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ABSTRACT

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COMBINED DISORDER: CURRENT STATUS OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE IN PATIENTS WITH HYPOTHYROIDISM AND PROSPECTS FOR PATIENT PATHWAY IMPLEMENTATION

Introduction. Metabolic dysfunction-associated steatotic liver disease is recognized as a leading manifestation of metabolic dysfunction in the general population. Along with this, hypothyroidism is becoming increasingly important as a metabolic trigger that contributes to the formation of hepatic steatosis, insulin resistance, lipid profile disorders, and progression to steatohepatitis and fibrosis. Despite abundant evidence of a pathogenetic link between hypothyroidism and metabolic dysfunction-associated steatotic liver disease, current clinical practice remains fragmentary regarding the early detection of the associated pathology. This necessitates the development of integrated approaches to screening, diagnosis, and management of patients with this comorbidity, including the formation of a patient pathway at an interdisciplinary level.

Objective. The objective of the study was to summarize current data on the pathogenetic links between hypothyroidism and metabolic dysfunction-associated steatotic liver disease, analyze current approaches to the diagnosis of this combined disorder, and determine the prospects for implementing an individualized patient pathway taking into account the characteristics of both diseases.

Methods. A comprehensive literature review was conducted using sources from PubMed, Scopus, and Web of Science databases over the past 5–10 years. Publications related to the pathophysiological relationship between hypothyroidism and hepatic steatosis, as well as the epidemiology of the associated disorder, diagnostic approaches, and recommendations for the management of such patients, were reviewed. Special attention was paid to the analysis of clinical guidelines and modern patient pathway algorithms for patients with metabolic disorders.

Results and Discussion. The analysis demonstrated a close relationship between hypothyroidism and the risk of developing metabolic dysfunction-associated steatotic liver disease, with an emphasis on the role of thyroid hormones in the regulation of lipid metabolism, glucose metabolism, inflammation, and fibrogenesis in the liver. Even subclinical hypothyroidism was found to be associated with a significantly increased risk of steatosis, especially in patients with obesity, type 2 diabetes, or dyslipidemia. At the same time, modern patient management algorithms rarely include mandatory assessment of thyroid status, which complicates the identification and control of secondary factors of disease progression. The prospects are discussed for implementing a patient pathway that includes early thyroid function testing, interdisciplinary coordination among a gastroenterologist, endocrinologist, and family physician, as well as the potential role of therapy in certain categories of patients with concomitant metabolic dysfunction-associated steatotic liver disease.

Conclusions. Hypothyroidism is an important factor in the progression of metabolic dysfunction-associated steatotic liver disease, affecting lipid metabolism, inflammation, and fibrosis. The establishment of a pathogenetic link between these diseases justifies the need for an integrated approach to patient management with mandatory thyroid screening, which, in combination with non-invasive stratification of liver fibrosis, allows for the timely detection of progressive forms of steatosis. The implementation of a clinical pathway will allow for optimizing treatment management with enhanced interdisciplinary interaction, and will also improve the long-term prognosis for patients with this comorbidity.

Keywords: metabolic dysfunction-associated fatty liver disease, hypothyroidism, thyroid hormones, insulin resistance, liver fibrosis, metabolic syndrome.

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РЕЗЮМЕ

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ПОЄДНАНА ПАТОЛОГІЯ: СУЧАСНИЙ СТАН ПРОБЛЕМИ МЕТАБОЛІЧНО-АСОЦІЙОВАНОЇ ЖИРОВОЇ ХВОРОБИ ПЕЧІНКИ ПРИ ГІПОТИРЕОЗІ ТА ПЕРСПЕКТИВИ ВПРОВАДЖЕННЯ МАРШРУТУ ПАЦІЄНТА

Вступ. Метаболічно-асоційована стеатозна хвороба печінки визнана провідним проявом метаболічної дисфункції у загальній популяції. Поряд із цим, гіпотиреоз набуває все більшого значення як метаболічний тригер, що сприяє формуванню стеатозу печінки, інсулінорезистентності, порушенню ліпідного профілю та прогресуванню до стеатогепатиту і фіброзу. Незважаючи на численні докази патогенетичного зв'язку між гіпотиреозом і метаболічно-асоційованою стеатозною хворобою печінки, сучасна клінічна практика залишається фрагментарною щодо раннього виявлення поєднаної патології. Це зумовлює потребу в розробці інтегрованих підходів до скринінгу, діагностики та ведення пацієнтів з даною коморбідністю, включаючи формування маршруту пацієнта на міждисциплінарному рівні.

Мета роботи. Узагальнити сучасні дані щодо патогенетичних зв'язків між гіпотиреозом і метаболічно-асоційованою стеатозною

хворобою печінки, проаналізувати актуальні підходи до діагностики цієї поєднаної патології та визначити перспективи впровадження індивідуалізованого маршруту пацієнта з урахуванням особливостей перебігу обох захворювань.

