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Review Paper

Metabolic dysfunction-associated steatotic liver disease: Prevalence and progression in lean patients

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Abstract

Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), is a common liver disease linked to metabolic dysfunction. While often associated with obesity, MASLD also affects lean individuals, raising questions about its underlying mechanisms and clinical implications.

Aim: This paper aims to review the latest insights into MASLD, with a specific focus on lean individuals, exploring its prevalence, pathogenesis, cardiovascular risk and treatment strategies.

Material and methods: A systematic review was conducted using PubMed and Google Scholar to examine recent studies on MASLD, particularly in lean patients. Key terms included 'metabolic dysfunction-associated steatotic liver disease' and 'nonalcoholic fatty liver disease.'

Results and discussion: Approximately 10%–20% of MASLD cases occur in lean individuals, who exhibit impaired glucose metabolism and visceral fat accumulation. Despite fewer metabolic comorbidities, lean MASLD patients show similar disease severity and poorer outcomes compared to obese patients. The condition is linked to insulin resistance, genetic factors, and alterations in the gut microbiome. Cardiovascular risk in lean MASLD patients is lower than in obese counterparts, but advanced age and hepatic fibrosis increase the likelihood of cardiovascular complications. Moreover, lean patients face higher overall mortality rates, with hepatocellular carcinoma more prevalent among them.

Conclusions: Lean MASLD remains an under-recognized but significant condition. Early diagnosis, personalized treatment approaches, and further research are essential for improving outcomes. Future studies should focus on refining diagnostic tools, identifying biomarkers, and developing tailored therapies for lean patients.

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1. INTRODUCTION

The metabolic dysfunction-associated fatty liver disease (MAFLD), previously named non-alcoholic fatty liver disease (NAFLD), and now named metabolic dysfunctionassociated steatotic liver disease (MASLD) is a common disease, especially in patients with cardiovascular and metabolic diseases.[1,7] In this paper, the collective term MASLD will be used to describe and refer to all the aforementioned names of this medical condition. Around 25% of the global population is affected by chronic liver diseases, and a rise in the prevalence and significance of these conditions at the population level is expected.[2] The pathophysiology of MASLD is characterized by the buildup of fat (steatosis), inflammation, and, in some cases, fibrosis. Steatosis is caused by the accumulation of triglycerides in the liver. While obesity is the primary factor contributing to MASLD, approximately 10%–20% of individuals with the condition are not overweight or obese.[3] It is often an incidental finding during ultrasound examination. The disease is associated with symptoms of portal hypertension, including hepatomegaly and splenomegaly. The primary approach to treating lean MASLD involves improving general fitness and reducing visceral fat, with weight loss strategies being central to the therapeutic plan.

2. AIM

The aim of this paper was to provide an overview of the latest insights into MASLD, with a particular emphasis on patients with lean body mass. MASLD is a condition that has primarily been linked to obesity in the research literature; however, there is substantial evidence suggesting distinct underlying etiologies for these diseases and a non-obvious co-occurrence between them.

3. MATERIAL AND METHODS

To undertake this review, we performed a systematic search of relevant databases including pubmed and google scholar for articles on MASLD, employing the terms 'metabolic dysfunction-associated steatotic liver disease,' 'metabolic-associated fatty liver disease' and 'nonalcoholic fatty liver disease.' Our primary focus was on recent publications, particularly those investigating the disease in lean patients. This paper includes elaboration of the articles of choice.

