSH level over 4.5 mIU/L, with a normal T4 level, low-normal thyroid function as TSH level 2.5–4.5 mIU/L and normal FT4 level	Ultrasound, unexplained high levels of ALT or liver biopsy	A strong relationship between subclinical hypothyroidism and NASH with higher prevalence of NASH in these subjects
18	Prospective, population-based cohort study with 9419 subjects	Abnormal thyroid function test (TSH, T4 and TPOAb measurement)	Ultrasound and FLI measurements	Hypothyroidism was associated with a higher risk of NAFLD development in contrast to euthyroid
19	Systematic review of 11 clinical studies with 13,354 adults (>18 years)	Thyroid function tests or history of hypothyroidism on levothyroxine replacement therapy	Liver ultrasound or liver biopsy	Inconsistent results
20	Case-control study with 160 subjects	Hypothyroidism defined as TSH >5 mIU/L, history of hypothyroidism	Histopathology or clinical and imaging criteria	Hypothyroidism is significantly higher prevalent in subjects with hepatocellular carcinoma of unknown etiology compared to controls with viral or alcoholic liver disease
21	Case-control study with 420 subjects with hepatocellular carcinoma and 1104 healthy controls	History of hypothyroidism established during personal interviews	pathologically confirmed	Long-term hypothyroidism is significantly associated with hepatocellular carcinoma only among women
22	Cross-sectional, retrospective population study with 10,116 subjects \geq 45 years	Subclinical hypothyroidism as TSH > 4,94 UI/mL and normal T4; overt hypothyroidism as elevated TSH and decreased T4	Ultrasound	Hypothyroidism is not associated with NAFLD
23	Retrospective cohort study with 18,544 Korean subjects aged 20-65 years	Subclinical hypothyroidism, defined as TSH >4.2 mIU/L, normal FT4 and overt hypothyroidism as TSH >4.2 mIU/L, FT4 <0.97 ng/dL	Ultrasound	No association between subclinical or overt hypothyroidism and increased incidence of NAFLD

Abbreviations: ALT, alanine transaminase; FLI, fatty liver index; FT4, free thyroxine; HCC, hepatocellular carcinoma; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; T4, thyroxine; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone.