Методи. Проведено цілісний огляд літератури з використанням джерел з баз даних PubMed, Scopus, Web of Science за останні 5-10 років. Розглядалися публікації, що стосуються патофізіологічного взаємозв'язку між гіпотиреозом та стеатозом печінки, епідеміології поєднаної патології, діагностичних підходів, а також рекомендації щодо ведення таких пацієнтів. Особлива увага приділена аналізу клінічних гайдлайнів та сучасних алгоритмів маршрутизації пацієнтів з метаболічними порушеннями.

Результати та їх обговорення. Аналіз продемонстрував наявність тісного взаємозв'язку між гіпотиреозом та ризиком розвитку метаболічно-асоційованої стеатозної хвороби печінки з акцентом на роль тиреоїдних гормонів у регуляції ліпідного обміну, метаболізму глюкози, запалення та фіброгенезу у печінці. Встановлено, що навіть субклінічний гіпотиреоз асоціюється зі значним підвищенням ризику стеатозу, особливо у пацієнтів з надмірною масою тіла, діабетом 2 типу чи дисліпідемією. Водночас, сучасні алгоритми ведення пацієнтів рідко включають обов'язкове оцінювання тиреоїдного статусу, що ускладнює виявлення та контроль вторинних чинників прогресування хвороби. Обговорюються перспективи впровадження маршруту пацієнта, який включає раннє тестування функції щитоподібної залози, міждисциплінарну координацію між гастроентерологом, ендокринологом та сімейним лікарем, а також потенційну роль терапії у певних категорій пацієнтів із супутньою метаболічно-асоційованою стеатозною хворобою печінки.

Висновки. Гіпотиреоз є важливим чинником прогресування метаболічно-асоційованої стеатозної хвороби печінки, впливаючи на ліпідний обмін, запалення та фіброз. Встановлення патогенетичного зв'язку між цими захворюваннями обґрунтовує необхідність інтегрованого підходу до ведення пацієнтів з обов'язковим тиреоїдним скринінгом, що в поєднанні з неінвазивною стратифікацією фіброзу печінки дозволяє своєчасно виявляти прогресуючі форми стеатозної хвороби. Впровадження клінічного маршруту дозволить оптимізувати лікувальну тактику з удосконаленням міждисциплінарної взаємодії, а також поліпшить довгостроковий прогноз для пацієнтів з поєднаною патологією.

Ключові слова: метаболічно-асоційована жирова хвороба печінки, гіпотиреоз, тиреоїдні гормони, інсулінорезистентність, фіброз печінки, метаболічний синдром.

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ABBREVIATIONS

MASLD – Metabolic dysfunction-associated steatotic liver disease

MAFLD – Metabolic dysfunction-associated fatty liver disease

MASH – Metabolic dysfunction-associated steatohepatitis

NAFLD – Nonalcoholic fatty liver disease

NASH – Non-alcoholic steatohepatitis

HCC – Hepatocellular carcinoma
TSH – Thyroid-stimulating hormone
T4 – Thyroxine
T3 – Triiodothyronine
SREBP-1c – Sterol regulatory element-binding protein 1c
ApoB – Apolipoprotein B
D1 – Type 1 iodothyronine deiodinase
ALT – Alanine aminotransferase
AST – Aspartate aminotransferase
FIB-4 – Fibrosis-4 Index
HbA1c – Hemoglobin A1c
HDL – High-density lipoproteins
LDL – Low-density lipoproteins
VLDL – Very low-density lipoproteins
MRI – Magnetic resonance imaging
VCTE – Vibration-controlled transient elastography
p-SWE – Point shear wave elastography
D1 – Deiodinase enzyme type 1
2D-SWE – Two-dimensional shear wave elastography
EASL – European Association for the Study of the Liver
EASD – European Association for the Study of Diabetes
EASO – European Association for the Study of Obesity
AACE – American Association of Clinical Endocrinology
AASLD – American Association for the Study of Liver Diseases
APASL – Asian Pacific Association for the Study of the Liver
ALEH – Latin American Association for the Study of the Liver
ETA – European Thyroid Association
ATA - American Thyroid Association
FDA – Food and Drug Administration

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease, previously known as nonalcoholic fatty liver disease, has become a major cause of chronic liver disease worldwide and is considered a distinct phenotype of liver disorder closely associated with metabolic disorders [1, 2]. MASLD has been increasing rapidly over the past two decades; it is the most common cause of abnormal liver function tests worldwide [3] and affects ~30% of adults in the general population. Its prevalence increased over 30% in 2023, which is directly related to the global epidemic of obesity, type 2 diabetes, and disorders of lipid and carbohydrate metabolism [4–6].

The pathogenesis of MASLD is closely related to metabolic disorders, which are the most common risk factors for the development and progression of metabolic dysfunction-associated steatotic liver disease; however, hypothyroidism, although considered a secondary cause of this disease, remains poorly understood in this context [7]. Hypothyroidism affects lipid and carbohydrate metabolism, modulates the activity of liver enzymes, and can contribute to the progression of steatosis to fibrosis and cirrhosis [8, 9].

Thyroid hormones, T4 and T3, play an important role in the regulation of hepatic lipid homeostasis [7]. They affect lipid and glucose metabolism and hepatic energy balance through transcriptional regulation mechanisms and activation of various signaling pathways. In hypothyroidism, lipid homeostasis is disrupted, which creates the prerequisites for fat accumulation in hepatocytes [9].

