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Review Article

Quality and Quantity? The Clinical Significance of Myosteatosis in Various Liver Diseases: A Narrative Review

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Abstract

Myosteatosis is associated with poor outcomes in various liver diseases. However, standardized methods for assessing, defining, and diagnosing myosteatosis in the context of liver diseases remain unclear. Furthermore, the underlying mechanisms by which myosteatosis leads to pathophysiological progression and adverse health outcomes remain elusive. Therefore, in this review, we elaborate on the currently available measures, definitions, and diagnostic criteria of myosteatosis in the existing literature. We thoroughly clarify the recent evidence and data regarding the possible involvement of myosteatosis in the progression and deterioration of various liver diseases and resulting complications, including liver cirrhosis, chronic viral hepatitis, nonalcoholic/metabolic-associated fatty liver disease, primary sclerosing cholangitis, liver transplantation, and hepatocellular carcinoma. Additionally, it synthesizes insights from basic research on the pathogenesis of myosteatosis, which involves multifactorial mechanisms, including insulin resistance, mitochondrial dysfunction, and chronic inflammation. Finally, from an operational and pragmatic perspective, several regimens, including physical, nutritional, and pharmacological therapies, have been discussed as potential treatments for myosteatosis.

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Introduction

Body composition has been widely investigated in the medical field, defined as the proportion and distribution of fat and lean tissues in the human body.[1] Abnormalities in body composition are highly prevalent among patients with chronic liver disease and have been closely associated with adverse clinical outcomes.[2,3] Body mass index (BMI) serves as a widely used metric in clinical practice to evaluate body composition. However, it has limited accuracy in distinguishing between muscular tissue and fat tissue, which can be masked by the presence of edema or ascites, common complications in the context of decompensated cirrhosis. Given these substantial limitations in the applicability and validity of BMI for patients with various liver diseases, there has been growing interest in exploring alternative methods to evaluate body composition abnormalities and their clinical implications.[4] Muscles are primarily involved in the process of mechanical activity, along with the production of various myokines. Adipose tissue is capable of regulating energy levels through metabolic activity. The body composition of patients with liver disease differs considerably in terms of muscle and adipose tissue characteristics.[5]

In recent years, changes in the skeletal muscle compartment have been shown to possess predictive value in a wide range of pathological conditions, including but not limited to chronic kidney disease, cardiovascular diseases, and cancer.[6] Skeletal muscle abnormalities, including myosteatosis (abnormal muscle quality) and sarcopenia (abnormal muscle quantity), are frequently observed in the context of liver diseases. Accumulating evidence has shown that the presence of sarcopenia is linked to inferior outcomes in different pathological conditions, while little is known about the clinical relevance of myosteatosis.[7] Recently, several studies have demonstrated that myosteatosis, an entity distinct from sarcopenia, exhibits a close relationship with worsening physical status, debilitating conditions, and poor prognosis in cirrhosis.[8–11] Nachit *et al*. found that myosteatosis significantly increased the mortality risk in asymptomatic adults.[12] According to the updated guideline by the European Working Group on Sarcopenia in Older People, evaluation of muscle quality has attracted extensive attention due to its clinical significance, as skeletal muscle mass not only predicts longevity in older adults but also serves as a critical prognostic marker for mortality in conditions like cancer, type II diabetes, and cardiovascular disease.[13,14]

Despite the growing recognition of myosteatosis as a clinically relevant phenotype in chronic liver diseases, three interrelated challenges have impeded its translation into clinical practice and the advancement of research: first, the lack of a unified definition for myosteatosis in the context of liver disorders; second, the absence of standardized diagnostic criteria and measurement modalities, which preclude cross-study comparison and consistent clinical assessment; and third, the underappreciation of myosteatosis as an independent prognostic factor, given that it is frequently conflated with

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sarcopenia in prior literature. Collectively, these gaps create ambiguity in interpreting the clinical significance of myosteatosis, underscoring the need for a systematic synthesis to resolve inconsistencies and clarify its relevance to liver disease management.

To address these critical gaps, our narrative review critically examines three core aspects: (a) existing definitions, measurement modalities, and the challenges inherent in standardizing diagnostic criteria for myosteatosis in liver diseases; (b) the independent contributions of myosteatosis to the progression and outcomes of diverse liver conditions; and (c) mechanistic insights into the pathogenesis of myosteatosis derived from experimental and clinical studies. We further synthesize the available evidence to develop practical management strategies, while explicitly highlighting unresolved knowledge gaps and prioritizing directions for future research.

Methodology

To address the research questions, a comprehensive search was conducted in PubMed, which analyzed the pathogenesis and clinical implications of myosteatosis in the context of liver disease. Search terms comprised [(Non-alcoholic fatty liver disease) or (metabolic associated fatty liver diseases) or (NAFLD) or (MAFLD) or (liver cirrhosis) or (hepatocellular carcinoma) or (PSC) or (primary sclerosing cholangitis) or (hepatitis C virus) or (hepatitis B virus) or (chronic viral hepatitis) or (liver disease)] AND [(myosteatosis) or (muscle quality)], and publication dates from January 1, 2014 to November 1, 2023 were included. Among 687 publications identified through the database search, we excluded non-full-text or irrelevant clinical studies, duplicates, and case reports. To identify additional relevant publications, the identified articles were manually searched. Finally, 85 studies were collected.

Notably, non-alcoholic fatty liver disease (NAFLD) was officially renamed "metabolic dysfunction-associated fatty liver disease (MAFLD)" by an international expert panel in June 2023, to better reflect the disease's pathogenesis, centered on metabolic dysfunction rather than the exclusion of alcohol. Throughout this review, we use "MAFLD" to denote this condition.[15,16]

Definition, measuring modalities, and diagnostic criteria of myosteatosis

Definition of myosteatosis

Myosteatosis represents a distinct clinical entity that can occur independently of sarcopenia or obesity. Unlike sarcopenia or obesity, there is currently no standardized diagnostic approach for myosteatosis.

Myosteatosis refers to the abnormal accumulation of adipose tissue within skeletal muscle, resulting in detrimental metabolic effects and musculoskeletal dysfunction.[17] This condition encompasses three distinct adipose depots: intramyocellular lipids (within fibers), intramuscular adipose tissue (between fibers), and intermuscular adipose tissue (between muscle groups).[18] Since intramyocellular lipids serve as an energy substrate for muscle activity, their classification as a pathological factor may not be fully justified. On the contrary, intramuscular fat can disrupt muscle fiber alignment, leading to a loss of pennation angle and, therefore, weakening mechanical action due to reduced muscle quality.[19,20] Taken together, we argue that intramuscular and intermuscular adipose tissue-defined myosteatosis appears to be more appropriate.