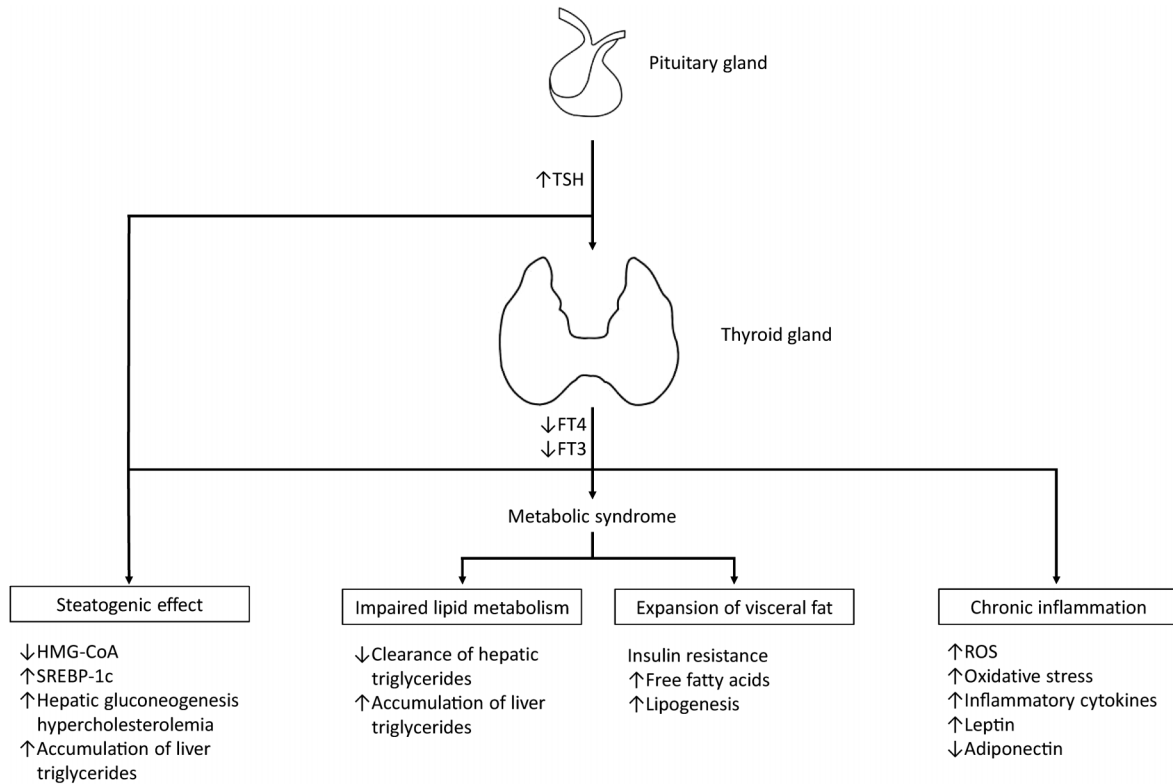


Fig. 1. Possible pathophysiological mechanisms leading to NAFLD in hypothyroidism.¹⁰ ↑ indicates up-regulation or increased concentrations, ↓ indicates down-regulation.

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; ROS, reactive oxygen species; TSH, thyroid stimulating hormone.

HMG-CoA) reductase phosphorylation, ultimately leading to development and progression of NAFLD.⁵¹⁻⁵³

One of the potential pathophysiological mechanisms of hypothyroidism-induced NAFLD is oxidative stress. Hepatocytes' mitochondria play a key role in the fatty acid metabolism by β-oxidation of free fatty acids, electron transfer and production of adenosine triphosphate, and reactive oxygen species (referred to as ROS).⁵⁴ In NAFLD, impaired mitochondrial function initiates an increase of nonmetabolized fatty acids in the cytosol as a result of the blockade of fatty acid β-oxidation. Consequently, increased production of ROS occurs.⁵⁵ An increase in ROS production leads to hepatocyte damage and inflammation.⁵⁶ Since patients with hypothyroidism have elevated markers of oxidative stress, oxidative stress in this patients could be the cause of cellular damage in liver tissue by reducing β-oxidation of fatty acids and increasing peroxidation of lipids.^{10,27}

On the other hand, liver plays a significant role in metabolism of thyroid hormones and liver dysfunction could cause variations in the bioavailability of such.⁵⁷ Thyroid hormone metabolism is regulated by iodothyronine seleno-deiodinase enzymes. Two of these enzymes are expressed in liver: type 1, which converts thyroxine to triiodothyronine, thus activating it; and type 3, which prevents activation of thyroxine by converting it to an inactive metabolite reverse triiodothyronine.⁵⁸ Liver also extracts 5-10% of thyroxine in plasma during a single passage, and it synthesizes major transport proteins for thyroid hormones, including thyroxine-binding globulin, transthyretin and albumin, which provide a pool for

rapid exchange of circulating thyroid hormones.⁵⁷ However, these changes in liver and thyroid metabolism in NAFLD would not have a significant influence on thyroid function

Treatment implications

Since hypothyroidism is often associated with clinical features of metabolic syndrome,¹⁰ while NAFLD and metabolic syndrome are connected bidirectionally,⁵ special attention should be given to patients with NAFLD and hypothyroidism, specifically in obese or overweight individuals.⁵⁹ Although there are no specific guidelines recommending treatment of these diseases combined, epidemiological and pathophysiological background support the rationality that both diseases should be taken into consideration when choosing the right therapeutic modality.

Fortunately, therapy for hypothyroidism is well known and easy to apply. Replacement therapy with levothyroxine can significantly decrease serum lipids and decrease body mass,¹⁴ thus improving clinical features of metabolic syndrome. It has been reported that implementation of levothyroxine replacement therapy in patients with subclinical hypothyroidism and dyslipidemia can decrease prevalence of NAFLD. Results supporting this were more convincing in severe subclinical hypothyroidism in comparison to a mild form.⁶⁰ Improvement in intrahepatic lipid deposits using low doses of levothyroxine in euthyroid male patients with NAFLD and type 2 diabetes mellitus was also demonstrated.⁶¹

A major issue in NAFLD patients is progression to NASH, and the development of any therapeutic options that could potentially address this problem would be welcome. It seems that liver lipotoxicity can be one of the main contributors leading to NASH development and possibly to its progression.⁶² One of the potential agents preventing liver damage is thyroid hormone receptor (THR) agonists since thyroid hormone potentiates TG degradation, decreases fatty acid synthesis and stimulates hepatocyte regeneration.^{43,63,64}