Despite the significant prevalence of both hypothyroidism and metabolic dysfunction-associated steatotic liver disease, current clinical guidelines predominantly consider these conditions as separate phenomena, without sufficient attention to their interrelationship. New clinical guidelines, in particular the 2024 EASL, EASD, and EASO joint guidelines, define modern approaches to screening, diagnosis, and management of patients with MASLD. Particular attention is paid to the patient's step-by-step pathway, which includes an initial assessment using Fibrosis-4 Index (FIB-4) followed by non-invasive imaging – transient elastography – in case of borderline or suspicious values [10].

In addition to classical therapeutic approaches, new pharmacological agents are currently being actively studied and approved, in particular selective thyroid hormone beta-receptor agonists (e.g., Resmetirom), which demonstrate promising results in reducing steatosis and fibrosis, opening a new era of personalized therapy in patients with hypothyroidism and MASLD [11, 12].

Currently, there are no standardized approaches or interdisciplinary protocols that would regulate the examination, diagnosis, risk stratification, and treatment of patients with combined hypothyroidism and MASLD [13, 14]. Guidelines of leading endocrinological and hepatological societies (AASLD, EASL, ETA, ATA) contain only occasional mentions of a possible relationship between hypothyroidism and steatosis, but do not offer specific algorithms for the management of such patients. In particular, the AASLD in its MASLD guidelines does not indicate hypothyroidism as an

independent risk factor requiring mandatory screening or specific management [15]. Similarly, the ETA does not offer routine assessment of liver function or liver structural changes in its clinical guidelines for hypothyroidism, despite the existence of pathophysiological evidence of their association [16].

There is also a lack of practical recommendations for family physicians, who are often the first to deal with such patients. As a result, there is an underestimation of the impact of hypothyroidism on the progression of liver pathology. Another problem lies in the delayed detection of severe stages of MASLD (fibrosis, steatohepatitis, cirrhosis), which can significantly worsen the prognosis [8].

In addition, recent studies have emphasized the need to integrate endocrinological and hepatological monitoring for the timely identification of at-risk patients, as well as the potential benefits of creating personalized patient pathways that take into account both hormonal status and liver function [9].

The **objective of the study** was to summarize current data on the pathogenetic links between hypothyroidism and MASLD, analyze current approaches to the diagnosis of this combined disorder, and determine the prospects for implementing an individualized patient pathway taking into account the characteristics of both diseases.

MATERIALS AND METHODS

The review article is based on a systematic analysis of the scientific literature highlighting current aspects of the combined MASLD/hypothyroidism disorder. The search was conducted in the PubMed, Scopus, Web of Science, and Google Scholar databases. The analysis includes mainly ten-year-old publications (2014–2024), as well as current clinical recommendations from leading international organizations.

RESULTS AND DISCUSSION

In order to eliminate terms that can cause social stigma, such as “non-alcoholic” and “fatty,” and clearly emphasize the role of metabolic dysfunction in the pathogenesis of the disease, the term MAFLD was proposed in 2020 to replace the old term NAFLD [2, 13, 17]. In 2023, the international group of liver societies introduced a new nomenclature for fatty liver disease – MASLD [13]. It is a unified and officially accepted term that replaces NAFLD in clinical practice and research. MAFLD was an important milestone in the development of the concept of metabolic dysfunction-associated steatosis, but did not become a global standard.

New nomenclatures for fatty liver disease emphasize the need to assess individual characteristics of the metabolic syndrome [18, 19].

Metabolic dysfunction-associated steatosis is a common chronic liver disease characterized by hepatic steatosis affecting more than 5% of hepatocytes with no relation to excessive alcohol consumption (which is ≥ 30 g/day for men and ≥ 20 g/day for women) or other chronic liver diseases, and is usually associated with metabolic risk factors such as obesity and type 2 diabetes [10].

According to the updated EASL, EASD, and EASO recommendations, MASLD and progressive fibrosis should be checked in individuals having type 2 diabetes or abdominal obesity and ≥1 additional metabolic risk factor(s) or persistently elevated liver enzymes [10].

MASLD includes a spectrum of progressive steatotic liver diseases, ranging from isolated hepatic steatosis to MASH with varying degrees of liver fibrosis, which can progress to cirrhosis (Fig. 1) [20–22]. MASLD is associated not only with an increased risk of liver-related complications such as cirrhosis, end-stage liver disease, and hepatocellular carcinoma, but also with an increased risk of numerous extrahepatic manifestations such as cardiovascular disease, chronic kidney disease, and certain types of extrahepatic cancers [23–29].Although cardiovascular diseases are the leading cause of mortality in patients with MASLD, patients with more severe liver fibrosis are at increased risk of liver-related mortality, and the risk increases exponentially with the stage of fibrosis [30]. The burden of MASLD and its complications, including hepatocellular carcinoma, is expected to continue increasing in the coming years [31, 32].