Measuring modalities and diagnostic criteria of myosteatosis

As myosteatosis is primarily a histological diagnosis, biopsy is regarded as the gold standard for evaluation. Given the invasiveness of tissue sampling, biopsies are not widely adopted in daily clinical practice.[19] Accordingly, a myriad of direct and indirect instruments have been proposed to estimate adipose infiltration in skeletal muscle. Non-invasive measuring tools based on imaging include computed tomography (CT), peripheral quantitative CT, magnetic resonance imaging (MRI), magnetic resonance spectroscopy, and quantitative ultrasound.[18,21] However, studies have not been able to use dual-energy X-ray absorptiometry to determine muscle density as a measure of myosteatosis.[18]

CT accounts for the most widely applied tool to indirectly evaluate myosteatosis, which has been recommended by the Clinical Practice Guidelines of the European Association for the Study of the Liver in 2019.[22] Myosteatosis represents a clinically relevant biomarker for assessing degenerative muscular changes. Standardized measurement is performed through cross-sectional area segmentation at the third lumbar vertebra (L3) level, which has been established as the reference anatomical site. This region consistently encompasses both core musculature (including the psoas and paraspinal muscles) and adipose tissue compartments, and has been strongly correlated with whole-body muscle mass.[23] In contrast, some studies prioritize the psoas major alone, arguing it is less affected by abdominal adiposity and simpler and more convenient to measure. However, a recent study found that a psoas-only analysis underestimates the prevalence of myosteatosis compared to the total L3 musculature (27.7% vs. 66.0%, $P < 0.0001$).[24]

Although low radiation attenuation (RA) values in Hounsfield units (HU) are the standard method for determining myosteatosis, other groups have also introduced and employed heterogeneous selection criteria to characterize myosteatosis and identify patients susceptible to this muscle quality irregularity. The frequent metrics include absolute muscle attenuation values judged by gender-specific cut-offs concerning the total skeletal muscle area versus the bilateral psoas muscle area.[25–27] A significant increase in muscle RA following contrast administration suggests that non-contrast imaging may be more feasible in accurately identifying myosteatosis.[28] In oncological populations, RA cut-off values were established as follows: <33 HU for patients with BMI ≥ 25 kg/m^2 and <41 HU for those with BMI <25 kg/m^2, based on L3-level muscle assessment. The effectiveness has been verified by a range of observational studies regarding myosteatosis.[10,25,29–33] Bannangkoon *et al*. defined it as skeletal muscle density ≤ 44.4 HU and ≤39.3 HU in males and females, respectively.[34] Zeng *et al*. determined the diagnostic threshold for myosteatosis as skeletal muscle density < 32.82 HU in females and <38.93 HU in males among the Chinese population.[35]

Given the marked prevalence of fluid retention in patients with cirrhosis, the validity and feasibility of these BMI-adjusted cut-offs are ambiguous. Fluid accumulation increases tissue water content, which can artificially lower muscle RA and lead to the overdiagnosis of myosteatosis, as edematous muscle may fall below the standard HU thresholds even without significant fat infiltration. To address this limitation, intramuscular adipose tissue content (IMAC), a novel selection criterion for assessing myosteatosis, has been proposed. IMAC is calculated as the L3 region of interest of the multifidus muscle divided by the region of interest of subcutaneous

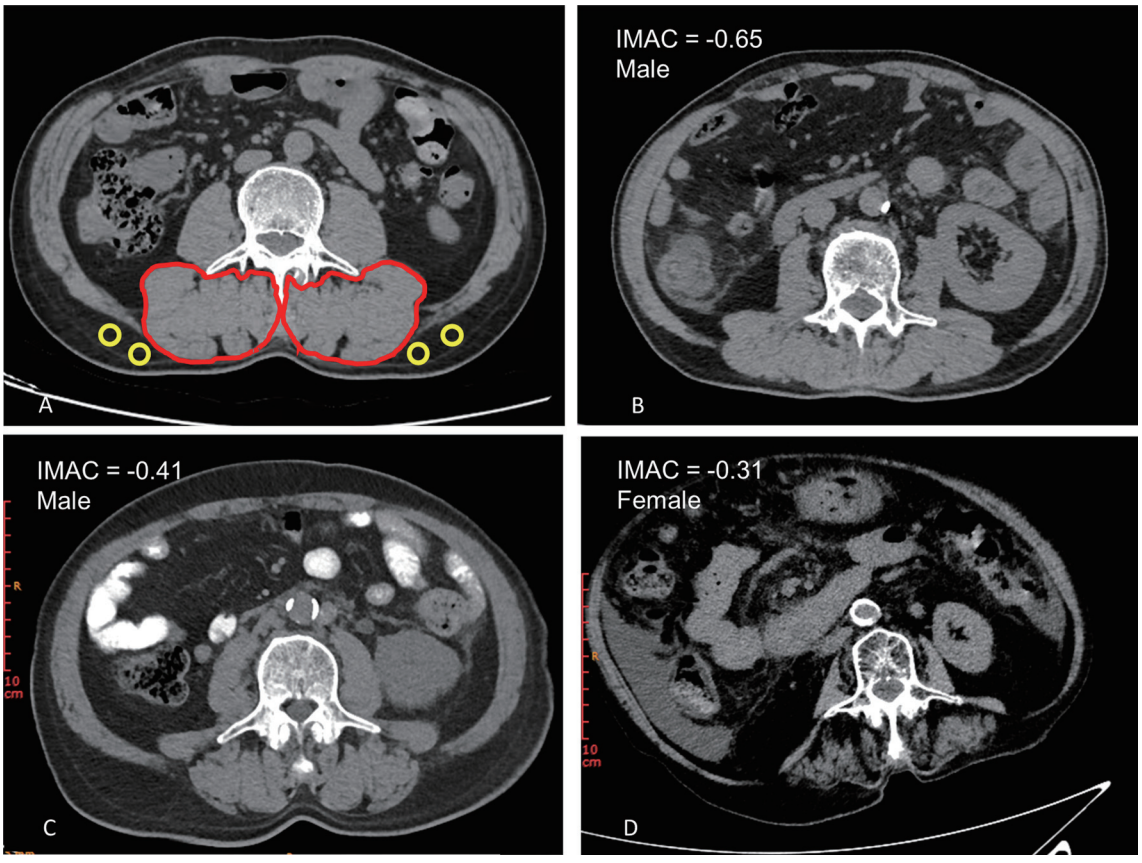

Fig. 1. Abdominal computed tomography images taken at the third lumbar vertebra to quantify intramuscular adipose tissue and muscle radiodensity in patients with cirrhosis. (A) Cross-sectional computed tomography image of subfascial muscular tissue in the multifidus muscle (two red circles) and subcutaneous fat (four yellow circles). (B) Cross-sectional computed tomography image for a male patient with IMAC of −0.65. (C) Cross-sectional computed tomography image for a male patient experiencing myosteatosis with IMAC of −0.41. (D) Cross-sectional computed tomography image for a female patient experiencing myosteatosis with IMAC of -0.31. IMAC, intramuscular adipose tissue content.

adipose tissue (Fig. 1).[36,37] Accordingly, we utilized IMAC-defined myosteatosis at the L3 level, with cut-offs of >−0.44 and >−0.37 in males and females, respectively.[38] It is highlighted that there are other selection criteria or relevant cut-offs to define and diagnose myosteatosis (Table 1).[39–44]

However, CT is incapable of directly measuring fat deposition and the location of lipid droplets in the muscle or discriminating between possible fat distribution phenotypes. Hence, it is necessary to investigate further the specific location and features of infiltrated muscle fat in the context of different liver diseases.[18,45] The magnitude of myosteatosis can be accurately captured by using chemical shift MRI to determine the muscle fat fraction, which shows a strong correlation with histopathologic analyses.[46] In this respect, a study measured the fat fraction of erector spinae muscles based on MRI and identified myosteatosis as a fat fraction less than 0.8 in liver transplantation (LT) recipients.[47]

Notably, the prevalence of myosteatosis in liver diseases is not a fixed value. Still, it varies substantially by the diagnostic criteria employed, including the choice of measurement modality and associated cut-off values. This methodological variability explains the wide range of prevalence estimates across studies and underscores the need to contextualize all prevalence data with the specific tools used to define myosteatosis.

The choice of myosteatosis assessment modality depends on a balance of accuracy, practicality, and patient factors (Supplementary Table 1). CT remains the most widely used method in clinical research due to its high accessibility and robust correlation with histopathological findings (the gold standard for myosteatosis). However, its radiation risk limits use in longitudinal studies or vulnerable populations. MRI offers superior accuracy for quantifying intramuscular fat fraction with no radiation but is constrained by high cost, long scan time, and limited availability. The potential of ultrasound as a low-cost, point-of-care tool for screening is limited by its operator dependency and current lack of standardized diagnostic criteria for myosteatosis. For researchers designing cohort studies, CT is recommended for large-scale analyses (balancing accuracy and feasibility), while MRI is prioritized for mechanistic studies requiring precise fat fraction quantification.