4. RESULTS

4.1. Epidemiology

MASLD is now described as the most common liver disease worldwide and strictly connected with sedentary lifestyle. The disease is typically associated with the complications of excess adipose tissue at a population level; however, it has also been documented in lean individuals who do not exhibit excess body fat. Approximately 10%–15% of the MASLD population consists of lean patients.[3] As per Asian population, lean MASLD is 25.2% of all MASLD diagnoses. An Asian population was the first one to document this data. In general population lean MASLD patients ranges between 7.8% and 74.0%. This discrepancy may be due to differences in used diagnostic techniques and ethnic diversity.[4] Studies suggest that men with higher body weight experience higher levels of liver steatosis and fibrosis than women.[5] In contrast analysis made by Younossi et al. showed that, when comparing lean MASLD with overweight-obese MASLD, lean MASLD was independently linked to younger age and female gender.[6]

4.2. Definition of MASLD in lean patient

The 2023 Delphi consensus aimed to determine if experts and patient advocates were in favor of revising the terminology and definitions for NAFLD and nonalcoholic steatohepatitis (NASH), which were viewed as flawed and stigmatizing. The consensus led to replacing NAFLD with MASLD, introducing new diagnostic criteria, and creating a non-stigmatizing, widely supported nomenclature that includes metabolic risk factors and new categories like metabolic and alcohol-related liver disease (MetALD).[7] Lean MASLD refers to the presence of MASLD in individuals who have a BMI within the normal range and are not considered overweight or obese. The term is suggested when discussing MASLD in those with a normal BMI, considering in race-based BMI cutoffs.[8] Due to the old classification criteria for MASLD, many patients with normal body weight and waist circumference were not classified correctly, even when the histological evidence of hepatic steatosis was present. Despite lean body, as per recent studies. MASLD patients face similar liver disease severity as obese patients. Therefore not only body weight management should be stressed, but also lifestyle changes. Severe health outcomes are not only a risk for obese MASLD patients.[9]

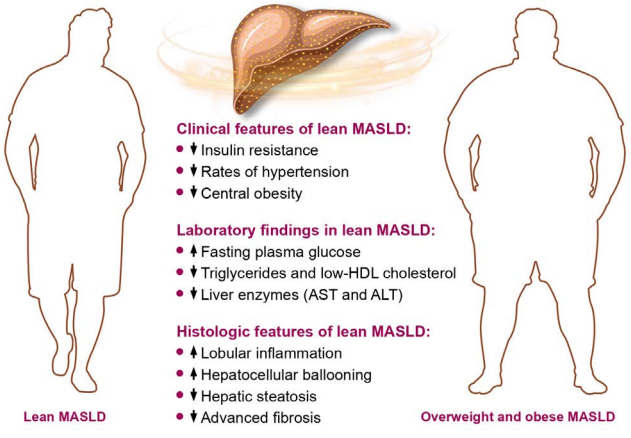

Figure 1. Compilation of the histological and clinical features along with laboratory findings common in lean MASLD.

4.3. Pathogenesis of lean MASLD

In 1836, Thomas Addison was the first to describe fatty liver associated with alcohol consumption. Over time, it was discovered that individuals who don't drink but possess metabolic risk factors might also exhibit the same histological changes.[10] The causes of MASLD in individuals with abnormal body weight and comorbidities are well understood and documented. However, the disease's characteristics in lean individuals draw researcher's particular attention. MASLD requires a risk of metabolic diseased to be properly diagnosed. Obesity is a key factor in the development of liver diseases including MASLD. In individuals with a normal body weight, MASLD is similarly linked to visceral fat accumulation.[11] Lean MASLD patients, by definition, are not affected by obesity, yet the condition still reflects adiposopathy. The impact of adiposopathy extends beyond MASLD, influencing metabolic dysfunction, cardiovascular diseases, and liver cancer as well.[12] The development of MASLD was primarily associated with disruptions in lipid and glucose metabolism. Insulin resistance is a critical factor in the development of MASLD and significantly contributes to other elements of metabolic syndrome including obesity, type 2 diabetes and dyslipidemia. Also elevated fasting glucose level in lean individuals may be an indicator of NASH[13] Moreover, the development of lean MASLD appears to be partly influenced by changes in gut microbiota composition, as well as genetic factors.[12] The clear MASLD mechanism in lean and obese patients is not well described yet. Impaired glucose metabolism and dysfunctional adipose tissues however are linked with lean MASLD in Caucasian populations.[13] Zeng et al. (2020) studied the Chinese population did not reveal a significant difference in Single Nucleotide Polymorphism (SNP) in the following genes: SIRT1, APOC3, PNPLA3, AGTR1, and PPARGC1A, between lean MASLD and lean non-MASLD individuals. Therefore the metabolic factors must play a predominant role in the progression of MASLD, rather than genetic factors.[14] An earlier study by Wei et al. (2015) found that SNPs in the PNPLA3 gene were more prevalent in lean MASLD patients compared to obese patients with MASLD. The presence of the GG allele in the PNPLA3 gene increases the risk of MASLD in the general population, particularly in patients without metabolic syndrome.[15] The described SNP has no proven association with dietary factors.[16] The epidemiological landscape of MASLD in individuals with a normal body weight remains poorly defined, highlighting the need for comprehensive future studies to better explain its prevalence, risk factors, and clinical implications in lean patients.

