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REVIEW

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Sarcopenic obesity in liver disease: Handling both sides of the penny

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Abstract

Skeletal muscle and fat tissue show distinct pathophysiological roles and pivotal functions. The culmination of muscle wasting and fat accumulation represents an opposite terminal of each state. Specifically, this situation has been designated as sarcopenic obesity. However, sarcopenic obesity still lacks a unanimous definition, diagnostic criteria, and generalized modalities for assessment in the context of versatile liver diseases. Moreover, the underpinning mechanisms by which a combination of abnormal skeletal muscle and fat tissue leads to the progression of liver disease and impairs health-related consequences are still elusive. Additionally, the interplay between skeletal muscle and fat, and the driving factors that shift different body compositions are not well understood. Therefore, in this review, we discuss skeletal muscle and fat components, with the purpose of conceptualization, as well as interpret their roles in liver diseases. We focus on the definitions, diagnostic criteria, and currently available measurements for sarcopenic obesity in the literature. We comprehensively discuss recent data and evidence regarding the potential role of sarcopenic obesity in the development and progression of numerous liver diseases and associated conditions, including nonalcoholic fatty liver disease, chronic viral hepatitis, cirrhosis, and liver transplantation. Furthermore, explicit information related to the pathogenesis of sarcopenic obesity from basic research is also provided in this narrative review. Finally, we discuss, from the clinical perspective of view, how to manage sarcopenic obesity using nutritional, physical, and pharmacological methods.

KEYWORDS

hepatocellular carcinoma, liver cirrhosis, NAFLD, pathogenesis, sarcopenic obesity

Highlights

- Sarcopenic obesity may contribute to the development and progression of various liver diseases.
- The pathogenesis of sarcopenic obesity in the context of liver diseases is multifactorial and complicated.
- Potential avenues for therapeutic intervention by modifying sarcopenic obesity are urgently required.

Yangyang Hui, Binxin Cui, and Xiaoyu Wang contributed equally to this study.

1 | INTRODUCTION

Body composition, which refers to the proportion and distribution of bone, skeletal muscle, and fat tissue in the human body, has attracted attention in the medical field.[1,2] The body mass index (BMI) is widely used to assess body composition in daily clinical practice, but it is unable to discriminate between skeletal muscle and fat tissue. Notably, the potential role of BMI in the context of liver diseases appears to be enigmatic. A study using the National Health and Nutrition Examination Survey (NHANES) database, with a mean follow-up of 13 years, identified obesity (BMI ≥ 30 kg/m^2) as a risk factor for cirrhosis-related mortality or hospitalization.[3] Intriguingly, Li et al.[4] found that a lower BMI was associated with a higher liver-related mortality rate and shorter survival time among patients with hepatocellular carcinoma (HCC). In contrast, BMI was not an independent risk factor in post-transplant patients or graft survival after correction for ascites, which counteracts findings in other series.[5] Taking into account the limited applicability of BMI for prognostication, more reliable, replicable, and reproducible metrics aiming at risk stratification and the prediction of outcomes need to be developed. Accordingly, the assessment of other body composition abnormalities, such as skeletal muscle depletion or visceral adiposity and their synergism, may lead to an objective reflection of individual metabolic and nutritional status.

The clinical implication and relevance of body composition abnormalities, such as sarcopenia (low skeletal muscle mass) or high visceral adiposity, on poor outcomes in a number of pathological conditions, have been extensively demonstrated by our research laboratory and others.[2,6] Recently, scientific endeavors have focused on the synergistic effect of sarcopenia in the context of coexisting obesity, known as sarcopenic obesity, especially its relationship with adverse health consequences. The concordance of these two conditions may be greater than the sum of the contribution of obesity or sarcopenia separately.[1] Fat deposition leads to massive production of adipokines and infiltration of proinflammatory macrophages and other immune cells, leading to a chronic low-grade inflammatory milieu.[7–9] However, fat tissue can accumulate ectopically in skeletal muscle tissue, promoting the excretion of detrimental myokines responsible for an inflammatory cascade and muscle dysfunction. These myokines then also facilitate fat tissue inflammation by generating a vicious circle.[10] However, the abovementioned evidence was predominantly derived from observational studies or results in animal models. Therefore, the validity of classifying sarcopenic obesity as a syndromic entity remains hypothetical and warrants further in-depth investigation. In this narrative review, we provide a conceptual framework of definitions, diagnostic criteria, and applied methodologies for assessing sarcopenic obesity. The effect of sarcopenic obesity in a versatile setting of hepatic pathologies has been comprehensively demonstrated. The mechanisms underlying the development and progression of sarcopenic obesity based on findings in vivo/vitro are discussed. We finally suggest a management strategy and envision the potential to consider sarcopenic obesity as a therapeutic target in the context of liver diseases.

2 | DEFINITION, DIAGNOSTIC CRITERIA, AND PREVALENCE OF SARCOPENIC OBESITY

The majority of the scientific literature considers sarcopenia and obesity as two distinct pathological categories, which can be evaluated individually in each patient. However, a lack of consensus on its definition leads to inconsistent information regarding the estimated prevalence, patient classification, clinical relevance, and therapeutic strategy.

2.1 | Definition and diagnostic criteria of sarcopenia

Although three decades have passed since the proposal of sarcopenia, a universal concept of sarcopenia has not been achieved.[11] As a generic physical syndrome, sarcopenia refers to a gradual decline and impairment in skeletal muscle mass, strength, and functional performance. In light of pathophysiological similarities between the aging process and chronic advanced diseases, such as persistent low-grade inflammation, insulin resistance, oxidative stress, and metabolic and hormonal disturbances, the conceptual model of sarcopenic obesity proceeds to numerous disorders, including liver diseases. The European Working Group for the Study of Sarcopenia 2 (EWGSOP2) has released and updated its diagnostic criteria of sarcopenia by considering muscle strength as a fundamental determinant compared with skeletal muscle mass because of its better capacity for prognostication.[12,13] This working group suggested screening subjects with sarcopenia for decreased hand grip strength (HGS), which serves as a primary feature of sarcopenia. Additionally, healthcare providers may verify the diagnosis of sarcopenia by subsequently measuring muscle quantity and quality, whereas the severity of sarcopenia can be judged according to a physical performance-based metric such as usual gait speed. In 2019, the Asian Working Group for Sarcopenia (AWGS) proposed a revised diagnostic algorithm and criteria based on accumulating evidence from clinical practice.[14] This working group proposed diagnosing sarcopenia in people with concurrent low muscle strength (HGS < 28 kg in men and <18 kg in women) and decreased muscle quantity, or in those with a decreased physical performance (e.g., 6-m gait speed < 1.0 m/s). Other international initiatives have suggested identifying sarcopenia among high-risk populations by evaluating HGS, appendicular lean mass adjusted for BMI/height^2, or gait speed.[15,16]