Contributory role of myosteatosis in various liver diseases

Effect of myosteatosis in NAFLD

MAFLD (formerly NAFLD) has progressively emerged as a leading etiology of chronic liver disease and the predominant cause of hepatocellular carcinoma (HCC) among LT candidates in the United States.[48,49] During the last two decades, the global prevalence of MAFLD has approached 30%, and a trend analysis indicates that 37% of adults worldwide are likely to experience MAFLD by 2019.[50] Notably, the prevalence of myosteatosis in the context of MAFLD without obe-

Table 1. Different assessing modalities regarding myosteatosis and relevant cut-off values

Study	Specific study population	Country of study population	Body composition	Area and definition[a]	Interpretation	Patient cut-off values	
						Female	Male
Geladari *et al*., 2023[29]	Cirrhotic patients	Greece	L3 Muscle-RA (HU)	L3 psoas, erector spinae, quadratus lumborum, abdominal obliques, and rectus abdominis muscle	Decreased values indicated lower attenuation in myosteatotic muscle, suggestive of inferior muscle quality	<33 in BMI ≥25 kg/m^2, <41 in BMI <25 kg/m^2	
Ebadi *et al*., 2022[30]	Cirrhotic patients	Canada	L3 SMD (HU)	L3 rectus abdominus, external/internal oblique muscles, transversus abdominus, psoas, and paraspinal (quadratus lumborum, erector spinae)	Decreased values indicated lower attenuation in myosteatotic muscle, suggestive of inferior muscle quality	<33	<28
Bhanji *et al*., 2019[32]	Patients undergoing LT	America	L3 Muscle-RA (HU)	L3 psoas, paraspinal, and abdominal wall (including rectus abdominis, transverse abdominis, and internal and external oblique) muscles	Decreased values indicated lower attenuation in myosteatotic muscle, suggestive of inferior muscle quality	<33 in BMI ≥25 kg/m^2, <41 in BMI <25 kg/m^2	
Meister *et al*., 2021[27]	Cirrhotic patients undergoing LT	Germany	L3 Psoas-RA (HU)	L3 bilateral psoas area	Decreased values indicated lower attenuation of myosteatotic muscle, thus inferior muscle quality (similar to L3 Muscle-RA)	<38.9	<40.0
Sano *et al*., 2021[33]	Patients with HCC	Japan	L3 Muscle-RA (HU)	L3 psoas, erector spinae, quadratus lumborum, abdominal obliques, and rectus abdominis muscle	Decreased values indicated lower attenuation in myosteatotic muscle, suggestive of inferior muscle quality	<33 in BMI ≥25 kg/m^2, <41 in BMI <25 kg/m^2	
Bannangkoon *et al*., 2023[34]	HCC patients undergoing TACE	America	L3 SMD (HU)	L3 abdominal wall and back muscles	Decreased values indicated intramuscular fat deposition and low-grade skeletal muscle	≤44.4	≤39.3
Zeng *et al*., 2023[35]	Cirrhotic patients	China	L3 SMD (HU)	L3 psoas major, erector spinalis, quadratus psoas, external abdominal oblique, and internal abdominal oblique on the right and left sides, and the transverse abdominis	Decreased values indicated intramuscular fat deposition and low-grade skeletal muscle	<32.82	<38.93
Wang *et al*., 2022[37]	Cirrhotic patients	China	L3 IMAC (HU)	L3 ROI of the multifidus muscle/ROI of the subcutaneous	Increased values indicated lower attenuation of myosteatotic muscle, thus inferior muscle quality	> −0.37	> −0.44
Kaibori *et al*., 2015[41]	HCC patients undergoing R0 resection	Japan	L3 IMAC (HU)	L3 ROI of the multifidus muscle/ROI of subcutaneous fat	Increased values indicated lower attenuation of myosteatotic muscle, thus inferior muscle quality	> −0.31	> −0.44

[a]The following attenuation cut-off values were used to differentiate between various tissue components on CT images according to definitions in the existing literature: muscle, −29 to 150 HU; visceral adipose tissue, −150 to −50 HU; and subcutaneous adipose tissue, −190 to −30 HU. Low attenuation muscle area: −29 to +29 HU; Normal attenuation muscle area: +30 to +150 HU. BMI, body mass index; HU, Hounsfield units; HCC, hepatocellular carcinoma; IMAC, intramuscular adipose tissue content; L3, third lumbar vertebra; LT, liver transplant; RA, radiation attenuation; ROI, region of interest; SMD, skeletal muscle density; TACE, transarterial chemoembolization.

Table 2. Summary of studies concerning the clinical relevance of myosteatosis in patients with MAFLD

Author	Study population	Diagnostic criteria	Cut-off	Mean (± SD)/ median (IQR)	Prevalence	Outcome associated with myosteatosis/ Major findings
Kitajima *et al*. 2013[54]	208 patients with MAFLD (formerly NAFLD)[c]	CT: L3 IMAC	NA	−0.23 ± 0.13	NA	IMAC and aging were risk factors associated with the severity of NASH
Hsieh *et al*. 2023[55]	338 patients with MAFLD (formerly NAFLD)	CT: L3 muscle RA	<40.03 HU in female[a]; <47.13 HU in male	47.39 ± 5.75 in MAFLD; 45.63 ± 5.98 in early NASH	21.1% in the MAFLD; 33.3% in early NASH	Severe myosteatosis was significantly associated with early NASH and fibrosis progression in early-stage MAFLD
Hsieh *et al*. 2021[56]	521 patients with MAFLD (formerly NAFLD)	CT: L3 muscle RA	<39.77 HU in BMI ≥25kg/m^2; <42.57 HU in BMI <25kg/m^2	46.81 ± 6.63 in F0-F1; 44.32 ± 7.15 in F2-F4	46.1% in significant fibrosis	Myosteatosis had additive values for predicting significant fibrosis
Nachit *et al*. 2021[57]	48 obese patients	CT: L3 SMFI	NA	32.9 ± 6.5	NA	Myosteatosis, but not sarcopenia, was strongly and independently associated with liver stiffness in obese patients with MAFLD
Kim *et al*. 2023[58]	13,452 subjects	CT: L3 NAMA/ TAMA index	NA	MAFLD; 68.3 ± 9.9 in females; 76.4 ± 7.9 in males	NA	The NAMA/TAMA index may help identify subjects at a high risk of MAFLD and liver fibrosis for further evaluation
Nachit *et al*. 2023[59]	72 patients with MAFLD (formerly NAFLD)	MRI: L3 $PDFF_{ES}$	NA	9.6 ± 5.5% in NAFLD with HCC; 5.7 ± 3.0% in those without	NA	Myosteatosis was associated with the presence of HCC in a population of biopsy-proven MAFLD patients
Linge *et al*. 2023[60]	10,138 subjects	MRI: thighs MFI[b]	High MFI: >8.82% in females; >7.69% in males	8.03% ± 2.16%	NA	High muscle fat was a strong predictor of all-cause mortality in individuals with MAFLD

