ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2024 May 27; 16(5): 661-862

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (ESCI), Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

PUBLICATION DATE
May 27, 2024

PUBLISHING PARTNER
Department of Infectious Diseases, the Second Affiliated Hospital of Xi'an Jiaotong University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

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https://www.wjgnet.com/bpg/GerInfo/288

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
https://www.f6publishing.com

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http://2yuan.xjtu.edu.cn/Html/Departments/Main/Index_21148.html

World Journal of Hepatology

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World J Hepatol 2024 May 27; 16(5): 671-677

DOI: 10.4254/wjh.v16.i5.671

ISSN 1948-5182 (online)

EDITORIAL

Liver disease in patients with transfusion-dependent β-thalassemia: The emerging role of metabolism dysfunction-associated steatotic liver disease

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B

Novelty: Grade A, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade A, Grade B

P-Reviewer: Jiang W, China; Yan LJ, United States

Received: December 27, 2023

Revised: March 2, 2024

Accepted: April 17, 2024

Published online: May 27, 2024

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Abstract

In this Editorial, we highlight the possible role that metabolism dysfunction-associated steatotic liver disease (MASLD) may play in the future, regarding liver disease in patients with transfusion-dependent β-thalassemia (TDBT). MASLD is characterized by excessive accumulation of fat in the liver (hepatic steatosis), in the presence of cardiometabolic factors. There is a strong correlation between the occurrence of MASLD and insulin resistance, while its increased prevalence parallels the global epidemic of diabetes mellitus (DM) and obesity. Patients with TDBT need regular transfusions for life to ensure their survival. Through these transfusions, a large amount of iron is accumulated, which causes saturation of transferrin and leads to the circulation of free iron molecules, which cause damage to vital organs (primarily the liver and myocardium). Over the past, the main mechanisms for the development of liver disease in these patients have been the toxic effect of iron on the liver and chronic hepatitis C, for which modern and effective treatments have been found, resulting in successful treatment. Additional advances in the treatment and monitoring of these patients have led to a reduction in deaths, and an increase in their life expectancy. This increased survival makes them vulnerable to the onset of diseases, which until recently were mainly related to the non-thalassemic general population, such as obesity and DM. There is insufficient data in the literature regarding the prevalence of MASLD in this population or on the risk factors for its occurrence. However, it was recently shown by a study of 45 heavily transfused patients with beta-thalassemia (Padeniya *et al*, BJH), that the presence of steatosis is a factor influencing the value of liver elastography and thus liver fibrosis. These findings suggest that future research in the field of liver disease in patients with TDBT should be focused on the occurrence, the risk factors, and the effect of MASLD on

these patients.

Key Words: Metabolism dysfunction-associated steatotic liver disease; Transfusion-dependent thalassemia; Metabolic syndrome; Hepatic steatosis; Non-invasive markers; Liver fibrosis

Core Tip: Transfusion-dependent β-Thalassemia (TDBT) is one of the most frequent congenital diseases. Advances in the care of patients with TDBT over the past two decades have managed to significantly increase their life expectancy, making them more vulnerable to the onset of diseases related to the metabolic syndrome. Recent data from a relatively small study have highlighted the significance of the presence of hepatic steatosis in these patients. We herein discuss the available data concerning the presence of hepatic steatosis in this population, and the potential implications that these findings could have in the management of patients with TDBT, should these results be confirmed in larger cohorts.

Citation: Fragkou N, Vlachaki E, Goulis I, Sinakos E. Liver disease in patients with transfusion-dependent β-thalassemia: The emerging role of metabolism dysfunction-associated steatotic liver disease. *World J Hepatol* 2024; 16(5): 671-677
URL: https://www.wjgnet.com/1948-5182/full/v16/i5/671.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i5.671