2.2 | Measurement techniques of sarcopenia in patients with liver disease

In hepatology, the majority of published studies have defined sarcopenia as a reduced skeletal muscle mass.[6,17] Accordingly, numerous direct and indirect techniques have been developed to quantitively assess the loss of muscularity. Measurement tools comprise anthropometric metrics, bioelectrical impedance analysis (BIA), and radiological methodologies, which include computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and dual-energy X-ray absorptiometry (DEXA).[18,19] Because of the specificity of decompensated cirrhosis and HCC, using CT/MRI-based cross-sectional imaging is more accurate and reliable in the context of advanced and end-stage liver disease. In these subgroups, cross-sectional imaging is a routine examination required for regular surveillance, close monitoring of disease progression, and early detection of malignant transformation. The confounding effect of fluid retention (ascites and edema), which is a major complication due to portal hypertension, can be more effectively eliminated using CT than using BIA or DEXA. In other settings, such as fatty liver, performing nonradiative and reproducible approaches is feasible and applicable. In the setting of cirrhosis, our research group constructed a mortality cutoff by calculating the skeletal muscle index (SMI) of the third lumbar vertebra (L3) on CT scans in a cohort of 414 patients as follows: SMI < 46.96 cm^2/m^2 in men and <32.46 cm^2/m^2 in women.[20] Other commonly used thresholds include an L3 SMI < 50 cm^2/m^2 in men and <39 cm^2/m^2 in women among Western populations,[21] while a Japanese guideline suggests <42 cm^2/m^2 and <38 cm^2/m^2 in men and women, respectively.[22] Because of the considerable variability regarding the body habitus, quality of life, dietary regimens, and eating behavior between Western and Eastern populations, the estimation of SMI values as a continuous variable may be superior to a single global cutoff.

2.3 | Definition and diagnostic criteria of obesity

The World Health Organization regards obesity as the largest chronic health problem globally in adults. Notably, the worldwide prevalence of obesity approximately doubled between 1980 and 2008, when 50% of the European population were overweight and nearly 20% were obese.[23] Recently, the European Society for Clinical Nutrition and Metabolism proposed a consensus definition of overweight and obesity as abnormal or excessive fat deposition.[24] Moreover, adipocyte dysfunction secondary to fat accumulation may result in metabolic disturbance, potentiating the risk of various chronic diseases and malignancies. Most guidelines define obesity as a BMI of ≥30 kg/m^2 in Western populations and ≥25 kg/m^2 in Asian populations. However, there are no universally accepted and firmly established diagnostic criteria for obesity, especially in the context of several pathological conditions (e.g., metabolic, cardiovascular, and liver diseases). An example of this situation is that the utility and validity of using the BMI for classifying the obese phenotype in advanced liver disease have been impeded because a large proportion of these patients have a fluid imbalance. Fukuda et al.[25] showed that patients with sarcopenia, type 2 diabetes mellitus (T2DM), and a high android-to-gynoid ratio, which is an index strongly related to the visceral fat area (VFA), had a risk of cardiovascular disease, but significance was lost if the BMI was used instead of the VFA. Collectively, these findings suggest that the use of BMI is limited because of its incapability in assessing different body compositions and discerning lean mass from fat depots.

2.4 | Definition of sarcopenic obesity and other candidate terminologies

The confluence of sarcopenia and obesity leads to a unique body habitus (i.e., sarcopenic obesity), where individuals reach the opposite ends of skeletal muscle and fat mass distribution (Supporting Information: Table S1). In line with the ambiguous definition of sarcopenia and obesity as mentioned above, no explicit or standardized criteria for sarcopenic obesity have been proposed. Notably, the literature suggests the coexistence of excess fat mass and wasting skeletal muscle mass as a diagnostic clue by using various methodologies across distinct settings of populations. In hepatology, studies have always lacked muscle functional parameters, such as HGS or usual gait speed. Therefore, the term sarcopenic obesity is inappropriate. Intriguingly, recent data have suggested visceral fat as a potential link between sarcopenia and insulin resistance triggered by obesity.[26] Accordingly, our findings have indicated that "myopenic obesity" as determined by the VFA (L3 VFA ≥ 100 cm^2 and a low SMI) rather than the BMI (≥25 kg/m^2) can stratify patients with cirrhosis who have a short survival time.[27] We found that the estimated prevalence rate of obesity greatly varied when using BMI or VFA. A total of 30% of enrolled subjects were defined as having obesity according to the BMI compared with 67.5% as having obesity according to the VFA. We speculate that the BMI cannot recognize more than half of individuals with accumulative fat mass because this parameter fails to accurately delineate the distribution of fat. Furthermore, an increasing amount of data have implied that a low HGS is associated with nonalcoholic fatty liver disease (NAFLD) and metabolic disorders.[28] A longitudinal study that enrolled 5953 older patients showed an association between "dynapenic obesity" (determined by HGS and BMI) and a higher risk of T2DM.[29] Taken together, these findings suggest that more effort is necessary to seek more valid and suitable metrics for identifying this pathological trait.

3 | CONTRIBUTING EFFECT OF SARCOPENIC OBESITY IN VARIOUS LIVER DISEASES

3.1 | Effect of sarcopenic obesity in NAFLD

NAFLD comprises a wide spectrum of manifestations ranging from nonalcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) and ultimately progresses to advanced conditions consisting of progressive fibrosis, cirrhosis, and HCC.[30] Almost all patients with obesity will develop NAFLD and sometimes NASH to a greater extent, which is severe comorbidity of obesity leading to acute liver failure.[31,32] The advent of NAFLD is considered an early indicator of obesity-associated diseases and pathological entities, such as myocardial dysfunction, atherogenesis, and insulin resistance.[33] A meta-analysis of 8.5 million participants showed that >80% of patients with NASH tended to be overweight or obese.[34] The interplay between ectopically accumulated fat tissue and the liver may be responsible for perpetuating liver function per se. Two recent review articles stated the potential role of sarcopenic obesity in the context of NAFLD.[19,35] In this review, we aim to further summarize the current knowledge regarding the interaction between these two separate, but intimately relevant, disorders.