[a]The lowest quartile stratified by sex was regarded as the cut-off for muscle attenuation to define severe myosteatosis. [b]Muscle fat infiltration: The mean fat fraction in the "viable muscle tissue" of the right and left anterior thighs. [c]MAFLD replaces the former term NAFLD per the June 2023 international nomenclature update, emphasizing metabolic pathogenesis over alcohol exclusion. NA indicates that the original study did not report data; these entries do not represent missing data from our analysis but reflect unreported information in the cited literature. BMI, body mass index; CT, computed tomography; HCC, hepatocellular carcinoma; HU, Hounsfield units; IMAC, intramuscular adipose tissue content; L3, third lumbar vertebra; MAFLD, metabolic-associated fatty liver disease; MFI, muscle fat infiltration; NAFLD, non-alcoholic fatty liver disease; NAMA, normal attenuation muscle area; NASH, nonalcoholic steatohepatitis; $PDFF_{ES}$, proton density fat fraction of erector spinae; RA, radiation attenuation; SMFI, skeletal muscle fat index; TAMA, total abdominal muscle area.

sity is reported to be around 31.7%.[39]

Adverse muscle composition (AMC), characterized by high muscle fat and low muscle volume, is prevalent in subjects with MAFLD (14.0%).[51] This AMC phenotype is also linked to a high prevalence of metabolic comorbidity along with reduced function. Ding *et al*. demonstrated a positive, independent connection between plasma Cathepsin D (CTSD) levels and myosteatosis in patients with MAFLD, supporting the notion that skeletal muscle plays a pivotal role and its derangement may lead to metabolic disturbances, consequently resulting in the progression of metabolic syndrome.[52] In children with MAFLD, researchers have found that intermuscular abdominal adipose tissue mediates the reduction of hepatic steatosis via a multicomponent intervention.[53] Kitajima *et al*. showed a correlation between the stage of non-alcoholic steatohepatitis (NASH) and IMAC (odds ratio = 2.444, $P < 0.05$).[54] Hsieh *et al*. demonstrated that severe myosteatosis may give rise to an increased risk of NASH in patients at an early stage of MAFLD.[55] Collectively, these findings suggest that muscle lipid infiltration may represent a potential biomarker associated with NASH progression.[43,55] In addition, severe myosteatosis exhibited a significant association with fibrosis progression in the context of MAFLD.[55–58] Furthermore, Nachit *et al*. used proton density fat fraction derived from MRI to evaluate myosteatosis within skeletal muscles at the L3 level and showed that the magnitude and heterogeneity of myosteatosis were linked to HCC independent of fibrosis stage in individuals with MAFLD. In particular, this phenomenon was more pronounced in those with NASH.[59] Linge *et al*. established a reference of high muscle fat infiltration over the 75th percentile of a whole population (40,177 subjects) with respective male and female thresholds (>7.69% and >8.82%), in the manner of MRI-screened thighs.[60] Their findings revealed that AMC could predict all-cause mortality in individuals diagnosed with MAFLD. In contrast, some other studies revealed that the degree of myosteatosis had no relation to the levels of transaminases, magnitude of hepatic fat, or significant hepatic fibrosis (Table 2).[46,61]

Effect of myosteatosis in chronic viral hepatitis

The mainstays of chronic viral hepatitis B (HBV) and chronic viral hepatitis C (HCV) have posed a heavy public burden on healthcare resources worldwide. In 2006, it was estimated that 360 million individuals were suffering from chronic hepatitis B, and two billion individuals were infected with HBV globally.[62] Chronic viral hepatitis causes permanent liver inflammation, resulting in severe and ultimately irreversible fibrotic damage to the hepatic parenchyma. Due to a proactive vaccination policy, the burden of HBV is markedly decreasing, but HBV prevalence remains endemic in specific regions.[63] HCV affects an estimated 3% of the global population, and subjects inaccessible to effective treatment are prone to a high risk of developing cirrhosis over a span of twenty years.

Endo *et al*. found that the IMAC values were significantly increased in response to interferon-free direct-acting antiviral treatment (−0.33 versus −0.34, $P < 0.01$), indicating a connection between myosteatosis and HCV.[64] Han *et al*. analyzed a cohort of patients with HBV and sarcopenia. They stated a higher prevalence of evident liver fibrosis relative to those without sarcopenia but experiencing central obesity, presented as BMI ≥ 25 kg/m^2.[65] Notably, another study reported that 96.5% of patients with sarcopenia also exhibited myosteatosis, implicating a reciprocal effect between sarcopenia and myosteatosis.[29] Taken together, further investigation is warranted to delve into the contributory role of myosteatosis in the context of chronic viral hepatitis.

Effect of myosteatosis in liver cirrhosis

About one million deaths worldwide annually are attributable to cirrhosis, which ranks as the eleventh most prevalent cause of death, alongside the third major cause among individuals aged 45–64 years, accounting for 3.5% of all global deaths in combination with liver cancer.[66] The prevalence of myosteatosis in cirrhosis varies substantially by diagnostic methodology. When defined using CT-derived muscle RA with BMI-adjusted cut-offs (<41 HU for BMI < 25 kg/m^2 and <33 HU for BMI ≥ 25 kg/m^2), the reported prevalence ranges from 52% to 74%.[9,10,29,31] In contrast, when diagnosed via IMAC at the L3 level (cut-offs: >−0.44 for males and >−0.37 for females), the prevalence in cirrhotic cohorts is markedly lower, at 17.55% (83/473 patients) and 18.8% (38/202 patients), respectively.[8,37] This discrepancy directly reflects the impact of diagnostic criteria on epidemiological estimates.

Previous studies have shown that myosteatosis worsens the prognosis of patients with cirrhosis, which is related to a higher Child-Pugh score, decompensated stage, and higher long-term mortality.[10,29,31] Compared with the traditional Model for End-stage Liver Disease (MELD) score, Lattanzi *et al*. constructed a MELD-Sarco-Myo-HE score by incorporating the presence of myosteatosis to improve predictive accuracy regarding three- and six-month all-cause mortality.[31] Ebadi *et al*. also revealed that a 2% decrease in the mortality risk accompanies every one HU increase in the muscle radio density.[30] Additionally, myosteatosis has been linked to overt hepatic encephalopathy (HE) and minimal HE among cirrhosis before and after transjugular intrahepatic portosystemic shunt.[9,67] Bhanji and colleagues demonstrated a significantly higher prevalence of myosteatosis in patients with overt HE (70%) compared to those without (45%; $P < 0.001$), suggesting a potential association between myosteatosis and complications in cirrhosis.[9] Relative to sarcopenia, myosteatosis also exhibited a closer correlation with portal hypertension ($r = −0.266$, $P < 0.001$). Moreover, myosteatosis has proved to be associated with several complications, such as variceal bleeding, spontaneous bacterial peritonitis, ascites, infections, and HCC.[35,68] Collectively, current evidence demonstrates a significant association between myosteatosis and worse clinical outcomes in cirrhosis. However, the exact nature of this relationship (whether causal, synergistic, or parallel processes) requires further investigation through longitudinal mechanistic studies (Table 3).

Effect of myosteatosis in LT

For patients with end-stage liver disease, LT remains the most effective treatment option. The influence of nutritional status on postoperative outcomes following LT is still under intensive investigation. Bhanji *et al*. noticed that the frequency of myosteatosis increased while awaiting LT.[69] In addition, they also revealed that the percentage change in mean HU per 100 days post-transplant exhibited a significant decrease (median of −2.7%, $P < 0.001$), suggestive of an increase in myosteatosis.

Myosteatosis has been identified as being interconnected with a spectrum of outcomes, including postoperative ventilation time, post-LT infections, hospital and intensive care unit stay, significant morbidity and mortality, graft- and patient survival, costs, and pulmonary outcomes.[25,70–73] A study recruiting 152 patients undergoing LT, with a long-term follow-up of 56 months, demonstrated that myosteatosis was associated with increased post-transplant mortality (three months, one year, and five years survival probabilities: 72% versus 95%, 63% versus 90%, 54% versus 84%, respectively, $P = 0.001$).[70] Incorporating myosteatosis into the MELD score can enhance its predictive accuracy regarding pre-LT mortality and improve the prognostic value of the Balance-of-Risk score, with the aim of screening patients for early LT and facilitating the utilization of organ resources.[25,31] These findings suggest that myosteatosis may serve as an important prognostic marker during the perioperative period. These results highlight the need for future studies to investigate whether multimodal interventions addressing myosteatosis and its underlying pathophysiology could potentially benefit high-risk patients (Table 4).