INTRODUCTION

β-Thalassemia is caused by mutations within the β-globin gene[1]. These mutations result in reduced production of β-globin chains and Adult Hemoglobin A. The severity of anemia, the subsequent need for transfusions, as well as the severity of the clinical manifestations of this disease are associated with the degree of imbalance between α-globin and β-globin chains. Free α-globin protein is unstable and leads to the production of cytotoxic reactive oxidant species (ROS) and cellular precipitates that impair the development and viability of red-cell precursors, thus causing ineffective erythropoiesis and premature hemolysis of circulating red blood cells[2]. The disease phenotypes are classified according to whether the patients require transfusions throughout the disease course, since this requirement has significant effects on both associated pathophysiological features and practical management, whereas patients with non-transfusion dependent thalassemia (NTDBT) require no transfusions, occasional transfusions because of special circumstances (*e.g.*, surgery, acute infection, or pregnancy), or frequent transfusions but for a limited time period (*e.g.*, for the management of a clinical complication or in order to support a growth spurt during childhood)[1] .

Patients with TDBT need regular transfusions for life to ensure their survival[1]. Through these transfusions, a large amount of iron is delivered, leading to saturation of transferrin and the circulation of free iron molecules, which cause damage to vital organs (primarily the liver and myocardium)[3]. In fact, cardiovascular events were the leading cause of death through time for patients with hemoglobinopathies[1]. The risk of death due to heart-related issues caused by iron overload in patients with TDBT was reduced since the introduction of iron chelation in and has further decreased with the introduction of oral chelators and advanced imaging in the early 2000s[4-6].

Over the past, the main mechanisms for the development of liver disease in these patients have been the toxic effect of iron and chronic hepatitis C[7]. The excessive iron intake through the transfusions results in the release of free ferrum molecules in the hepatocytes, which in turn cause elevated levels of ROS and oxidative stress. The subsequent inflammation in the hepatocytes causes the development of chronic fibrosis, which can result within years in liver cirrhosis[8,9]. For this reason, it is recommended that all patients with TDBT are subjected to a yearly assessment of liver iron overload with a special magnetic resonance imaging (MRI) protocol [MRI R2 or R2* using liver iron content (LIC)], along with regular serum ferritin measurements[1]. LIC levels > 7 mg Fe/g dry weight and 15 mg/g dry weight are indicative of moderate and severe iron deposition in the liver parenchyma respectively[10], while levels of serum ferritin > 2000 ng/mL have also been correlated with liver iron overload[11]. The therapeutic management of iron overload related liver disease is based on the administration of chelating agents, which have been proven very effective, and have been shown to even result in regression of liver fibrosis[12,13]. Chronic hepatitis C was transmitted to these patients mainly through transfusions before 1991. The treatment of this disease has been completely revolutionized by the wide access to the direct acting antivirals, resulting to the micro-elimination of this disease for this population and even making universal therapy-induced viral clearance possible[14,15].

Advances in the treatment and monitoring of these patients have led to a reduction in these deaths and an increase in their life expectancy, particularly in developed countries[4,5,16]. This increased survival makes them vulnerable to the onset of diseases, which until recently occurred mainly in the non-thalassemic general population, such as obesity, and further increase of the prevalence of diseases related to both iron overload and the metabolic syndrome, such as dyslipidemia and diabetes mellitus type 2 (DM2)[17-19].

METABOLISM DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

Metabolism dysfunction-associated steatotic liver disease (MASLD), which was up until recently known with the term non-alcoholic fatty liver disease (NAFLD), was defined as the presence of steatotic liver disease and at least one of five cardiometabolic risk factors, which include (1) Increase in body mass index (BMI) or waist circumference; (2) impaired glucose metabolism; (3) high blood pressure; (4) high triglyceride levels; and (5) low high-density cholesterol levels and no other discernible cause of steatosis[20]. This new term encompasses a wide range of liver diseases from metabolic dysfunction-associated steatotic liver, characterized by the presence of ≥ 5% hepatic steatosis, to metabolic dysfunction associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH), with or without fibrosis, which can then develop at later stages to cirrhosis, liver failure, and/or liver cancer.