Data on the relationship between sarcopenic obesity and NAFLD were initially derived from a prospective cohort study that recruited 452 apparently healthy subjects, known as the Korean Sarcopenic Obesity Study.[36] This study showed that individuals with a reduced skeletal muscle mass were more prone to having NAFLD than the control group. Moreover, sarcopenia may predispose individuals to more components of metabolic syndrome (MetS), a higher level of chronic inflammation, and a greater body mass in both manner relative to the total amount (sarcopenia: 20.0 kg vs. normal: 15.2 kg, $p < 0.001$) and percentage (sarcopenia: 32.3% vs. normal: 24.2%, $p < 0.001$). Poggiogalle et al.[37] enrolled 427 subjects in whom they identified NAFLD and sarcopenic obesity by the fatty liver index and truncal fat mass to appendicular skeletal muscle ratio, respectively. They observed a significant inverse correlation between the fatty liver index and truncal fat mass/appendicular skeletal muscle ratio after adjusting for insulin resistance. Impaired growth hormone and insulin-like growth factor 1 may contribute to the development of sarcopenic obesity and ectopic fat depots in the liver. A study showed a concurrent reduction in skeletal muscle and visceral fat mass accumulation, which were responsible for a higher risk of developing NAFLD and pathological evolution to liver fibrosis.[38] Similarly, Choe et al.[39] showed a significantly higher prevalence of NAFLD in participants with sarcopenia and obesity than in those without sarcopenia and obesity (76.6% vs. 63%, $p = 0.003$). Importantly, a low skeletal muscle should be appropriately measured by CT scanning. In another large cross-sectional study that enrolled 5132 participants, Gan et al.[40] evaluated muscle mass, muscle strength, and obesity using the DEXA-based skeletal muscle mass index, weight-adjusted HGS, and BMI/waist circumference (WC), respectively. They found that the presence of sarcopenic obesity was associated with a higher risk of NAFLD (BMI: odds ratio [OR] = 10.42; WC: OR = 11.64) than sarcopenia or obesity alone. Therefore, the intervention of increasing skeletal muscle mass and strength may be pivotal for the prevention of NAFLD, especially in obese populations. In another study on 156 patients with biopsy-proven NAFLD with abnormal transaminase concentrations, the ratio of skeletal muscle mass to body fat mass was superior to other parameters reflecting pathological changes longitudinally (steatosis, lobular inflammation, hepatocellular ballooning scores, and hepatic fibrosis stage).[41] Moreover, two other studies further investigated the relationship between NAFLD and sarcopenic obesity, defined by the skeletal muscle mass to visceral fat area ratio (SVR). Shida et al.[42] reported a progressive decline in the SVR during the clinical course, which exacerbated the hepatic condition characterized by fibrosis (a determinant relevant to the prognosis of NAFLD). In the T2DM setting, a lower SVR level is related to a higher risk of NAFLD-related complications.[43] Additionally, the SVR is independently associated with NAFLD in women, suggesting that sarcopenic obesity may be useful to predict hepatic steatosis in T2DM. A cross-sectional study (1925 individuals) using the 2017–2018 NHANES database showed that participants with sarcopenic obesity had a two-fold higher prevalence of NAFLD and NAFLD-associated fibrosis as determined by Fibroscan than those without sarcopenic obesity.[44] NAFLD has been persistently reported in lean individuals, especially in Asian populations.[45] Cheng et al.[46] showed that lean participants with NAFLD had less fat mass and skeletal muscle mass, which mainly constitute lean tissue than those with obesity and NAFLD. Attention should be paid to distinct body composition profiles between lean and obese NAFLD.

However, the true prevalence of sarcopenic obesity in the context of NAFLD is still controversial. Himoto et al.[47] showed that the frequency of sarcopenic obesity appeared to be low among Japanese patients with NAFLD because none of them fulfilled the diagnostic criteria. In contrast, another study showed a high prevalence of sarcopenic obesity (70.3%) in 128 patients with NAFLD, which was likely due to a discordant classification system indicative of the HGS/BMI ratio (<1.001 for men and <0.56 for women).[48] By defining sarcopenic obesity using the DEXA-based SMI (<7.0 kg/m^2 for men and <5.4 kg/m^2 for women) and the percentage of total body fat mass (≥25% for men and ≥30% for women), 13.9% (78/563) of patients in a study cohort were diagnosed with sarcopenic obesity.[49] Patients with sarcopenic obesity were at an approximately 137% higher risk of developing nonobese NAFLD after adjustment for metabolic confounders, such as hypertension, diabetes, hyperlipidemia, and homeostasis model assessment of insulin resistance. In the following investigation, the same research group found that 8.8% (54/614) of the recruited population had sarcopenic obesity, and lean NAFLD could be a predictor of sarcopenic obesity.[50] Furthermore, the sarcopenic

obesity phenotype may progress into the osteosarcopenic obesity phenotype in women >50 years. Data from the NHANES, which was a population-based study that enrolled 14,015 adults, showed that a high non-exercise-based estimation of cardiorespiratory fitness (reflecting better ability of the respiratory and circulatory systems) synergistically ameliorated the detrimental effect of sarcopenia and obesity on NAFL.[51] This evidence collectively supports lifestyle intervention as a therapeutic strategy for patients with NAFL.

A study conducted on children and adolescents with obesity, who were diagnosed with NAFLD also, showed that a small number of subjects had sarcopenic obesity (4/38, 10.5%) in terms of BMI and the percentage of body fat simultaneously.[52] Recently, Pacifico et al.[53] analyzed the association between NAFLD/NASH and a low skeletal muscle mass in 234 youths who were overweight/obese using the DEXA-derived relative muscle mass. They concluded that youths with overweight/obesity and a coexisting lowest tertile of relative muscle mass had a greater risk of NAFLD than those in the other two tertiles (OR = 2.80, $p = 0.001$). In a biopsy-confirmed NAFLD subclass, skeletal muscle mass was inversely associated with NASH manifested by steatosis with necroinflammation and hepatocyte ballooning (Table 1).

3.2 | Effect of sarcopenic obesity in chronic viral hepatitis

Chronic hepatitis C virus (HCV) infection is a problematic health issue. HCV is endemic in numerous countries/regions, thus resulting in a heavy burden on society and the healthcare system. Chronic HCV leads to persistent inflammation in the liver, which results in slow, but occasionally severe and ultimately irreversible, fibrotic injury to the liver. Approximately 15%–30% of patients with chronic HCV without effective treatment develop cirrhosis over a span of 20 years. Approximately 290,000 deaths can be attributed to complications due to HCV infection, including HCC and cirrhosis.[62] Chronic hepatitis B virus infection is also a major public health problem worldwide, despite the development of potent antiviral treatment and an effective vaccine.[63] There are still high morbidity and mortality rates of hepatitis B virus infection, as shown in recent Global Burden of Disease estimates, although a marked decrease has been achieved over the past decades.[64,65]