Effect of myosteatosis in HCC

HCC often originates from advanced hepatic parenchymal disorders in addition to cirrhosis, and is the third most common cause of cancer-associated mortality globally. Previous investigations covering both basic and clinical aspects have uncovered a robust association between chronic liver disease and pathological alterations of body composition.[74] Chen *et al*. identified myosteatosis in 15.2% of 138 patients receiving immune checkpoint inhibitor therapy, using a muscle RA with BMI-adjusted cut-offs (<41 HU for BMI < 25 kg/m^2 and <33 HU for BMI ≥ 25 kg/m^2).[75] In comparison, Hamaguchi *et al*. reported a preoperative myosteatosis prevalence of 43% among 606 patients undergoing hepatectomy, defining myosteatosis by IMAC (>−0.229 in females, >−0.358 in males).[76] Similarly, Masetti *et al*. observed the highest prevalence (76%) in their cohort of 151 patients treated with trans-arterial embolization, defined by IMAC with sex-specific cut-off values of >−0.229 for females and >−0.358 for males.[40] This wide range likely reflects variations in the study populations and diagnostic criteria.

Myosteatosis independently predicts worse outcomes in advanced HCC patients receiving immunotherapy. Multivariable analysis (adjusted for liver function, tumor extent, and demographics) revealed that myosteatosis was significantly associated with reduced disease control rates and worse progression-free survival (hazard ratio = 2.0, $P = 0.014$).[75] In a

Table 3. Summary of studies concerning the clinical relevance of myosteatosis in patients with cirrhosis

Author	Study population	Diagnostic criteria	Cut-off	Prevalence	Outcome associated with myosteatosis/Major findings
Feng *et al*. 2021[8]	202 patients with cirrhosis	CT: L3 IMAC	> −0.37 in female; > −0.44 in male	18.8%	Significant relationships between IMAC and frailty phenotype were exclusively expressed in males
Bhanji *et al*. 2018[9]	675 patients with cirrhosis	CT: L3 Musle-RA	<33 HU in BMI ≥ 25 kg/m^2; <41 HU in BMI <25 kg/m^2	52%	Myosteatosis was independently associated with overt hepatic encephalopathy in patients with cirrhosis
Montano-Loza *et al*. 2016[10]	678 patients with cirrhosis	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	52%	Myosteatosis was independently associated with a higher risk of long-term mortality in cirrhosis
Geladari *et al*. 2023[29]	197 patients with cirrhosis	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	73.6%	Myosteatosis was associated with advanced age, low skeletal mass, more severe liver cirrhosis, and poor prognosis
Ebadi *et al*. 2022[30]	855 patients with cirrhosis	CT: L3 Muscle-RA	<33 HU in males; <28 HU in females	34%	Myosteatosis was associated with increased mortality. The coexistence of myosteatosis and sarcopenia has been linked to worse outcomes
Lattanzi *et al*. 2019[31]	249 patients with cirrhosis	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	54%	Myosteatosis was independently associated with mortality
Zeng *et al*. 2023[35]	168 patients with cirrhosis	CT: L3-SMD	<32.82 in female; <38.93 in male	49.4% in those aged 60 - 69 years, 80.0% in those older than 70 years	Myosteatosis, rather than sarcopenia, had a close correlation with portal hypertension
Wang *et al*. 2022[37]	473 patients with decompensated cirrhosis	CT: L3 IMAC	> −0.37 in female; > −0.44 in male	17.55%	Higher VSR/VATI and advanced age were associated with myosteatosis. Myosteatosis was not significantly related to longer LOH
Yin *et al*. 2023[67]	108 cirrhotic patients undergoing TIPS	CT: L3 right psoas muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	32.4%	Myosteatosis can serve as a reliable predictor of developing overt HE and mortality in cirrhotic patients after TIPS

BMI, body mass index; CT, computed tomography; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HU, Hounsfield units; IMAC, intramuscular adipose tissue content; L3, third lumbar vertebra; LOH, length of hospitalization; $PDFF_{ES}$, proton density fat fraction of erector spinae; RA, radiation attenuation; SMD, skeletal muscle density; TIPS, transjugular intrahepatic portosystemic shunt; VATI, visceral adipose tissue index; VSR, visceral-to-subcutaneous adipose tissue ratio.

cohort of 606 patients with HCC, Hamaguchi and colleagues demonstrated that patients with a high IMAC had significantly lower recurrence-free survival (RFS) and overall survival (OS) rates.[76] Furthermore, high IMAC was identified as a significant risk factor for mortality after hepatectomy. Regarding a single-center HCC cohort, myosteatosis was linked to suboptimal outcomes, such as various clinical conditions, but had a limited impact on the RFS and long-term OS.[77]

Some articles have demonstrated that preoperative muscle steatosis, determined by IMAC, was strongly linked to an increased likelihood of major postoperative complications (intra-abdominal abscess, ascites, and pleural effusion), especially infectious complications.[78,79] Intriguingly, Masetti *et al*. found that myosteatosis was not related to the complication rate or OS rate in a cohort of 151 patients with cirrhosis receiving trans-arterial embolization.[40] On the other hand, Bannangkoon and colleagues found that the presence of myosteatosis was closely associated with reduced transarterial chemoembolization response (56.1% versus 68.7%, adjusted odds ratio = 0.49) and poor survival (15.9 versus 27.1 months, $P < 0.001$).[34] Although the existing literature reports conflicting results, preoperative identification of patients with elevated IMAC remains clinically recommended before hepatectomy. Therefore, preoperative optimization of myosteatosis may be beneficial to patient selection and improve postoperative outcomes in the context of hepatectomy (Table 5).

Effect of myosteatosis in primary sclerosing cholangitis (PSC)

As a chronic cholestatic liver disease, PSC is characterized by fibroinflammatory destruction of the biliary tree, leading to liver failure, cirrhosis, and eventually cholangiocarcinoma.[80] From a clinical perspective, significant challenges remain in improving outcomes for patients with PSC.

Total skeletal muscle mass has been established as a significant prognostic factor for diverse clinical outcomes in chronic liver disease, including risks of hepatic decompensation, post-treatment complications, and mortality. More recently, the clinical relevance of myosteatosis has also been recognized in this patient group. Praktiknjo *et al*. established intramuscular fat fraction as a proxy for myosteatosis, which is independently predictive of 10-year transplant-free survival in the PSC population.[81] The finding suggested that indices

Table 4. Summary of studies concerning the clinical relevance of myosteatosis in patients undergoing liver transplant

Author	Study population	Diagnostic criteria	Cut-off	Mean (± SD)/ median (IQR)	Prevalence	Outcome associated with myosteatosis/Major findings
Bhanji *et al*. 2019[69]	293 patients undergoing LDLT	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	42.8 ± 9.1 in non-sarcopenia; 41.4 ± 9.0 in sarcopenia	NA	Myosteatosis progressively increased in both pre- and post-transplant groups
Molwitz *et al*. 2023[70]	152 patients undergoing LDLT	CT: L3 Muscle-RA	NA	38 ± 8 in pre-LT; 35 ± 10 in post-LT	NA	Myosteatosis was associated with a higher post-transplant mortality, and did not improve after transplant
Czigany *et al*. 2021[71]	225 patients undergoing OLT	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2 <41 HU in BMI <25 kg/m^2	32 ± 11 in female; 35 ± 11 in males	44%	The probability of graft and patient survival was significantly lower in patients with myosteatosis
Irwin *et al*. 2021[73]	106 patients undergoing LT	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2 <41 HU in BMI <25 kg/m^2	32 ± 8	72%	Patients with myosteatosis had a higher risk of death and allograft failure at 1 year

NA indicates that the original study did not report data; these entries do not represent missing data from our analysis but reflect unreported information in the cited literature. BMI, body mass index; CT, computed tomography; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HU, Hounsfield units; IMAC, intramuscular adipose tissue content; L3, third lumbar vertebra; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; OLT, orthotopic liver transplantation; RA, radiation attenuation.

of body composition may constitute alternative indicators for organ allocation proposed for PSC patients at the stage of cirrhosis.