4.4. Cardiovascular risk in lean MASLD

According to Souza et al. Meta-analysis on about 1 million individuals, lean MASLD patients experience more severe liver outcomes, yet their cardiovascular outcomes are comparable to those of non-lean MASLD patients.17 In contrast similar studies by Nso el al. proved that lean MASLD patients tend to have higher cardiovascular mortality rates, despite of their better cardiometabolic profile and a lower frequency of major adverse cardiovascular events (MACE). According to the collected statistical data lean MASLD patients compared to non-lean MASLD patients exhibit 50% increased risk of death due to cardiovascular complications, 10% lower likelihood of experiencing MACE and overall 40% lower risk of developing cardiovascular diseases.[18] Review paper by Dapanichkul et al. showed that lean MASLD patients generally experience cardiovascular outcomes similar to or less severe than those with non-lean MASLD. They have a lower risk of type 2 diabetes and cardiovascular events, including the development of cardiovascular disease (CVD) risk factors. However, lean MASLD patients with hepatic fibrosis are more likely to develop CVD risk factors during follow-up than those without fibrosis or those with non-lean MASLD. Studies found that risk of CVD events in lean MASLD patients over 60 years is similar to their nonlean counterparts. This suggests that, regardless of body composition, the age is a key factor in the development of cardiovascular outcomes in elderly MASLD patients. Overall, lean MASLD patients tend to develop fewer cardiovascular issues than non-lean individuals, though increasing age remains a significant risk factor for both groups.[19] In addition when comparing lean individuals without MASLD with those with MASLD, patients with MASLD developed dyslipidemia, dysglycemia, metabolic syndrome, as well as a higher median Framingham risk score more often.[20] In conclusion it appears that within the lean MASLD group, some individuals with more significant metabolic abnormalities, which are linked to an increased cardiovascular risk and progression of liver disease, even without the presence of overweight or obesity, which highlights the need for close monitoring both of these groups.

4.5. Treatment

Due to the numerous factors predisposed to MASLD, such as genetic predispositions, metabolic processes, and epigenetic modifications, it is challenging to identify a single optimal method for the prevention and treatment of MASLD. Treatment process for the MASLD patients was traditionally initiated with weight loss recommendations and/or bariatric surgery. Nowadays, the new generation of anti-obesity drugs may be an effective tool to help patients lose weight without the need for invasive interventions or to support the effects of surgery. It is speculated that drugs targeting underlying metabolic issues like obesity and insulin resistance may be more effective in the early stages of the disease, when liver fibrosis is less severe. In contrast, drugs aimed specifically at liver inflammation and collagen buildup are necessary once substantial damage has already occurred.[21] Given the strong association between MASLD and type 2 diabetes, researchers focused on semaglutide; however, it did not show any notable improvement in liver fibrosis.[11] Future research on lean MASLD should focus on improving diagnostics, personalizing treatment, and deepening our understanding of the disease. Studies should aim to identify new biomarkers and imaging techniques for more accurate detection. Tailored therapies, including lifestyle changes,

Table 1. Summary of key data derived from population-based studies on patients with MASLD.