Against the background of the increasing number of such complications, studying the prevalence and risk factors of MASLD in different populations becomes relevant. Although obesity, metabolic syndrome, and type 2 diabetes mellitus remain the main risk factors for the development and progression of MASLD, increasing attention is being paid to the role of hypothyroidism as a secondary but significant etiological factor [8]. A number of international clinical guidelines provide justification for including thyroid dysfunction in the list of conditions to be evaluated when examining patients with MASLD, even though hypothyroidism itself is not a mandatory diagnostic criterion.

The joint EASL, EASD, and EASO guidelines state that hypothyroidism may act as a metabolic trigger for the development of MASLD [10]. Although not part of the formal diagnostic model of the disease, thyroid dysfunction is considered a factor that worsens the course of the pathology through its effects on metabolic homeostasis, namely through increased insulin resistance, stimulation of lipogenesis, and chronic systemic inflammation. It is recommended to consider

the presence of hypothyroidism when stratifying risks and developing an individual approach to the treatment of patients with MASLD [10]. At the same time, the AACE clinical guidelines for the diagnosis and management of patients with MASLD pay special attention to the role of thyroid dysfunction. In particular, the authors emphasize the need for routine screening of thyroid function in patients with metabolic disorders, including obesity, insulin resistance, and type 2 diabetes. This allows for the timely identification and correction of factors that may negatively affect hepatic metabolism [33].

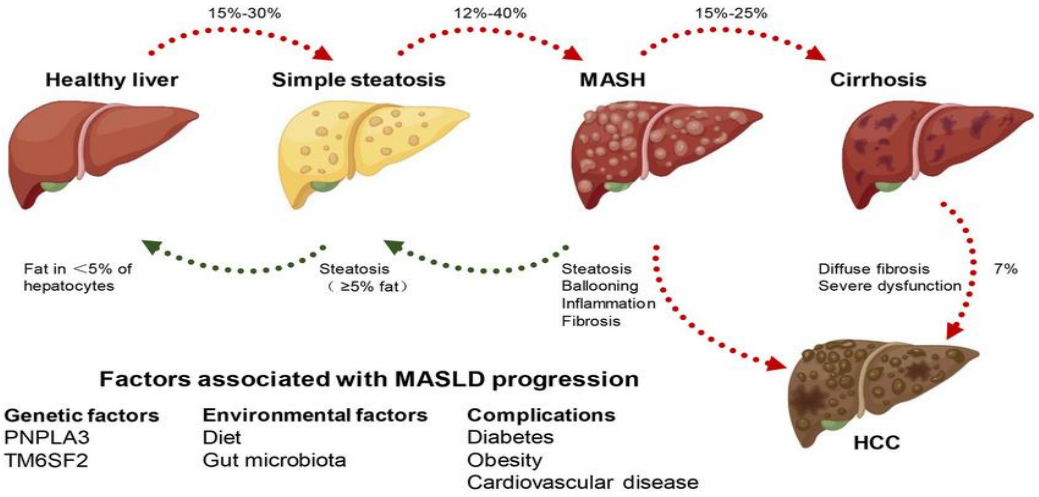

Figure 1 – MASLD spectrum. According to different clinical conditions, a healthy liver can develop into simple steatosis and metabolically associated steatohepatitis (MASH), which is still reversible. If MASH develops into cirrhosis, the histopathology becomes irreversible and may develop into hepatocellular carcinoma. At the same time, genetic, environmental factors and combined diseases can affect the occurrence and development of MASLD [22]

Thus, hypothyroidism is recognized as not only a concomitant but also a pathogenetically significant component in the context of MASLD, requiring assessment and correction within the comprehensive approach to the patient.

Hypothyroidism (both overt and subclinical) significantly increases the risk of MASLD developing and progressing. According to large meta-analyses and population studies, hypothyroidism is associated with a 43–71% increased risk of developing MASLD, while the risk of developing steatohepatitis or fibrosis in patients with hypothyroidism is increased almost threefold [34]. An updated meta-analysis that included 28 observational studies (24 cross-sectional and 4 longitudinal studies) with pooled data on approximately 76.5 million individuals from different countries provides substantial evidence that primary hypothyroidism was significantly associated with a higher risk of advanced MASLD [6]. A meta-analysis by Xiang et al. (2024) showed that elevated free T4 and T3 levels are associated with an increased risk of developing NAFLD, while high TSH concentrations are positively correlated with progression of liver fibrosis [35].

Thyroid hormones are essential for hepatic lipid homeostasis. They mobilize hepatic lipids, thus protecting the liver from the accumulation of toxic lipid forms, reactive oxygen species, endoplasmic reticulum stress, and unfolded protein response – processes that are a prerequisite for the development and progression of MASLD [7]. Triiodothyronine is a biologically active form of thyroid hormones that binds to thyroid hormone nuclear receptors (THRα, THRβ) in hepatocytes, regulating the expression of genes responsible for lipid metabolism [36, 37]. Thyroid hormones influence the liver through the thyroid hormone receptor isoforms α and β (THRα, THRβ), although THRβ is much more prevalent in the liver, while THRα dominates in the bone and heart. Thyroid hormones, which influence the THRα receptor, stimulate hepatic lipogenesis, whereas THRβ plays a greater role in fatty acid oxidation. The liver not only receives signals from thyroid hormones, but also has receptors for TSH, which cause hepatic steatosis and are the primary site for T4 to T3 conversion [38]. The main role of thyroid hormones is to activate β-oxidation of fatty acids, inhibit lipogenesis, and reduce the expression of SREBP-1c, which in turn inhibits the synthesis of triglycerides and cholesterol [36, 37]. Furthermore, T3 stimulates the secretion of VLDL lipoproteins by increasing ApoB expression and preventing fat accumulation in the liver [37, 39]. T4 is a prohormone that is converted to bioactive T3 by deiodinase type 1 (D1), an enzyme predominantly expressed in hepatocytes

[40]. In hypothyroidism, D1 activity decreases, which limits T4 → T3 conversion, reduces the effect of T3 on lipid metabolism, and contributes to the development of dyslipidemia and hepatic steatosis [39, 40].