Bering et al.[66] defined sarcopenic obesity as a concurrent presence of a low appendicular skeletal index (appendicular skeletal muscle mass [ASM]/height^2), low muscle strength, and body fat percentage >27% in men and 38% in women in 104 HCV-infected patients. Sarcopenic obesity was observed in four (3.8%) patients. Their findings suggested the clinical significance of detecting body composition abnormalities, even in the early stage of hepatic diseases before cirrhosis. Han et al.[67] performed a study using data from 506 in the NHANES database from respondents with hepatitis B virus. They found that the prevalence of considerable liver fibrosis, according to the NAFLD fibrosis score and fibrosis-4 index, was significantly higher in patients with sarcopenia than in those without sarcopenia with central obesity and a BMI ≥ 25 kg/m^2. Notably, sarcopenia may have an unfavorable effect on the fibrotic burden, especially among metabolically unhealthy individuals with fatty liver, insulin resistance, MetS, and obesity. A prospective cohort study was performed on community-dwelling adults (≥55 years) with a positive HBsAg.[68] In this study, 37 (7.4%) patients were categorized into the sarcopenic obesity group. Patients with sarcopenic obesity had a 7.5-fold greater odds of being in the poor physical health trajectory group ($p < 0.001$), 3.1-fold greater odds of being in the declining physical health trajectory group ($p = 0.028$), and 4.3-fold greater odds of being in the poor mental health trajectory group ($p = 0.010$).

3.3 | Effect of sarcopenic obesity in liver cirrhosis

Liver cirrhosis, which is characterized by the histopathological progression of fibrosis, is a terminal pathway because of chronic and persistent liver damage of various etiologies.[69] Cirrhosis accounts for 39% of death globally and represents a life-threatening condition with limited therapeutic strategies, leaving transplantation as the only curable option.[70] The 5-year mortality rate is nearly 85% without transplantation in case of decompensation.[71]

There have been two review articles on the relationship between sarcopenic obesity and cirrhosis.[18,72] Despite the fact that these reviews intended to provide an overview specific to cirrhosis, information is still limited because of the paucity of data in this field. The original evidence of this relation can be traced back to a study conducted by Montano-Loza et al.[54] with the largest sample (678 patients) to date. They found that patients with cirrhosis with concurrent sarcopenic obesity (defined by the BMI and SMI in terms of a CT-based mortality threshold) had a worse median survival than those with normal body composition (22 ± 3 months vs. 95 ± 22 months, $p < 0.001$). Hara et al.[55] set the cutoff of the VFA at 100 cm^2 for visceral obesity, and the threshold of upper limb skeletal muscle mass by BIA at 1.7 kg/m^2 for men and 1.2 kg/m^2 for women in 161 patients with cirrhosis. Notably, the prognosis was significantly worse in patients with sarcopenic obesity, followed by those with sarcopenia and visceral obesity during a mean observation time of 1005 days (67% vs. 48% vs. 36%, $p < 0.05$). Taking into account the limitations described above, especially fluid overload in the majority of patients with cirrhosis, our research team compared the predictive capability between the BMI-based and VFA-based definitions of sarcopenic obesity in 200 participants.[27] In fact, we preferentially use myopenic obesity when functional proxies of muscularity are missing (Figure 1). We found that myopenic obesity as determined by the

TABLE 1 Summary of major studies on sarcopenic obesity in patients with NAFLD and other liver diseases

Study	Study population	Sarcopenia criteria (or sarcopenic obesity)	Obesity criteria (or sarcopenic obesity)	Prevalence of sarcopenic obesity	Major findings
Hong et al.[36]	452 apparently healthy adults	ASM/weight percentage	Total body fat mass percentage	NA	Individuals with reduced muscle mass are prone to have NAFLD. Sarcopenia may predispose individuals to more components of MetS, higher level of inflammation, and more body mass in both total amount (sarcopenia: 20.0 kg vs. normal: 15.2 kg, $p < 0.001$) and percentage (sarcopenia: 32.% vs. normal: 24.2%, $p < 0.001$).
Poggiogalle et al.[37]	427 Caucasian Italian subjects	Truncal fat mass to appendicular skeletal muscle ratio	Fat mass percentage	NA	Impaired growth hormone and insulin-like growth factor 1 may contribute to the development of sarcopenic obesity and ectopic fat depot in the liver.
Shida et al.[38]	472 subjects (including 337 outpatients diagnosed with NAFLD)	Skeletal muscle mass area to VFA ratio	SVR	NA	Concurrent skeletal muscle reduction and visceral fat mass accumulation are responsible for a higher risk of developing NAFLD and pathologically resulting in liver fibrosis.
Choe et al.[39]	1828 subjects	CT-measured skeletal muscle area/BMI at L3	BMI	10.1%	A significantly higher prevalence of NAFLD in the sarcopenic obese participants than in the nonsarcopenic obese participants (76.6% vs. 63%, $p = 0.003$).
Gan et al.[40]	3536 subjects	Appendicular lean mass/weight	BMI or WC	18.5% according to BMI 21.2% according to WC	The presence of sarcopenic obesity is associated with a higher risk of NAFLD than respective sarcopenia or obesity.
Seko et al.[41]	156 patients with biopsy-proven NAFLD and ALT > 40 IU/L	ASM/height^2	BMI	NA	Increasing the ratio of skeletal muscle mass to body fat mass may be an important therapeutic strategy in NAFLD.
Shida et al.[42]	92 patients with NAFLD	SVR	SVR	NA	A progressive decline in skeletal muscle mass coupled with an increase in visceral fat mass is associated with a worsening of hepatic conditions and pathophysiology of NAFLD.
Su et al.[43]	445 patients with T2DM	Appendicular skeletal muscle	VFA	NA	A lower SVR level is a complication associated with the increased risk of NAFLD among female T2DM patients.
Wijarnpreecha et al.[44]	1925 subjects undergoing DEXA examination	Appendicular lean mass/BMI	Body fat percentage	10.1%	Individuals with sarcopenic obesity had a two-fold higher prevalence of NAFLD and NAFLD-associated significant fibrosis determined by Fibroscan than those without sarcopenic obesity.
Himoto et al.[47]	46 NAFLD patients	ASM/height^2 and HGS	BMI	0	Loss of skeletal muscle mass is frequently observed in nonobese NAFLD patients and the frequency of sarcopenic obesity seems to be rare in NAFLD patients.
Azevedo and Dall'Alba[48]	128 patients with NAFLD	HGS/BMI ratio	HGS/BMI ratio	70.3%	No association is found between fructose intake and NAFLD or risk of hepatic fibrosis.