Miscellaneous

Horii *et al*. recruited 115 subjects who underwent initial liver resection for colorectal liver metastasis (CLM) and found that high IMAC was linked to postoperative complications of Clavien-Dindo grade 3 or worse, in addition to lower OS and RFS.[42] Dijk *et al*. verified that myosteatosis was independently associated with shorter OS.[82] Additionally, Shiozawa *et al*. indicated that IMAC before the second liver resection was the most important predictor for RFS and OS in patients undergoing two-stage hepatectomy for CLM.[83] Early identification of apparent variations in body composition is imperative to perform timely perioperative intervention and thereby enhance postoperative outcomes in the context of CLM.

Etiological determinants and pathophysiological pathways of myosteatosis

Both intermuscular and intramuscular fat deposition are significantly influenced by age and race.[20,45] Aging is associated with diminished differentiation capacity of muscle stem cells into myocytes, which promotes preferential adipocyte differentiation. This process ultimately leads to increased intermuscular fat deposition in both males and females.[84–86] Miljkovic and colleagues demonstrated that the incidence of intermuscular fat was higher among African individuals compared to Caucasian individuals. However, the precipitating factors responsible for these differences remain unknown, and they hypothesized that the variation in skeletal muscle fat accumulation may be triggered by ethnic variation in carnitine palmitoyltransferase-1B allele frequencies.[87]

The pathogenesis of myosteatosis involves multifactorial and complex mechanisms, primarily driven by alterations in fatty acid and glycogen metabolism. Previous fundamental studies have stated that muscular changes not only contribute to hepatic dysfunction but also reflect disease-stage progression in liver disorders.[45] Data explaining the mechanisms by which excess muscle fat infiltration and accumulation in chronic liver disease occur are scarce. Therefore, further research is warranted to elucidate the mechanical pathways from both clinical and molecular perspectives. Based on current evidence, we herein propose several potential pathogenic mechanisms, with a particular focus on conducting a preliminary analysis of the liver-muscle axis (Fig. 2).

Hyperammonemia

Liver dysfunction impairs urea cycle activity, leading to systemic hyperammonemia, which may be a predisposing factor in the development of myosteatosis in cirrhosis. Research has shown that hyperammonemia can induce the transcriptional upregulation of myostatin, which subsequently suppresses muscle protein synthesis and promotes fat accumulation.[88,89] Stretch *et al*. found that all 18 differentially abundant genes (DAGs) linked to oxidative phosphorylation were downregulated in the muscles of patients with myosteatosis, implying that oxidative phosphorylation is a canonical pathway.[90] Increased uptake of ammonia by muscular tissue induces mitochondrial dysfunction through the cataplerosis of α-ketoglutarate, which further leads to impaired mitochondrial oxidative phosphorylation in addition to reduced muscular lipid oxidation.[91]

Insulin resistance (IR)

IR is a key mediator of the liver-muscle axis in myosteatosis, which is a common pathophysiological dysregulation in patients with MAFLD or cirrhotic patients.[92] Additionally, it is hypothesized that IR in the context of cirrhosis is associated with a reduction in peripheral (muscle) glucose uptake, rather than an increase in liver glucose production.[93] Fat load in the muscle and hepatocyte cells is closely linked to IR in lean, obese, and diabetic individuals. IR leads to compensatory hyperinsulinemia, which impairs the suppression of gluconeogenesis, decreases glycogen synthesis, increases the uptake of free fatty acids and lipogenesis, alters the transport of triglycerides, and inhibits beta-oxidation in steatotic

Table 5. Summary of studies concerning the clinical relevance of myosteatosis in patients with hepatocellular carcinoma

Author	Study population	Diagnostic criteria	Cut-off	Mean (± SD)/ median (IQR)	Prevalence	Outcome associated with myosteatosis/Major findings
Bannangkoon *et al*. 2023[34]	611 HCC patients undergoing TACE	CT: L3-SMD	≤39.3 in female; ≤44.4 in male	39.7 (35.0, 43.3) in females; 46.0 (41.9, 50.2) in males	38.8%	Patients with myosteatosis had shorter overall survival than those without
Masetti *et al*. 2022[40]	151 HCC patients undergoing TAE	CT: L3 IMAC	> −0.31 in female; > −0.44 in male	NA	76%	Myosteatosis was not associated with a different burden of HCC, length of hospitalization, complication rate, or readmission within the first 30 days after discharge, and it also showed no association with overall survival
Kaibori *et al*. 2015[41]	141 HCC patients undergoing hepatectomy	CT: L3 IMAC	high IMAC: > −0.31 in female; > −0.44 in male	NA	NA	High IMAC was significantly correlated with liver dysfunction, higher intraoperative blood loss, the need for blood transfusion, and comorbid diabetes mellitus
Chen *et al*. 2023[75]	138 HCC patients undergoing ICI immunotherapy	CT: L3 Musle-RA	<33 HU in BMI ≥25 kg/m^2 <41 HU in BMI <25 kg/m^2	45.7 ± 7.4	15.2%	Myosteatosis was an independent prognostic factor in patients receiving immunotherapy for advanced HCC
Hamaguchi *et al*. 2019[76]	606 HCC patients undergoing hepatectomy	CT: L3 IMAC	high IMAC: > −0.229 in female; > −0.358 in male	NA	high IMAC: 43%	A high VSR, low SMI, and high IMAC contributed to an increased risk of death and HCC recurrence in an additive manner
Meister *et al*. 2022[77]	100 HCC patients undergoing partial hepatectomy	CT: L3 Muscle-RA	<33 HU in BMI ≥25 kg/m^2; <41 HU in BMI <25 kg/m^2	33 ± 10	60%	Myosteatotic patients had significantly inferior outcomes in terms of major postoperative complications
Hamaguchi *et al*. 2016[78]	492 HCC patients undergoing hepatectomy	CT: L3 IMAC	high IMAC: > −0.138 in female; > −0.324 in male	−0.169 ± 0.171 in female; −0.336 ± 0.129 in male	NA	IMAC was closely correlated with increased postoperative complications, especially infectious complications
Harimoto *et al*. 2018 [79]	146 hepatic malignancy patients undergoing curative hepatic resection	CT: L3 IMAC	high IMAC: > −0.502 in female; > −0.730 in male	−0.60 (−1.25, −0.27)	NA	High IMAC was an independent risk factor for postoperative complications

NA indicates that the original study did not report data; these entries do not represent missing data from our analysis but reflect unreported information in the cited literature. BMI, body mass index; CT, computed tomography; HCC, hepatocellular carcinoma; HU, Hounsfield units; ICI, immune checkpoint inhibitor; IMAC, intramuscular adipose tissue content; IMAT, intramuscular adipose tissue; L3, third lumbar vertebra; RA, radiation attenuation; RAM, ramucirumab; SMD, skeletal muscle density; SMI, skeletal muscle index; TACE, transarterial chemoembolization; TAE, trans-arterial embolization; VSR, visceral-to-subcutaneous adipose tissue ratio.