Decreased thyroid hormone function in the liver disrupts all metabolic processes and therefore leads to steatosis and progression of MASLD to more severe liver disorders.

Defects in hepatic lipid metabolism accelerate intrahepatic lipid accumulation and contribute to lipid accumulation in non-hepatic tissues, highlighting the central role of the liver in systemic lipid homeostasis [41].

According to the results of modern studies, patients with hypothyroidism often exhibit characteristic morphological changes in liver tissue, including fatty infiltration (steatosis), steatohepatitis, and even fibrosis, which can subsequently progress to cirrhosis. Such patients also exhibit abnormalities in a number of functional parameters, including dyslipidemia, decreased liver detoxification capacity, and decreased biliary function [42]. MASH is a more severe clinical and morphological variant of MASLD, histologically characterized by the presence of lobular inflammation, ballooning degeneration of hepatocytes, and a significantly higher risk of fibrosis [43].

Therefore, MASLD, as a manifestation of metabolic dysfunction, has a close pathogenetic relationship with hypothyroidism due to impaired thyroid function, which indirectly and directly affects lipid and carbohydrate metabolism, promotes insulin resistance, affects adipokines secretion, and increases oxidative stress. All of these mechanisms are crucial to the pathogenesis of MASLD. T3 and T4 stimulate β-oxidation of fatty acids in the liver and regulate the expression of genes responsible for the transport and excretion of lipids. In hypothyroidism, these processes are inhibited, which contributes to the accumulation of triglycerides in hepatocytes and the formation of steatosis [42]. Hypothyroidism contributes to the development of insulin resistance – a central component of the MASLD pathogenesis. Impaired insulin action leads to increased fat breakdown in adipose tissue. This causes an excessive amount of free fatty acids to enter the liver. They are not processed or excreted properly and result in lipotoxicity. In addition, hypothyroidism activates de novo lipogenesis caused by elevated blood glucose levels and activation of lipogenic enzymes, which also contributes to fat accumulation in the liver [42]. Of particular importance is the increase in TSH levels – it is able to directly stimulate receptors in hepatocytes, activating lipogenesis genes regardless of T3/T4 levels, which further contributes to the accumulation of lipids in the liver [42]. Also, hypothyroidism is associated with mitochondrial dysfunction in hepatocytes, which disrupts fatty acid oxidation and enhances the development of steatosis [42]. Thus, hypothyroidism is an important pathogenetic factor in the development of MASLD, mediating its influence through impaired energy metabolism, insulin resistance, hormonal, and inflammatory pathways.

The diagnosis of metabolic dysfunction-associated steatotic liver disease in patients with hypothyroidism is challenging due to the presence of nonspecific symptoms that overlap significantly between the two disorders. Symptoms such as fatigue, weight gain, general weakness, and decreased performance can be caused by both metabolic disorders of the liver and thyroid hormone deficiency.

Despite its increasing prevalence and proven role in the development of systemic complications, MASLD often remains underestimated among both primary care physicians and specialized doctors. This is likely due to the slow progression of the disease, limited therapeutic options at the current stage, and its lower priority compared to other diseases, such as type 2 diabetes and cardiovascular diseases. While endocrinologists may underestimate the risks of liver damage, hepatologists, for their part, often have insufficient training in the field of concomitant endocrine disorders, which are often combined with MASLD, and as a result, do not take these disorders into account when forming a diagnostic and treatment strategy, especially in patients that respond poorly to standard treatment. In this context, the implementation of a clear, simple, and standardized patient pathway based on the use of non-invasive tests is of particular importance. This approach allows for the effective identification of individuals at high risk of severe liver injury and their timely referral to specialized centers, while patients with uncomplicated forms of the disease can remain under primary care observation, where optimal management is ensured [7].

In the context of hypothyroidism, accompanied by metabolic disorders, in particular dyslipidemia and an increased risk of steatosis, timely detection of liver damage is extremely important, since in the early stages of the disease, changes may not be manifested in liver enzyme levels, which increases the risk of underestimation of the process severity. In this case, more sensitive and specific diagnostic tools are needed. Early diagnosis of fibrosis and subsequent appropriate treatment can potentially prevent progression to liver cirrhosis and its complications and can justify screening in at-risk groups [10]. Non-invasive tests for such screening can be classified into serum assays and imaging examinations. Imaging examinations include various techniques using ultrasound and magnetic resonance elastography. Instrumental methods, in particular ultrasound, are widely available and used for the initial

detection of steatosis. However, a limitation of ultrasound is that it often fails to detect steatosis when it involves less than 20% of the liver parenchyma. In addition, ultrasound examination may be limited by the presence of morbid obesity [44]. In addition, the interpretation of ultrasound examination is subjective: it depends on the clinician's experience and the quality of the image. Moreover, due to the variability of the examination conditions (operator, equipment parameters, patient position), it is difficult to compare ultrasound series to track steatosis-related changes.