(Continues)

TABLE 1 (Continued)

Study	Study population	Sarcopenia criteria (or sarcopenic obesity)	Obesity criteria (or sarcopenic obesity)	Prevalence of sarcopenic obesity	Major findings
Kashiwagi et al.[49]	563 subjects	ASM/height^2	Total body mass percentage	13.9%	Nonobese NAFLD has a significant association with sarcopenic obesity, independent of metabolic confounders.
Kashiwagi et al.[50]	614 subjects	ASM/height^2	Total body mass percentage	8.8%	Nonobese NAFLD has a significant association with osteosarcopenic obesity, independent of age or other plausible confounders.
Choi et al.[52]	38 boys diagnosed with NAFLD	A body composition chart on account of fat-free mass index and fat mass index	A body composition chart on account of fat-free mass index and fat mass index	10.5%	Body composition zones on a body composition chart might be useful in risk assessment in obesity-related diseases such as NAFLD.
Montano-Loza et al.[54]	678 patients with cirrhosis	CT-based muscle tissue area/height^2 at L3	BMI	20%	Patients with concurrent sarcopenic obesity have a worse median survival as compared to those with normal body composition.
Hara et al.[55]	161 patients with cirrhosis	BIA-measured upper limb skeletal muscle mass/height^2	VFA	9.3%	The prognosis was significantly worse in the subjects with sarcopenic obesity
Feng et al.[27]	200 patients with decompensated cirrhosis	CT-based skeletal muscle area/height^2 at L3	VFA or BMI	16.5% according to VFA5% according to BMI	Myopenic obesity by VFA rather than BMI can clarify specific subclass representing worse outcomes. Compared to the reference group, myopenic obese individuals has a higher risk of 2-year mortality.
Carias et al.[56]	207 adult cirrhotic patients undergoing LT	CT-based skeletal muscle area/height^2 at L3	BMI	13%	Worse survival has been observed with 60% at 5 years as compared to 71% in patients without sarcopenic obesity.
Choudhary et al.[57]	82 LDLT recipients	BIA-measured muscle mass	BMI combined with visceral fat mass	88%	Subjects with sarcopenic obesity display significantly higher BMI, WC, and MetS.
Kamo et al.[58]	227 adult patients undergoing LDLT	CT-based skeletal muscle area/height^2 at L3	VFA or BMI	3% according to VFA2% according to BMI	Patients with sarcopenic obesity had worse survival after LDLT compared with normal body composition counterparts.
Itoh et al.[59]	153 HCC patients undergoing LDLT	Skeletal muscle mass area to VFA ratio	Skeletal muscle mass area to VFA ratio	24.8%	A low SVR (proxy of sarcopenic obesity) is a complication associated with poorer recurrence-free and overall survival.
Kobayashi et al.[60]	465 HCC patients	CT-based skeletal muscle area/height^2 at L3	VFA	6.7%	Perioperative sarcopenic obesity is an independent risk factor for mortality and HCC recurrence.
Runkel et al.[61]	94 CRLM patients	CT-based skeletal muscle area/height^2 at L3	VFA	19.1%	Sarcopenic obesity is significantly associated with postoperative complications.

Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CRLM, colorectal liver metastases; DEXA, dual-energy X-ray absorptiometry; HCC, hepatocellular carcinoma; HGS, hand grip strength; L3, third lumbar vertebra; LDLT, living donor liver transplantation; MetS, metabolic syndrome; NA, not applicable; NAFLD, nonalcoholic fatty liver disease; SVR, skeletal muscle mass to visceral fat area ratio; T2DM, Type 2 diabetes mellitus; VFA, visceral fat area; WC, waist circumference.

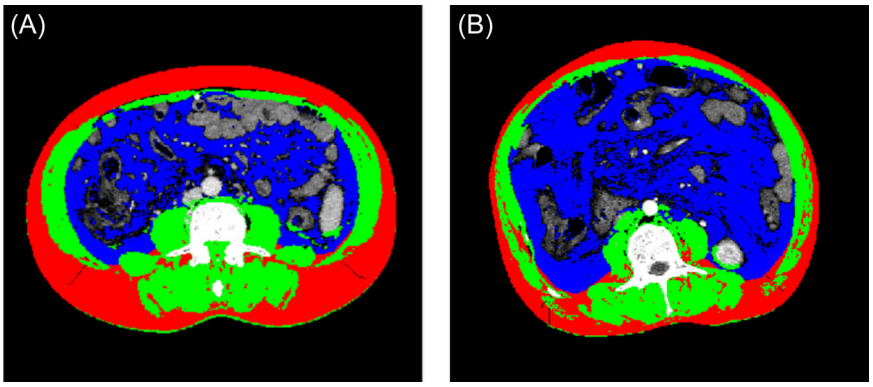

FIGURE 1 Comparison of two patients with cirrhosis and obesity, with and without sarcopenia, according to our previous study. (A) One patient had no sarcopenic obesity, whereas one patient (B) had sarcopenic obesity. Blue area: Visceral fat tissue; Green area: Skeletal muscle tissue; Red area: Subcutaneous fat tissue.

VFA rather than the BMI could clarify a specific subclass representing a worse outcome. Individuals with myopenic obesity had a 149% higher risk of 2-year mortality than the reference group ($p = 0.130$). Additionally, we highlighted the interactions regarding the muscle–liver–fat axis partially driving the pathogenic pathway of myopenic obesity in male patients.

3.4 | Effect of sarcopenic obesity in liver transplantation

Because of the considerable clinical implications of body composition disturbances and constantly changing etiologies of end-stage liver disease, NASH is expected to be the leading cause of liver transplantation by 2030 in the United States.[73] A recent meta-analysis (1515 subjects) showed that patients with sarcopenic obesity had worse survival after liver transplantation.[74] The presence of preoperative sarcopenic obesity appears to be associated with an approximately two times higher mortality rate during short- and long-term follow-up. In 2011, Schütz et al.[75] showed that changes in body composition in transplant recipients were characterized by excess body fat and obesity, which were accompanied by a deficit in skeletal muscle mass. A study that recruited 207 adult patients with cirrhosis who underwent liver transplantation showed sarcopenic obesity in 27 (13%) patients who had a poor survival rate at 5 years.[56] After controlling for confounders, NASH was associated with an increased risk of developing sarcopenic obesity (OR = 6.03, $p = 0.014$). Choudhary et al.[57] reported a strikingly high prevalence of sarcopenic obesity detected by BIA (72/82, 88%) in a cohort of living donor liver transplantation (LDLT) recipients. Patients with sarcopenic obesity had a significantly higher BMI, WC, and MetS than those without sarcopenia and obesity. Kamo et al.[58] analyzed 227 patients who underwent LDLT and showed that patients with sarcopenic obesity, as determined by a low SMI and a high BMI had significantly worse survival after LDLT. Similarly, Itoh et al.[59] found that a low SVR, representing an increased VFA and decreased skeletal muscle mass, was an independent predictor of recurrence-free and overall survival in patients with HCC who underwent LDLT. However, this negative effect of sarcopenic obesity on survival after LDLT was not found in a retrospective study by Hammad et al.[76] In their study, preoperative sarcopenic obesity did not confer an additional marked morbidity or mortality risk than sarcopenia alone. Furthermore, recipients with sarcopenia and obesity had a significantly lower incidence rate of postoperative bacteremia and major complications than those with only sarcopenia.