Study	Population	Main findings
Nso et al. (2024)[18]	Twenty-one worldwide studies were identified, encompassing 7153 lean MASLD patients	1. Lean MASLD patients had a better cardiometabolic profile than non-lean MASLD patients. 2. Lean MASLD patients had 1.5 times higher cardiovascular mortality risk. 3. The risk of MACE was similar between the two groups. 4. Lean MASLD patients had lower risks of hypertension, dyslipidemia, and CVD. 5. All-cause mortality risk was similar in both groups.
Sun et al. (2024)[25]	1762 patients with type 2 diabetes mellitus from 16 centers in China	1. In the lean group, liver steatosis and fibrosis were present in 44.7% and 23.4%, respectively. 2. Lean individuals had higher rates of hypertension and cardiovascular disease compared to non-lean individuals. 3. Lean patients with liver conditions were older, had a longer duration of diabetes, and had lower insulin resistance and lipid levels. 4. No link was found between insulin resistance, BMI, or lipids and fibrosis in the lean group.
Almomani et al. (2023)[26]	68 892 260 lean and non-lean MASLD individuals from United States extracted from twenty-one studies combined	1. Despite a better cardiometabolic profile, lean MASLD patients had a 1.5 times higher risk of cardiovascular mortality compared to non-lean MASLD patients. 2. The risk of MACE was similar between lean and non-lean MASLD patients. 3. Lean MASLD patients had a lower risk of hypertension, dyslipidemia, and CVD. 4. All-cause mortality risk was similar in both lean and non-lean MASLD patients.
Lee et al. (2024)[27]	9676 blood donors from South Korea	1. PNPLA3 was strongly linked to MASLD and its subtypes in the Korean population. 2. These results suggest that genetic factors play a crucial role in the development of MASLD.

diet, and medications, must be tested for effectiveness and safety in lean patients. Additionally, developing and validating fibrosis assessment tools specific to lean MASLD is crucial for better risk stratification in clinical practice.[22] In 2024, the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO), published clinical practice guidelines that included current lean MASLD patients treatment strategies. The treatment of lean MASLD focuses primarily on lifestyle changes, with pharmacotherapy reserved for high-risk patients. A Mediterranean diet, reduction of visceral fat, and regular physical activity are recommended despite a normal BMI. In advanced cases, GLP-1 RAs (e.g., semaglutide), pioglitazone for insulin resistance, and vitamin E for non-diabetic patients may be used. As per above managing metabolic comorbidities such as dyslipidemia and hypertension is essential. Regular fibrosis assessment helps monitor disease progression and prevent complications.[23] The ideal treatment for MASLD is a combined approach that should target not only the progression of liver disease but also the metabolic risk factors that promote cardiovascular disease and cancer.

4.6. Outcomes in lean MASLD

MASLD in lean patients is a progressive disease, as the most recent studies confirm. Obese MASLD patients experience surprisingly better outcomes than lean MASLD, who can sometimes display characteristics of metabolic syndrome.[24] As Danpanichkul et al. (2024) stated, individuals with lean MASLD are more in risk of death compared to non-lean MASLD patients. MASLD progression is strongly influenced by patients body weight and age. Diagnosed lean patients have a lower likelihood of developing cardiovascular issues but face the higher mortality compared to non-lean MASLD. Hepatocellular carcinoma is more prevalent in lean MASLD, whereas the risk of extrahepatic cancers is comparable between the lean and non-lean groups.[19] A reduction of 5%–10% in body weight or a decrease in waist circumference can lead to significant decrease in steatosis and improvement in metabolic disorders.[3]

5. DISCUSSION

This paper provides a comprehensive overview of the key aspects of the often-overlooked issue of MASLD in lean patients. Current solutions, therapeutic strategies, and imperfect diagnostic systems have led to a significant number of patients suffering from this condition being inadequately treated due to their low body weight. However, with the introduction of new nomenclature and improved diagnostic criteria, we are now able to identify and appropriately address the problem. This work presents a cross-section of the knowledge gathered so far regarding the newly established definition of this disease entity, emphasizing various aspects of the issue and its clinical presentation. Lean MASLD remains an insufficiently researched condition that should not be overlooked in future studies, especially given the clearly rising prevalence.