However, induced hyperthyroidism causes many problems which could be avoided with selective THR- β agonists. THRs have two main subtypes (THR- α and THR- β), with heart rate being primarily controlled by THR- α while stimulation of THR- β decreases LDL, TG, hepatic steatosis and body weight.⁶² Initially, selective THR- β agonists were developed for treatment of hypercholesterolemia, due to their capability of lowering LDL cholesterol.⁶⁵⁻⁶⁷ Regardless of successful phase 2 trials, further investigations were terminated due to significant increase in liver enzymes with one of the agents in question, eprotirome.⁶⁸ Nonetheless, efforts were taken to investigate a new generation of THR- β agonist in NAFLD treatment, irrespective of thyroid function.^{69,70} In a phase 2 clinical trial investigating such, the drug resmetirom (MGL-3196) was applied to patients with biopsy-confirmed NASH and a significant decrease in liver fat after 12 and after 36 weeks of the treatment was achieved.⁷¹ In March 2019, initiation of a phase 3 trial testing the use of resmetirom in patients with fibrotic NASH was announced by Madrigal Pharmaceuticals. A phase 2 clinical trial of another selective thyromimetic, VK2809, demonstrated similar results.⁷²

Other thyroid hormone metabolites that could improve NAFLD/NASH treatment are T2 and 3-iodothyronamine (referred to as T1AM). A study performed in rats demonstrated that exogenous T2 could decrease liver fat, TGs and LDL cholesterol;⁷³ however, small human studies including up to 40 patients with metabolic syndrome treated with T2 showed no effect on lipid profile and insulin resistance.⁷⁴ The other compound in question is T1AM, a biogenic amine affecting lipid and glucose metabolism at relatively low doses and so far tested in animal models only; although, it has shown beneficial effects on cholesterol and TG levels.^{75,76}

So far, use of selective THR- β agonists has been investigated in euthyroid patients. Although they are selective agonists, beta receptors are also found in the pituitary gland and stimulation of TSH secretion is possible. The questions arise whether hypothyroid patients should be treated with these drugs at all and, if so, how to monitor adequate substitution and adjust dosage of substitution therapy. In order to determine whether potential benefits outweigh the risks, further research is necessary.

Last but not the least, the role of lifestyle modifications should not be ignored in treatment of patients with NAFLD, hypothyroidism and metabolic syndrome; it is important to note, as well, that in combination with levothyroxine replacement therapy, significant improvement of metabolic components can be achieved.⁹ There are also still no published studies investigating currently used therapies recommended in NASH, such as antioxidative agents (vitamin E) and insulin sensitizers (pioglitazone)⁷⁷ for this particular subset of patients.

Research questions

The major issue is progression of NAFLD from simple steatosis to end-stage liver disease, both in other diseases and in

hypothyroidism. Thus, further studies are needed that specifically compare the natural course of NAFLD secondary to hypothyroidism and primary NAFLD, which would clarify whether, for example, patients with hypothyroidism, despite substitution therapy with levothyroxine, have an accelerated progression of liver fibrosis.

Regarding treatment of NAFLD and hypothyroidism, some improvements have been made by levothyroxine replacement therapy in addition to lifestyle changes. However, a major breakthrough in NAFLD/NASH treatment could be accomplished with selective THR- β agonists, so far investigated in euthyroid patients exclusively. Still, application of these drugs in hypothyroid patients remains questionable and pending the results of future studies. Presently, there are no studies available investigating the effect of insulin sensitizers and antioxidants in patients with NAFLD and hypothyroidism; thus, it would be interesting to explore these therapy options in *in vivo* and *in vitro* settings.

Conclusions

NAFLD is characterized by intrahepatic depositions of fat, which causes an intricate web of histological, metabolic and extrahepatic ramifications. Its pathogenesis is still not fully understood, and therefore treatment is still not very successful, while its global epidemiological, clinical and economic burdens are rapidly increasing.

The role of thyroid hormones and their derivatives as well as TSH levels and oxidative stress in lipid and glucose metabolism is well substantiated. Based on the available evidence, causative association of NAFLD and hypothyroidism, both clinical and subclinical is highly conceivable; although, both hypothyroidism and NAFLD share standard features, such as obesity, metabolic syndrome, insulin resistance, and dyslipidemia. Therefore, more data are required in order to assess the causal relationship between hypothyroidism and NAFLD.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceived of and designed the article, and critically revised the manuscript (IBC, MS), obtained funding, and provided administrative, technical and material support (IBC, MS), performed literature searches and wrote the manuscript (TK, IM, DM), updated the text of the manuscript (IBC, TK), figure drawing (TK), critical revision of the manuscript for important intellectual content (DP).

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