Some authors studied holistic profiles with regard to distinct body composition and its changes over time. Vidot et al.[77] showed that obesity coexisting with muscle wasting was common in patients with cirrhosis who were evaluated for liver transplantation. Muscle decline was greatly exaggerated in individuals with obesity regarding corrected total cross-sectional psoas muscle area. Anastácio et al.[78] prospectively assessed changes in body composition at two different times after liver transplantation in 100 patients during a median period of 7 years. They found that sarcopenia (19%–22%), obesity (32%–37%), and sarcopenic obesity (0%–2%), as defined by BIA, increased over the surveillance time.

3.5 | Effect of sarcopenic obesity in HCC

HCC is one of the most frequent liver malignancies worldwide.[79] Several risk factors for HCC have been found, such as alcoholism, chronic viral infection, a family history, the presence of NASH, and obesity.[80] The effect of sarcopenic obesity on health outcomes in the HCC setting has been examined in several studies. Kobayashi et al.[60] divided 465 patients who underwent primary hepatectomy for HCC into four body composition categories according to the SMI and VFA. They found that perioperative sarcopenic obesity was an independent predictor for decease and HCC recurrence. The conflicting results in the HCC setting were addressed by Kroh et al.,[81] where sarcopenia, obesity, and sarcopenic obesity represented superior postoperative overall survival. They compared the survival curves in 70 patients with HCC who planned to have hepatectomy. Hopancı Bıçaklı et al.[82] found that 30% of all geriatric patients with gastrointestinal cancer had sarcopenic obesity. Chemotherapy leads to a greater risk of developing sarcopenic obesity.

3.6 | Miscellaneous

Lodewick et al.[83] classified 49 (28.7%) patients after an operation for colorectal liver metastases (CRLM) into the sarcopenic obese group and showed no detrimental effect of sarcopenic obesity on overall or disease-free survival. These authors also suggested that there are no disadvantageous consequences of sarcopenic obesity on liver volume or function.[84] However, patients with obesity have larger, but less functional livers, than those without obesity, which suggests that the dissociation of function and volume is most likely due to fat deposition. Another study showed that visceral obesity, sarcopenia, and sarcopenic obesity were independently related to overall complications after resection for CRLM.[61] Early recognition of extremes in body composition is important to facilitate perioperative intervention and to improve postoperative outcomes.

4 | PATHOPHYSIOLOGICAL MECHANISM OF SARCOPENIC OBESITY

The pathogenesis of sarcopenic obesity appears to be multifactorial and complicated. Further research is required to delineate the underpinning pathway from clinical and molecular facets (Figure 2). We propose that the involved mechanism is as follows.

Recently, researchers have attempted to dissect the putative interrelation within the muscle–liver–fat tissue axis as the leading cause of sarcopenic obesity in the context of liver disease. Two principle and concurrent pathological machineries are involved, namely, anabolic resistance and insulin resistance.[85] In sarcopenic obesity, muscle atrophy induced by anabolic resistance and the deleterious effect of insulin resistance on skeletal muscle and fat tissue appears to act synergistically. Skeletal muscle can modulate energy substrate homeostasis and synchronically partition with the liver and fat tissue. Skeletal muscle produces various myokines acting in an autocrine and paracrine manner and participating in tissue cross-talk. Therefore, skeletal muscle is regarded as an endocrine organ per se.[86] In insulin resistance, glucose uptake via skeletal muscle considerably decreases, which, in turn, leads to the progression of MetS and evolution to T2DM.[87] The consequence of insulin resistance in skeletal muscle is muscle loss, and a dysregulated insulin signaling pathway leads to an imbalance between protein synthesis and proteolysis through mammalian target of rapamycin (mTOR) inactivation and enhanced transcription of E3 ubiquitin ligases.[88,89] An inability of glucose uptake further promotes the progression of MetS due to muscle wasting, which perpetuates a vicious circle. In end-stage liver disease, such as cirrhosis, skeletal muscle is required for excessive ammonia uptake. This enhances the transcription of myostatin, which is a potent negative regulator of muscularity belonging to the transforming growth factor-β superfamily.[90]

Fat tissue serves as a multifaceted organ, which potentiates energy homeostasis and endocrine balance by secreting paracrine adipokines to affect the surrounding cells and subsequently affect other metabolic organs. Consistent with the progression of obesity, fat tissue appears to be dysfunctional.[91] Fat is incapable of storing additional dietary and endogenous lipids and results in higher lipid concentrations in the circulation, lipid deposition in peripheral metabolic organs, and altered skeletal muscle health.[92] However, fat tissue may cause a proinflammatory milieu, posing a detrimental effect on adipocyte biology. As obesity develops, various immune cells, such as T cells, mast cells, and adipose tissue macrophages, are recruited in the vicinity of adipocytes.[93] The culmination of immune cell infiltration and the associated proinflammatory milieu synergistically cause the development of whole-body glucose intolerance, insulin resistance, and T2DM.[94] Furthermore, adipose tissue macrophages produce a wide array of proinflammatory mediators, such as IL-1β, IL-6, TNF-α, MCP-1, and nitric oxide. Notably, necrosis of obese and dysfunctional fat tissue leads to the generation of damage-associated molecular patterns and the activation of Nod-like receptor protein 3.[95,96] Numerous fat tissue-derived signals, such as cytokines, adipokines, lipids, and lipid derivatives, may negatively affect metabolism and inflammation of skeletal muscle tissue, all of which are interrelated in the context of sarcopenic obesity.[97]

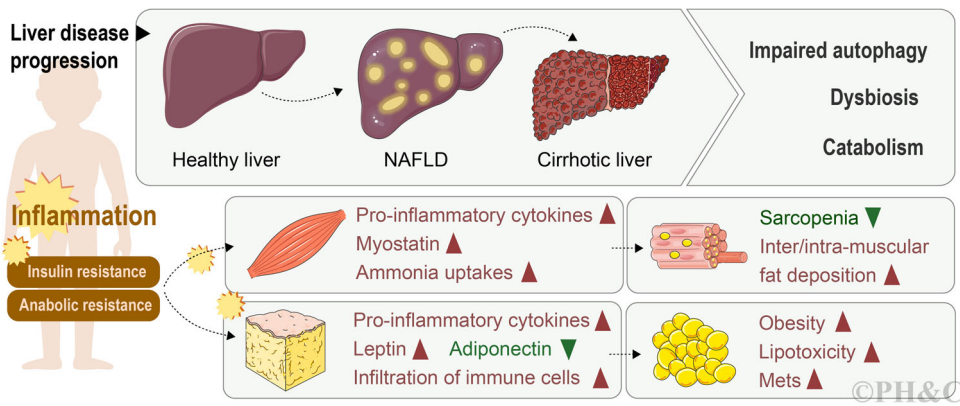

FIGURE 2 Interplay regarding the muscle–liver–fat tissue axis may potentiate the onset and progression of sarcopenic obesity in the context of versatile liver diseases. The underpinning mechanisms are multifactorial and complex, involving several mechanistic pathways, such as anabolic resistance, insulin resistance, and persistently chronic inflammation. MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease.