MASLD, previously known as NAFLD, is now recognized as a condition linked to metabolic dysfunction. While often associated with obesity, it is crucial to acknowledge its prevalence in lean individuals, accounting for 10%–15%

of cases. These patients, despite having no excess adiposity, show similar pathophysiological traits, such as impaired glucose metabolism and visceral fat accumulation. Interestingly, the progression of MASLD in lean individuals appears to be independent of obesity-related comorbidities, yet they share similar disease severity and risk factors for adverse outcomes. Notably, lean MASLD patients experience a higher risk of cardiovascular complications and have a greater likelihood of developing hepatocellular carcinoma, despite a lower incidence of metabolic syndrome. This highlights the importance of early diagnosis and targeted interventions in this population. Furthermore, while treatment approaches often focus on weight management, lifestyle changes, including physical activity and dietary modifications, are equally crucial for managing lean MASLD and improving long-term outcomes. More research is needed to refine diagnostic tools and develop personalized treatment strategies for this unique patient group.

The findings of this paper highlights the importance of recognizing lean MASLD as a distinct clinical entity that requires tailored diagnostic and therapeutic approaches. Despite the growing body of research, lean MASLD remains inadequately understood and underdiagnosed, particularly due to the historical focus on obesity as the primary risk factor for liver disease. Future research should focus on better defining the pathophysiology of lean MASLD, identifying genetic and environmental risk factors, and developing more effective treatments.

In particular, future studies should aim to refine diagnostic criteria for lean MASLD, incorporating factors such as visceral fat distribution, insulin resistance, and genetic predisposition. Additionally, more research is needed to explore the long-term outcomes of lean MASLD, including its potential progression to more severe liver conditions, such as cirrhosis and hepatocellular carcinoma.

In conclusion, lean MASLD is an emerging condition that warrants greater clinical attention. The prevalence of lean MASLD is expected to rise, driven by the increasing recognition of the disease in lean individuals and the growing awareness of its unique pathophysiology. By improving diagnostic accuracy, understanding the underlying mechanisms, and developing personalized treatment strategies, we can enhance the care and outcomes for lean MASLD patients.

6. CONCLUSIONS

(1) Although MASLD (previously NAFLD) is often associated with obesity, it affects around 10%–15% of lean individuals, with varying prevalence due to diagnostic techniques and ethnic factors. Lean MASLD patients often exhibit metabolic dysfunction and impaired glucose metabolism similar to those with obesity.
(2) Lean MASLD is linked to metabolic dysfunction, including visceral fat accumulation and insulin resistance, despite normal body weight. Genetic factors may contribute, but metabolic factors, such as disruptions in lipid and glucose metabolism, play a more significant role in its progression.
(3) Lean MASLD patients have a lower risk of severe cardiovascular events compared to obese patients but still face a 50% higher mortality rate due to cardiovascular complications. Age is a significant risk factor, and close monitoring is needed, especially for those with hepatic fibrosis.
(4) Lean MASLD patients have a higher overall mortality rate compared to obese counterparts, with an increased risk of developing hepatocellular carcinoma. Lifestyle changes, including weight reduction and dietary adjustments, are recommended to improve both liver function and metabolic health.
(5) Effective treatment of MASLD requires a multifaceted approach, focusing on weight loss, metabolic management, and liver inflammation. New anti-obesity drugs and personalized therapies should be explored, with a focus on early-stage interventions. Research should also focus on improving diagnostics and risk stratification specific to lean MASLD patients.

Conflict of interest

None declared.

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