MASLD is considered to be the most frequent liver disease worldwide, affecting 25%–30% of the global population[21-25]. It is also more prevalent in individuals with cardiovascular/metabolic risk factors, including hypertension, DM2, abdominal obesity, dyslipidemia, and metabolic syndrome[26,27]. Its occurrence has also been positively associated with the consumption of ultra processed food, red meat, fast food, sugars and refined cereal, whereas the consumption of whole-wheat cereal, fiber and olive oil seems to have a protective effect[28-32]. The prevalence of MASLD ranges from 13.5% in Africa to 31.8% in the Middle East. Some forecasts predict that its global prevalence could reach up to 55.7% of global adult population by 2040[33], rising alongside global increases in obesity and diabetes. The estimated global prevalence of MASLD in patients with DM2 is 55.5%[27]. Although expected to increase even further, MASH related cirrhosis is already the most frequent indication for liver transplantation in women and those > 65 years of age and the second most frequent indication overall[34,35]. Apart from liver-related events, MASLD is also associated with increased all-cause mortality, mainly due to non-hepatic comorbidities and their complications[36], with cardiovascular events being the most common cause of death in MASLD[37]. In this context, MASLD has been related to a significantly higher risk than non-MASLD patients for occurrence of cardiovascular disease, chronic kidney disease and all types of cancer, according to recent reports[38-40]. Furthermore, accumulating evidence suggests a strong and independent association between MASLD and an increased risk of functional, structural and arrhythmic cardiac complications that promote the development of heart failure[37,41].

The gold standard for the diagnosis of MASLD is liver biopsy. However, due to the fact that it is an invasive, costly and not easily repeatable procedure, and the fact that its accuracy has been questioned in relation to high rates of inter- and intra-observer variability[42], render this examination impractical, and therefore, not ideal. A variety of radiological or serological non-invasive tests have been developed, that can accurately detect hepatic steatosis. Conventional ultrasound is recommended as a first-line tool for the diagnosis of steatosis in clinical practice, despite its well-known limitations [43]. Several scores deriving from clinical and serological components have been proposed for the detection of steatosis, including Fatty Liver Index[44] and Hepatic Steatosis Index[45] and NAFLD Liver Fat Score[46], which were shown to be adequately accurate and have been individually validated. Their diagnostic performances are difficult to compare, due to the fact that they have been designed and validated against different standards (magnetic resonance spectroscopy, ultrasonography).

Magnetic resonance proton density fat fraction (MRI-PDFF) is an accurate, reproducible, quantitative imaging-based technique that has the ability to quantify liver fat in its entire dynamic range[47]. In a meta-analysis of 6 studies and totally 635 patients with biopsy-proven MASLD[48], the summary AUROC values of MRI-PDFF for detecting steatosis > 5%, and > 33%, > 66% were 0.98, 0.91, and 0.90, respectively. Pooled sensitivity and specificity were 93% and 94%, 74% and 90%, and 74% and 87%, respectively. Of note, the accuracy of MRI-PDFF does not seem to be influenced by the presence of liver iron overload, except possibly for its severe (grade 4) stage[49]. Despite the high accuracy of MRI-PDFF for detecting and grading steatosis, its substantial cost and limited availability restrict its use in everyday clinical practice.

In recent years, the use of transient elastography (TE) with Fibroscan® equipment (Echosens, Paris, France) to simultaneously obtain controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) has shown a lot of promise for the noninvasive quantification of hepatic steatosis and fibrosis, respectively. It showed low failure rates (3·2%), high reliability (> 95%) and reproducibility[50]. The development of the XL probe for patients with obesity seemed to solve the limitations of the clinical application of CAP and LSM[51], since it can increase the detection depth in patients with obesity to improve the measurement success rate. However, as the use of CAP and LSM became more popular, results began to diverge, particularly regarding differences in diagnostic accuracy and cut-off values between different BMI populations and between different probes. A meta-analysis from 2022[52] found that the AUROC of CAP were 0.924 for the detection of mild (S1) steatosis. The mean cut-off value and range was 268.5 (233.5-304) dB/m. The summary sensitivity and specificity of 14 studies were 84% and 86% respectively. The mean cut-off values for the detection of steatosis varied across different subgroups, and specifically there were significant differences in CAP values among different BMI populations.