Elastography is a much more informative method in this context. It allows for non-invasive assessment of liver tissue stiffness, which correlates with fibrosis. Ultrasound elastography techniques include vibration-controlled transient elastography (VCTE or Fibroscan®), point shear wave elastography, and two-dimensional shear wave elastography. VCTE is a widely used, well-validated method with high diagnostic and prognostic accuracy [45]. Its limitations include the lack of established thresholds for diagnosing advanced fibrosis and cirrhosis, and the need to purchase equipment [46, 47]. Serum markers can be classified into indirect and direct. Indirect serum markers, such as the Fibrosis Index-4 (FIB-4) and NAFLD Fibrosis Score (NFS), are based on routine laboratory parameters [48, 49].

Liver biopsy is currently the gold standard for diagnosing metabolic dysfunction-associated steatotic hepatitis and staging liver fibrosis, but is limited by invasiveness, risk of complications, and sampling variability [50].

In response to these challenges, the AASLD proposed a two-step approach in 2023 that takes into account factors such as diagnostic accuracy, financial considerations, and availability [51]. A two-step approach combining the FIB-4 score and VCTE test contributed to improving the positive predictive value and specificity for MASLD diagnosis. Also, according to the new 2024 EASL, EASD, and EASO guideline, non-invasive techniques based on combinations of blood tests and imaging methods that measure mechanical properties and/or fat content in the liver should be used to detect fibrosis in adults with MASLD, as their diagnostic accuracy is higher than the standard ALT and AST liver enzyme tests [10]. For adults with MASLD, a multi-step approach is recommended (Figure 2): a non-proprietary blood-based score, such as the Fibrosis Index-4 (FIB-4), should be used first [10]. The calculation requires

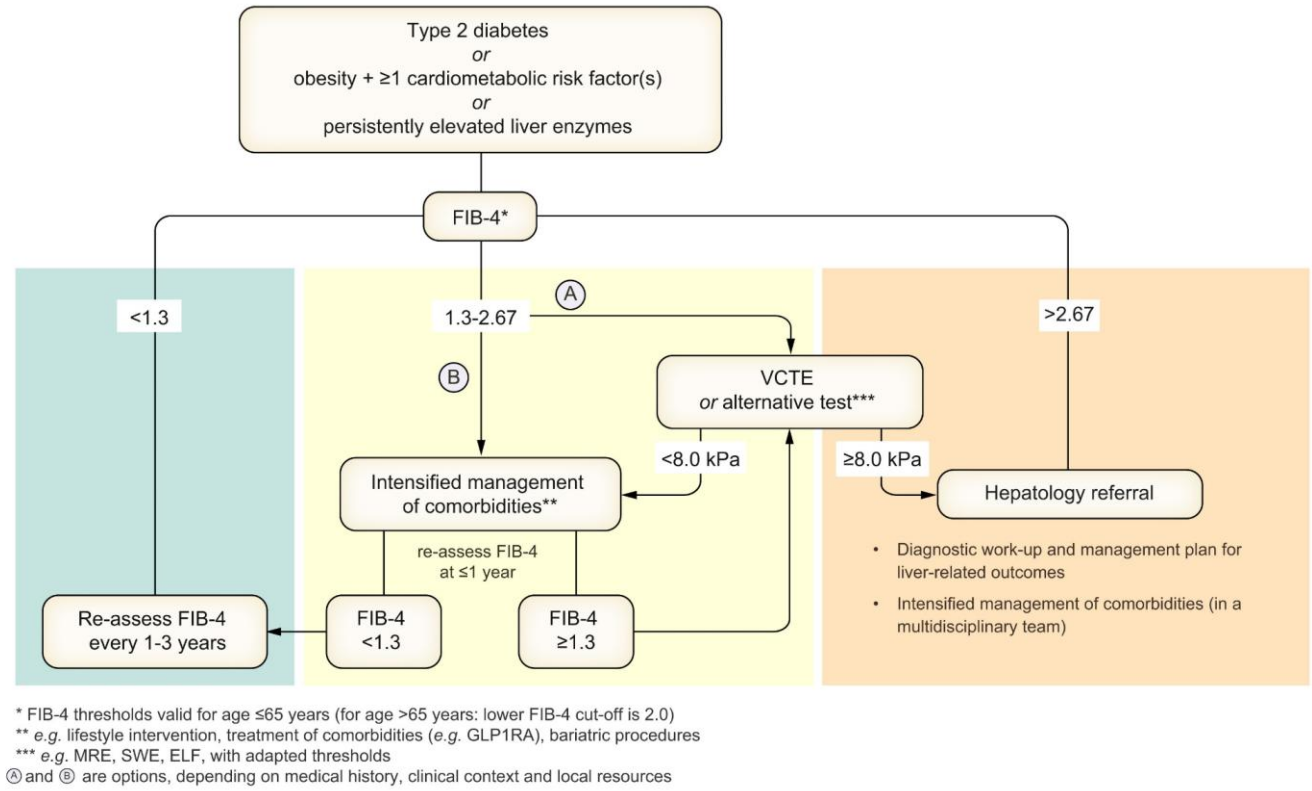

Figure 2 – Strategy for noninvasive assessment of progressive fibrosis risk and liver-related outcomes in individuals with metabolic risk factors or evidence of fatty liver disease [10]