This pathophysiological trait is evident in patients with sarcopenia and obesity who have high serum concentrations of IL-6, TNF-α, and C-reactive protein (CRP).[98] Wåhlin-Larsson et al.[99] found that a chronic increase in CRP concentrations was inversely associated with lean muscle mass in older women. From a mechanistic perspective, human myotubes exposed to CRP lead to a reduction in their size and a decreased skeletal muscle synthesis rate. Notably, decreased adiponectin concentrations result in insulin resistance and glucose intolerance, which subsequently lead to liver damage and, to a greater extent, fatty liver.[100] The enhanced fibrogenic process and inflammatory action in the liver can in part be attributed to leptin stimulation.[101]

Several novel molecular mechanisms in relation to the pathogenesis of sarcopenic obesity have recently been discovered. Ryu et al.[102] speculated that the dysregulation of autophagy plays a pivotal role in the pathological association between sarcopenic obesity and its comorbidities, such as NAFLD. Mounting evidence has indicated that reduced AMP-activated protein kinase and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha with overactivated mTOR signaling are responsible for deficient autophagic activity related to inflammation and insulin resistance.[103,104] Garcia et al.[105] showed that liver-specific AMP-activated protein kinase activation reprogramed lipid metabolism, mitigated steatosis, and inhibited the expression of inflammation and fibrosis genes. Furthermore, mitochondrial autophagy promotes mitochondrial fatty acid oxidation, represses hepatic fatty acid accumulation, and alleviates insulin resistance.[106] In recent decades, the gut microbiota has attracted attention in the medical field, and gut dysbiosis appears to negatively affect skeletal muscle health and hepatic status via the gut–liver–muscle tissue axis. The intestinal gut may lose tight junction integrity and exhibit increased permeability with a massive pathological microbiome. Lipopolysaccharide and short-chain fatty acids can cause a proinflammatory response through cytokines. A decrease in the *Firmicutes/Bacteroidetes* ratio can trigger deleterious inflammatory and metabolic pathways, such as short-chain fatty acid-induced lipogenesis, an altered bile acid profile, and lipopolysaccharide-induced hepatic inflammation, all of which promote NAFLD.[107] Skeletal muscle can be dysfunctional owing to gut dysbiosis-induced inflammation and dysfunctional mitochondria. Okun et al.[108] found that liver alanine catabolism driven by chronic glucocorticoid and glucagon signaling enhanced hyperglycemia and skeletal muscle loss in obese mice. Taken together, these findings suggest that the underpinning mechanism of sarcopenic obesity in liver disease is still unclear.

5 | PREVENTION AND TREATMENT OF SARCOPENIC OBESITY

To our knowledge, there is no consensus guideline regarding therapeutic strategies for sarcopenic obesity in the context of liver diseases, likely due to the paucity of evidence, especially data from randomized, controlled trials. Taking account into the conceptual framework of sarcopenic obesity, several critical issues regarding its management should be addressed: (1) enhancing muscle strength and improving physical performance; (2) increasing muscle quantity; and (3) decreasing excess fat accumulation and possibly fat-associated metabolic disorders and inflammation. However, available therapies are predominantly based on a deficiency of replacement rather than on mechanistic pathways or targets (Figure 3). A recent meta-analysis that included 15 studies (14 randomized, controlled trials and 1 quasi-experimental study) investigated the effects of nutrition and exercise on body composition, physical performance, and metabolic condition in participants with sarcopenic obesity.[109] This meta-analysis showed that exercise, in particular resistance exercise, was important for improving body composition and physical function. Furthermore, low-calorie high protein therapy results in the loss of fat mass, but may not affect HGS or skeletal muscle mass. Compared with exercise alone, no additional benefit is observed with protein supplementation on body composition or biomarkers in relation to metabolic disorders and inflammation.

5.1 | Nutritional intervention

As reviewed in detail elsewhere, the principles of nutritional therapy based on published recommendations on addressing body composition abnormalities, such as sarcopenic obesity, are supposed to be followed.[23,110,111] In NASH, weight loss is regarded as a cornerstone with the purpose of improving histological changes.[112,113] One of the best therapeutic strategies is energy restriction, with a low calorie, low fat, and low carbohydrate diet.[114] However, an existing dilemma is that caloric restriction-induced weight loss in patients with overweight/obesity may lead to concurrent skeletal muscle mass loss (accounting for 25%) and fat mass loss (accounting for 75%). Therefore, aggressive energy restriction/very-low-calorie diets (<1000 kcal/day) should be avoided in patients with sarcopenia and advanced liver disease, especially for cirrhosis. In this group of patients, the energy intake should be justified by the BMI, which is corrected for fluid retention (ascites/edema), small frequent meals, and late-night snacks to suppress skeletal muscle proteolysis, decreasing lipid oxidation, and improving skeletal muscle mass and nitrogen balance.[115,116] To replenish muscle wasting, the use of branched-chain amino acids (BCAAs) can trigger tolerability to meat protein and provide an adequate protein intake.[117] Tsien et al.[118] showed that BCAAs enriched in leucine reversed impaired mTOR1 signaling and increased autophagy in skeletal muscle of patients with alcohol-related cirrhosis.