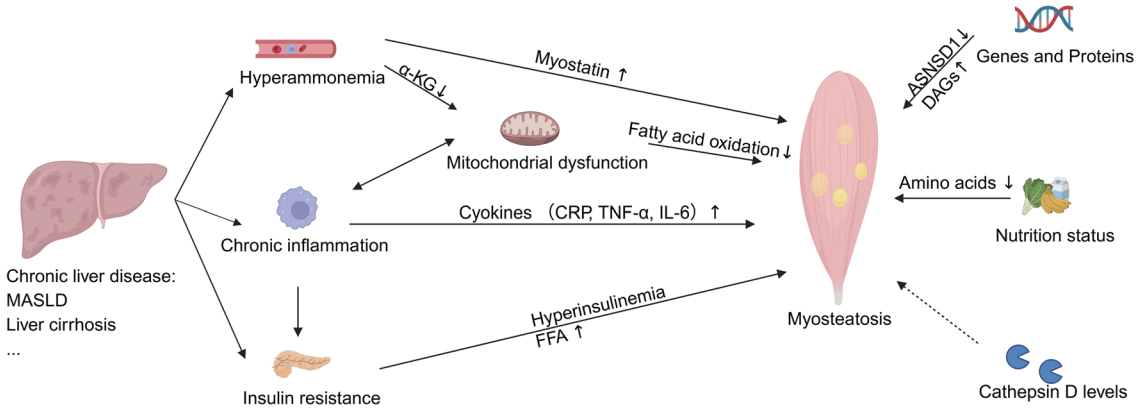

Fig. 2. A summary of mechanistic pathways responsible for the advent and progression of myosteatosis-center on the liver-muscle axis. Evidence-supported pathways are represented by solid lines. Hypothetical pathways are represented by dashed lines. Insulin resistance could impact glucose disposal and increase uptake of FAA, giving rise to lipogenesis. Hyperammonemia could increase uptake of ammonia by muscular tissue and induce mitochondrial dysfunction, responsible for reduced muscular lipid oxidation. Chronic inflammation, characterized by the release of proinflammatory cytokines, is positively correlated with fat mass accumulation. Nutritional status and functional genes and proteins could promote myosteatosis by influencing lipid metabolism. Mitochondrial dysfunction leads to impaired mitochondrial oxidative phosphorylation and decreased lipid oxidation, resulting in excessive lipid storage in the skeletal muscle. Cathepsin D may mediate the development of myosteatosis by instigating ectopic lipid accumulation. ASNSD1, asparagine synthetase domain containing 1; DAGs, differentially abundant genes; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; FFA, free fatty acid. α-KG, α-ketoglutarate; ↓, decrease; ↑, increase. (Created with bioRender.com)

hepatocytes.[94] Taken together, myosteatosis is associated with excessive circulating fatty acids and IR.

Chronic inflammation

Chronic liver disease triggers persistent hepatic inflammation, characterized by the activation of Kupffer cells and the release of proinflammatory cytokines. These cytokines, including C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α, enter the systemic circulation and target skeletal muscle, where they disrupt lipid metabolism and promote the accumulation of fat. High levels of interleukin-6 and CRP positively correlate with the magnitude of fat mass accumulation.[95] Kim *et al*. also revealed a significant correlation between myosteatosis indices and CRP levels, partially explaining the pathogenesis of inflammation-dictated myosteatosis.[58] In addition to their direct impact on insulin signaling, cytokines modulate the secretion of myokines from skeletal muscle. A consequent dysregulation of these myokines can exacerbate conditions of muscle wasting and metabolic dysfunction.[96]

Other underlying mechanisms in liver diseases

Shared pathogenic factors that can underlie the development of both chronic liver disease and myosteatosis are enumerated in the following section.

Mitochondrial dysfunction and energy metabolism: Mitochondrial dysfunction may lead to reduced oxidation of fatty acids, resulting in excessive lipid storage in the muscle cells. In a rat model of rotator cuff injury, Gumucio and colleagues observed a decline in the ability of mitochondria to oxidize lipids during the early process.[97] Meanwhile, transcriptional changes were evident, including an increase in lipid droplet storage with a decrease in fatty acid uptake and mobilization from lipid droplet stores. In patients with myosteatosis, transcriptomic analysis revealed a lower expression of DAGs linked to oxidative phosphorylation in the muscles (i.e., Ndufa3 and ATP5G1).[90] Mitoquinone Q, as a mitochondria-targeting antioxidant, was also verified to enhance the utilization of accumulated lipids and reduce the magnitude of myosteatosis in mice bearing C26 tumors.[98] Retinoic acid receptor-related orphan receptor-α was found to enhance mitochondrial oxidative capacity by controlling the expression of GABPα and TFAM, thus reducing muscular lipid accumulation.[99] Wu *et al*. demonstrated that adenosine monophosphate-activated protein kinase (a promoter of mitochondrial health) regulated lipid accumulation in skeletal muscle cells via fat mass and obesity-associated protein expression, which is responsible for the demethylation of N6-methyladenosine in experimental models of C2C12 cells and mice.[100] Therefore, adenosine monophosphate-activated protein kinase could regulate the energy state of skeletal muscle cells by facilitating mitochondrial biogenesis.

Collectively, current evidence suggests that decreased lipid oxidation and impaired mitochondrial oxidative phosphorylation in skeletal muscle significantly contribute to the development of myosteatosis. These findings suggest that targeting mitochondrial dysfunction may represent a promising therapeutic strategy; however, further research is needed to fully elucidate the multifactorial etiology.

CTSD levels: CTSD, a lysosomal aspartyl endopeptidase, is present in nearly all cell types and organ systems, where it plays critical roles in metabolic functions.[101] CTSD correlates with impaired lipid metabolism, disease severity, and higher levels of inflammation in MAFLD, and Ding *et al*. found a positive correlation between plasma CTSD levels and myosteatosis.[52] Furthermore, this connection was independent of BMI, age, sex, hepatic steatosis, and waist circumference. The authors proposed that CTSD, as a mediator instigating ectopic fat accumulation, promotes the onset and development of myosteatosis. Notably, Yadati and colleagues demonstrated that extracellular CTSD inhibition in mouse models promoted the activation of several lipid metabolic pathways (linoleic acid metabolism, steroid hormone biosynthesis, and fatty acid synthesis/elongation), partially responsible for a modest attenuation of systemic inflammation.[102] The protein encoded by the CTSD gene is involved in processes such as protein turnover and proteolytic activation of hormones and growth factors. Mutations in the CTSD gene may disrupt these normal physiological processes, impair muscle metabolism, and thereby contribute to the development and progression of myosteatosis. Further research is needed to precisely identify the genetic components that may underlie the observed correlation between CTSD and myosteatosis. Collectively, the

precise molecular mechanisms through which CTSD induces or exacerbates myosteatosis require further elucidation.