data such as ALT, AST, platelet count, and patient age. The calculation is carried out according to the formula: (Age × AST)/(Plts × (sqr (ALT)), where AST is aspartate aminotransferase, Plts is the platelet count, ALT is alanine aminotransferase [10]; or using an online calculator (Fig. 3) [52]. If FIB-4 is <1.3, these individuals can be considered at low risk of progressive fibrosis and can be re-assessed every 1–3 years. At values >1.3 (or >2.0 for people over 65 years of age), the risk is increased, but the accuracy remains limited due to a high proportion of false positive results. For patients with FIB-4 values between 1.3 and 2.67, two options are recommended depending on the history, clinical context, and local resources. One option is liver elastography (e.g., VCTE) as a second step to clarify the stage of fibrosis; this option is particularly recommended for individuals with FIB-4 values close to 2.67 or those at high risk. The other option is for patients with FIB-4 values between 1.3 and 2.67: it is a 1-year intervention involving lifestyle changes and intensified treatment of cardiometabolic risk factors. If the retested FIB-4 level is still elevated after 1 year, elastography is recommended as a second step to clarify the stage of fibrosis (Fig. 2) [10]. This algorithm allows for early identification of patients at risk of liver damage and referral to the appropriate specialist – a general practitioner, diabetologist, or hepatologist, depending on the degree of risk.

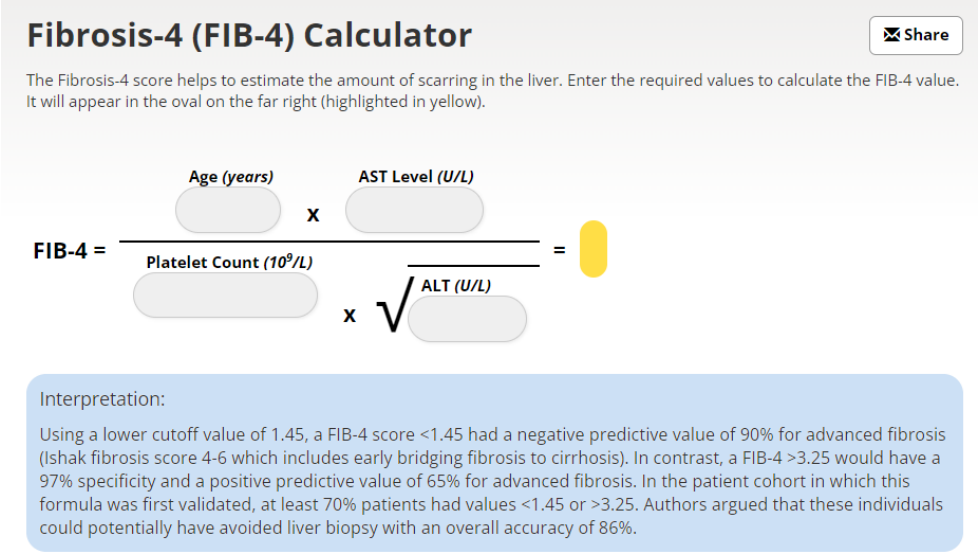

Figure 3 – Online calculator for fibrosis index [52]

Integrating the proposed diagnostic algorithm into the management of patients with hypothyroidism is appropriate and justified for several key reasons. First, both hypothyroidism and metabolic dysfunction-associated steatotic liver disease share nonspecific clinical manifestations, which significantly complicates differential diagnosis. Fatigue, weight gain, dyslipidemia, decreased exercise tolerance – all of these can be a consequence of both thyroid dysfunction and liver steatosis or fibrosis. Secondly, numerous studies demonstrate that even in subclinical hypothyroidism, lipid metabolism is disrupted, pro-inflammatory pathways are activated, and the risk of fatty liver infiltration increases. However, laboratory parameters, in particular liver enzyme levels (ALT, AST), may remain normal in the early stages, which creates the illusion of a safe condition and delays diagnosis, and they are not specific – their results may be affected by concomitant diseases [53].

In such cases, the use of an algorithm that combines non-invasive biochemical assessments (e.g., FIB-4 fibrosis index) with the subsequent use of instrumental imaging methods – elastography (VCTE, 2D-SWE, MRE) to assess the degree of fibrosis becomes particularly relevant. This approach not only increases diagnostic accuracy but also avoids excessive invasive procedures such as liver biopsy [51]. The proposed two-step algorithm (FIB-4 first, then VCTE or other elastography methods in case of high risk) is recommended by both the AASLD [51] and the EASL-EASD-EASO joint guidelines (2024) [10], and is particularly relevant for patients with hypothyroidism who are in the high-risk group. Using this approach ensures early detection of advanced fibrosis and allows for timely therapy initiation.