5.2 | Exercise prescription

Physical activity and exercise are anabolic stimuli capable of improving skeletal muscle mass and function. A meta-analysis of 12 studies showed amelioration in steatosis in NAFLD, despite an exercise level below that recommended for the management of obesity, and

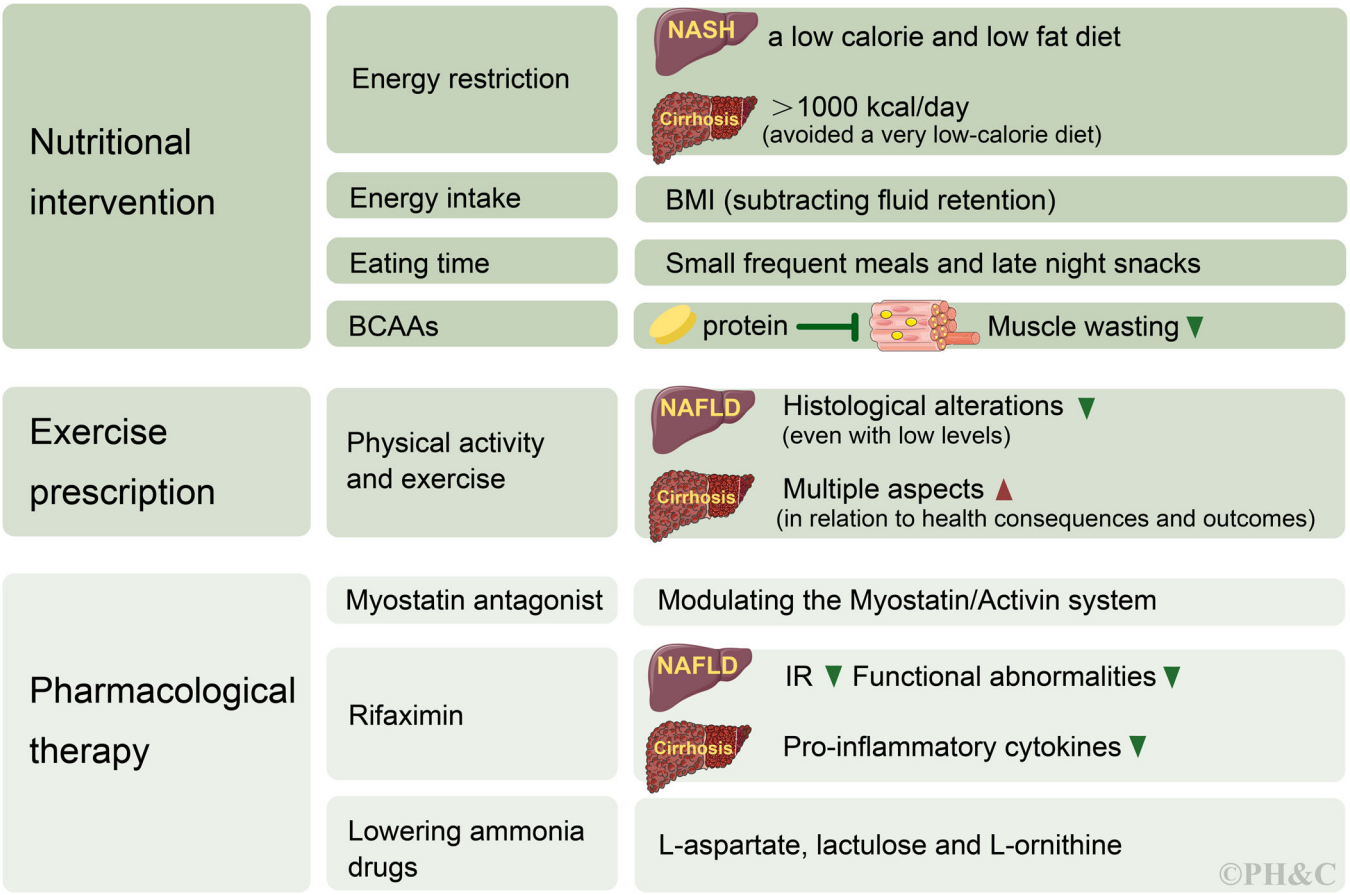

FIGURE 3 Summary of currently available avenues for therapeutic intervention of sarcopenic obesity in various liver diseases. BCAAs, branched-chain amino acids; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

even in presence of minimal or no weight loss.[119] Another meta-analysis reported that exercise showed the most benefit in subjects who were severely obese, and showed that this effect was not affected by the intensity of the intervention or a change in diet.[120] In cirrhosis, the reversal of sarcopenia, a gain in skeletal muscle mass and strength, improvement in health-related quality of life, and enhancement in aerobic ability have been observed following adequate exercise.[121–124] Recent reviews and meta-analyses in the field of exercise prescription aiming at counseling and delivering health care have been performed.[125–127]

5.3 | Pharmacological therapy

With regard to the pharmacological approach, further investigation of the effect of lowering ammonia therapies, such as L-aspartate, L-ornithine, and lactulose, on muscle quantity in humans is required. Kumar et al.[128] reported that ammonia-lowering therapy led to an improvement in the skeletal muscle phenotype and function and molecular perturbations of hyperammonemia. Myostatin and activin signaling is involved in multiple pathways (e.g., muscle anabolism, liver disease, and fibrosis).[129–131] Some clinical trials developed potential drug candidates for modulating the myostatin/activin/follistatin system in patients with chronic obstructive pulmonary disease and T2DM.[132] Mounting evidence has shown that rifaximin with treatment ranging from 4 to 12 weeks decreases plasma IL-6, IL-10, and/or TNF-α concentrations in patients with NAFLD and alcohol-related cirrhosis.[133,134] Additionally, rifaximin improves insulin resistance and serum glucose and aminotransferases concentrations in NAFLD after 6 months.[133] However, alterations in the gut microbiota composition can lead to chronic inflammation and anabolic resistance, accompanied by impaired muscle function/mass and adverse clinical consequences.[135]

6 | CONCLUSIONS

There is speculation on the role of sarcopenic obesity in the development and progression of various liver diseases. However, the actual prevalence and clinical implications of this role remain elusive because of a lack of a unified definition, diagnostic criteria, or assessed methodologies in the literature. In NAFLD, the onset of sarcopenic obesity appears to be indicative of a dysregulated metabolic condition and histological alterations. With the development of cirrhosis and decompensation, the presence of sarcopenic obesity has an additional detrimental effect on morbidity and mortality. In patients undergoing liver transplantation, sarcopenic obesity is associated with worse survival and adverse outcomes, but conflicting findings have been reported. The pathogenesis of sarcopenic obesity

in the context of liver diseases is multifactorial with several pathophysiological pathways, such as anabolic resistance, insulin resistance, and a persistent inflammatory response. Furthermore, the interplay of the muscle–liver–fat tissue axis and the gut–liver–muscle tissue axis may in part explain the evolution of different body composition abnormalities. The currently available therapies are predominantly based on a deficiency of replacement rather than on mechanistic pathways or targets, such as nutritional intervention, exercise prescription, and pharmacological therapy. Potential avenues for therapeutic intervention by stating this area of unmet clinical need are urgently required.

AUTHOR CONTRIBUTIONS

Yangyang Hui, Binxin Cui, Xiaoyu Wang, and Chao Sun were responsible for the review's concept and design. Binxin Cui, Mingyu Sun, Yifan Li, Wanting Yang, Gaoyue Guo, Zihan Yu, Xiaofei Fan, and Chao Sun did the literature search and synthesis of the evidence. 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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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Data available on request from the authors.

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The ethics statement is not available.

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