Nutritional status: Intriguingly, both nutrient overload and nutritional deficiencies can lead to myosteatosis. Previous studies demonstrate that excessive fat and calorie intake contribute to myosteatosis, as evidenced by animal models of myosteatosis that primarily employ diet-induced obesity paradigms.[103] Plin2, a lipid droplet protein repressing lipolysis, has been regarded as a causative factor of steatosis in the muscle and liver. A study showed that the E3 ubiquitin ligase Ubr1 targeted Plin2 for degradation in a specific amino acid-dependent manner. Specifically, Ubr1 is allosterically activated by binding to type 1 (arginine, histidine, and lysine) or type 2 (leucine, isoleucine, phenylalanine, tryptophan, and tyrosine) free amino acids via its UBR-box-1 and UBR-box-2 domains, respectively. In the absence of these amino acids, Ubr1 remains auto-inhibited, leading to the failure of Ubr1-mediated Plin2 ubiquitination and degradation, which ultimately promotes the accumulation of lipid droplets and the onset of steatosis.[104] Another study indicated that leucine can reduce intramyocellular lipid independent of the rapamycin complex 1 to upregulate gene expression associated with fatty acid metabolism in palmitate-treated C2C12 myotubes.[105] Muscle cell lipid infiltration has also been proven to correlate with reduced protein synthesis.[106]

Function of genes and proteins: Age-related changes in skeletal muscle include pathological fat accumulation. Through integrative analysis of single-nucleus transcriptomic data from aged human skeletal muscle and Laiwu pigs exhibiting elevated intramuscular adiposity, Wang and colleagues identified both conserved and species-specific cellular subpopulations linked to myosteatosis pathogenesis. Their findings demonstrated significant upregulation of established senescence markers (VIM and AGT) in elderly human muscle tissue, paralleled by enhanced expression of key adipogenic regulators, including ADIPOQ, FABP4, PPARG, CPT1A, and SCD.[107] The protein asparagine synthetase domain-containing 1 (hereinafter referred to as ASNSD1), which is structurally conserved across many species, exhibits maximum expression in skeletal muscle in humans, according to whole-body gene expression studies. One study found that ASNSD1$^{-/-}$ mice develop a progressively degenerative myopathy responsible for severe myosteatosis.[108] Furthermore, five DAGs impacting lipid metabolism (ADIPOR2, APOL1, APOL2, APOO, and PON3), which may contribute to lipid accumulation, were identified in myosteatosis but not, or to a much lesser extent, compared with sarcopenia.[90]

Prevention and treatment of myosteatosis

Currently, there is no consensus or guideline on the treatment options for myosteatosis in patients with liver diseases, a gap attributed to the lack of evidence, as well as a lack of solid data based on randomized controlled trials. The following are potential treatments and management strategies aimed at improving myosteatosis (Supplementary Table 2).

Nutritional intervention

Excessive fat and calorie intake have been reported to augment myosteatosis.[103] In NASH, one suitable treatment option is energy restriction, commonly achieved through a low-carbohydrate diet, low-fat, and low-calorie intake.[109] However, a dilemma exists, as caloric restriction-related weight loss in overweight/obese patients may result in concurrent loss of fat mass (75%) and skeletal muscle mass (25%). Therefore, energy intake should be adjusted according to the patient's BMI and corrected for fluid overload (edema/ascites).

Nutritional intervention serves as the foundation for managing myosteatosis, with tailored strategies based on the stage of the disease. For high-risk populations, the core goal of nutritional intervention is to maintain skeletal muscle metabolic homeostasis, thereby preventing the initiation of intramuscular fat accumulation. Specifically, the general high-risk population can adhere to a high-quality protein intake of 1.2–1.5 g per kilogram of ideal body weight per day, which provides essential amino acids to support muscle protein synthesis and preserve muscle mass.[110] Meanwhile, dietary patterns should prioritize balanced meals characterized by low saturated fat and high dietary fiber.

For patients with established myosteatosis, nutritional strategies should focus on halting disease progression and restoring muscle lipid balance. Implementing a "small, frequent meal" pattern, along with a late-evening protein-rich snack, has been shown to decrease lipid oxidation and improve nitrogen balance and skeletal muscle mass.[111] Accumulating evidence suggests that supplementation with specific amino acid subsets, including essential basic amino acids (arginine, histidine, and lysine) and hydrophobic amino acids (leucine, isoleucine, phenylalanine, tryptophan, and tyrosine), may be beneficial in reversing myosteatosis, particularly among patients deficient in protein.[104] Notably, recent clinical research has further indicated that polyunsaturated fatty acids exert a protective effect against myosteatosis.[112,113]

Exercise prescription

While exercise therapy has been proven to bring beneficial effects on myosteatosis in the elderly and obese,[114] its specific mechanisms of action regarding intramuscular lipid redistribution require further in-depth investigation. Current evidence suggests that exercise therapy, when combined with proper nutrition management, may be beneficial in preventing or slowing the progression of myosteatosis. Hoek *et al*. showed that exercise and dietary change can reverse evident NASH/fibrosis in obese Ldlr$^{-/-}$ mice. Leiden mice improved myosteatosis and muscle function with additional effects following joint treatments.[115] While these findings provide mechanistic insights, their direct applicability to clinical practice requires further validation through human studies. The effectiveness of exercise prescription has been analyzed in several recent reviews and meta-analyses that aim to deliver healthcare and counseling.[116,117] As a result, these physical approaches can serve as recommendations to relieve myosteatosis.

For high-risk populations, the primary goal of exercise intervention is to establish foundational exercise habits that preserve skeletal muscle function and metabolic homeostasis, thereby preventing the onset of myosteatosis. This stage focuses on initiating a combined regimen of aerobic and resistance exercises, modalities that synergistically maintain muscle mass and enhance lipid oxidation. As individuals transition to a confirmed diagnosis of myosteatosis, exercise progression should follow a gradual, individualized escalation principle, one that aligns with both personal physical capacity and disease-specific characteristics.

Pharmacological therapy

Given the pathogenic contribution of hyperammonemia to myosteatosis, researchers have shown increasing interest in nutritional and pharmacological interventions that modify ammonia metabolism. Pichon *et al*. already found that long-term supplementation with L-ornithine L-aspartate can efficiently prevent myosteatosis in mice.[118] AdipoRon is an

adiponectin receptor agonist that potently protects against myosteatosis due to aging or calorie excess in mice.[103] These findings provide a proof-of-concept for both AdipoRon and L-ornithine L-aspartate's potential in preventing myosteatosis. However, further investigation, particularly through human clinical trials, is indispensable for establishing broader clinical applicability.

Considerations for future clinical trials

Currently, some pioneers have conducted several clinical trials on the treatment of myosteatosis in the field of oncology. For instance, Pring *et al*. conducted a double-blind, randomized controlled trial investigating whether neuromuscular electrical stimulation can prevent myosteatosis, as determined by a CT scan.[119] Another research group carried out a single-blind randomized controlled study evaluating the combined effect of vibration treatment and dietary supplements on myosteatosis among patients with concomitant sarcopenia. These clinical trials have provided clues, prompting subsequent investigations in the context of liver diseases.[120] Additionally, we suggest that the measurement of myosteatosis should be CT-dictated and apply gender-specific cut-offs, since BMI-specific cut-offs may be curtailed by fluid retention.

Conclusions

The true prevalence and clinical significance of this distinct skeletal muscle abnormality remain unclear due to inconsistent assessment modalities and a lack of standardized definitions alongside diagnostic criteria across published studies. In the case of MAFLD, the onset of myosteatosis appears to be associated with dysregulated metabolic conditions and histological alterations. Myosteatosis accounts for additional negative impacts on morbidity and mortality in patients experiencing decompensated cirrhosis. In the context of LT, myosteatosis is linked to poor survival and adverse outcomes. Myosteatosis may also serve as an independent risk factor for the recurrence of HCC.

The underlying mechanisms of myosteatosis are multifaceted and complicated in the context of liver diseases, including but not limited to mitochondrial dysfunction, IR, and permanent inflammatory responses. Additionally, the development of various body composition abnormalities may be partly explained by an interplay between the muscle-liver tissue axis. Currently, all available therapies for myosteatosis, including exercise prescription, pharmacotherapy, and nutritional intervention, primarily aim to replace deficiencies rather than targeting mechanistic pathways. In light of concurrent myosteatosis and liver diseases, the identification of potential therapeutic strategies is of utmost importance due to those unmet clinical needs.

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Conflict of interest

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Author contributions

Review's concept and design (JY, CS), literature search and synthesis of the evidence (JY). All authors were involved in the writing and revision of the manuscript. All authors have read and approved the final manuscript.

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