In view of the above, the integration of this diagnostic algorithm into clinical practice for hypothyroidism patients allows for a personalized,

pathogenetically based approach to the management of such patients and significantly improves the long-term prognosis.

General recommendations for MASLD/MASH treatment include the management of comorbidities (e.g., hypertension, hyperlipidemia, obesity, cardiovascular disease, type 2 diabetes) and implementing lifestyle changes [33, 51–54]. Regarding pharmacological treatment of MASLD/MASH, previous AASLD guidelines recognized that in the absence of approved treatments for MASLD/MASH, drugs with beneficial effects on the liver, such as vitamin E, pioglitazone, liraglutide, semaglutide, tirzepatide, and sodium-glucose cotransporter-2 (SGLT2) inhibitors, could be considered for off-label use in appropriate patients [51–54].

The FDA has recently approved the first drug to treat MASH. Resmetirom (Rezdiffra®), a thyroid hormone receptor beta agonist, received accelerated approval from the FDA in March 2024 for the treatment of MASH in non-cirrhotic moderate to advanced liver fibrosis (stages F2–F3) based on 12 liver biopsies [54, 55]. The approval of resmetirom was based on clinical data from the MAESTRO NASH trial, with safety data from the MAESTRO-NAFLD-1 trial. Based on this approval, the AASLD issued new guidelines for resmetirom therapy, which serve as an update to the 2023 AASLD practice guidelines [54].

In its updated recommendations for resmetirom therapy, the AASLD emphasizes the need for assessment and correction of thyroid function before initiating resmetirom therapy, with TSH levels measured at least at the start of treatment or 6 months prior, while standard clinical monitoring (TSH and free T4 levels every three to six months) should be performed in individuals with thyroid disease [54].

The AASLD states that eligibility criteria for resmetirom therapy should include evidence of F2–F3 fibrosis obtained either by noninvasive testing for liver disease (preferably by imaging) or by biopsy and no evidence of concomitant histologically active autoimmune liver disease [54]. The recommended dose of resmetirom is 100 mg/day for patients weighing ≥100 kg or 80 mg/day for patients weighing <100 kg.

Despite the existence of separate guidelines for the management of patients with MASLD or hypothyroidism, there are no integrated clinical protocols for patients with the combined course of these disorders. Given the high co-existence rate of thyroid dysfunction among patients with MASLD, there is a need to develop a standardized approach to screening, diagnosis, and therapy of this comorbidity [10, 33]. Such recommendations should be based on a multidisciplinary approach involving gastroenterologists, endocrinologists, dietitians, and primary care physicians, which will improve clinical outcomes and reduce the risk of liver disease progression and cardiovascular complications.

One of the promising areas is the implementation of personalized medicine principles. Patients with MASLD and concomitant hypothyroidism have a heterogeneous metabolic profile that requires an individualized approach to risk assessment and therapy selection. For example, in patients with subclinical hypothyroidism, even a modest increase in TSH may be associated with increased hepatic steatosis or fibrosis, requiring early intervention [8]. Molecular stratification, assessment of gene polymorphisms (e.g., PNPLA3, TM6SF2), as well as metabolomic (the collection of all small molecules – metabolites – produced in cells, tissues, organs, or biological fluids of the body at a given time) and microbiome profiles may serve as the future basis for a personalized approach to such patients [56].

CONCLUSIONS

The introduction of the MASLD term reflects a modern approach to understanding the pathogenesis of nonalcoholic fatty liver disease, in which metabolic disorders occupy a central place.

Thyroid dysfunction is an important factor in the development and progression of MASLD. Hypothyroidism has a multifaceted effect on liver metabolism, contributing to lipid accumulation in hepatocytes, the development of inflammation, and the progression of fibrosis. The establishment of a pathogenetic link between these diseases justifies the need for an integrated approach to the management of patients with mandatory thyroid screening as part of the diagnosis of fatty liver disease. Available clinical and experimental data indicate the reasonability of timely diagnosis of liver fibrosis against the background of thyroid dysfunction and should be based on risk stratification using non-invasive algorithms: a combination of biochemical tests (FIB-4) and imaging methods.

The implementation of a step-by-step clinical pathway for a patient with comorbidity will contribute to the early detection of progressive MASLD forms, optimization of interdisciplinary interaction, reduction of the risks of complications, and improvement of prognosis.

PROSPECTS FOR FUTURE RESEARCH

Further research should be aimed at an in-depth study of the pathogenetic links between hypothyroidism and MASLD, determination of thyroid therapy effectiveness in modifying MASLD course, development and clinical

validation of personalized management pathways for patients with comorbidities, and evaluation of the effectiveness of targeted therapeutic strategies.

AUTHOR CONTRIBUTIONS

Valentyna Psarova: work concept and design, data collection and analysis, responsibility for statistical analysis, writing (not revising) sections of the manuscript, final approval of the article.

Anastasiia Cherkashyna: collection of data, writing (not revising) sections of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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