THE ISSUE OF HEPATIC STEATOSIS IN PATIENTS WITH TDBT

In the issue of October 4, 2022, of the *British Journal of Haematology*, Padeniya *et al*[53] published the results of a study, which showed that liver fibrosis as assessed with TE in patients with TDBT was associated with the presence of hepatic steatosis[53]. Up to now, this is the only study to show an association of increased risk of liver fibrosis with steatosis in patients with TDBT.

Padeniya *et al*[53] conducted a cross-sectional study in order to identify the participants with significant (> 33% of hepatocytes involvement) hepatic steatosis, to seek possible differences compared to the group of patients without

steatosis with emphasis on markers of iron overload and to investigate the factors associated with liver steatosis and fibrosis. The study included patients who had undergone a minimum of 100 blood transfusions and had elevated (higher than 2000 ng/mL) serum ferritin levels on three consecutive occasions. Patients with chronic viral hepatitis or a history of unsafe alcohol consumption were excluded. Liver fibrosis was assessed by LSM with TE, and steatosis was assessed with CAP. LSM with a score of more than 7 kPa was considered significant fibrosis (F2). The cut-off value for the M probe's significant liver steatosis was 251–267 dB/m. Liver iron was estimated at recruitment using the MRI R2. The total number of patients included was 45 with a mean age of 19 years old, 9 of whom had significant steatosis. The authors used multiple linear regression analysis to demonstrate that steatosis was associated only with increasing BMI, despite being within the normal range, but not with diabetes or iron overload. They also showed that liver fibrosis was associated with increasing age, male gender steatosis and diabetes, but surprisingly not with iron overload.

One major limitation of the study is its small size of the population, which renders the confirmation in larger series mandatory. Nevertheless, it puts forward a new hypothesis and novel fields of research. Liver steatosis, independently from iron overload, was found to affect patients with thalassemia at a very young age and accordingly to BMI, whose mean value indicated an overall normal-weighted population. One possible explanation for this phenomenon is that BMI values within normal range does not exclude for this group of patients an unbalanced body composition with central obesity and visceral fat. In fact, it may occur especially in patients with thalassemia, where reduced stamina due to anemia, results in reduced physical activity levels and subsequently in low muscle mass[54].

Hepatic steatosis is known to be associated with high ferritin levels both in the general population and in NTDBT[55, 56]. In a study conducted by Ricchi *et al*[56], which included 110 patients with NTDBT serum ferritin levels are disproportionately high in patients with steatosis. Serum ferritin levels correlated with LIC values (r = 0.558, P < 0.0001) but the correlation was weaker in patients with hepatic steatosis (r = 0.426, P = 0.05) than in those without hepatic steatosis (r = 0.656, P < 0.0001), concluding that the presence of liver steatosis is a confounder of the relationship between serum ferritin and LIC, since it could lead to an overestimation of the magnitude of iron overload in the absence of MRI evaluation of LIC and thus raising a question as to whether serum ferritin values alone are an adequate marker for iron overload monitoring in patients with TDBT as well.

CONCLUSION

As the life expectancy of these patients continues to increase, it is plausible that new ailments, that up until recently affected the general population, are going to affect patients with TDBT as well. If the results from the study of Padeniya *et al*[53] will be proven in the future in a larger cohort of patients, these data will have significant implications for the clinical management of patients with TDBT. Further studies should investigate the prevalence, the pathophysiology, the clinical features, and the long-term effects of these recently identified clinical entities among patients with TDBT. As with the general population, a more active lifestyle and changes in dietary habits could be recommended and a multidisciplinary care of these patients, with a team including a hepatologist and possibly an internal medicine specialist could be justified.

FOOTNOTES

Author contributions: Fragkou N drafted the article; Vlachaki E, Goulis I and Sinakos E designed the study, made critical revisions related to important intellectual content of the manuscript and approved the final version of the study.

Conflict-of-interest statement: All authors have no conflict of interest to declare.

Country/Territory of origin: Greece

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S-Editor: Fan JR
L-Editor: A
P-Editor: Cai YX

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