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REVIEW

The Role of Exercise in Steatotic Liver Diseases: An Updated Perspective

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ABSTRACT

Background: The increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), parallels the rise in sedentary lifestyles. MASLD is the most common form of steatotic liver disease (SLD), which represents the umbrella beneath which the vast majority of chronic liver diseases fall, including alcohol-related liver disease and their overlap. These conditions are the leading contributors to chronic liver disease, significantly impacting global morbidity and mortality. Despite the emergence of new pharmacotherapies, exercise represents the foundation of MASLD treatment.

Objective: This review aims to provide an updated perspective on the role of exercise in the management of SLD, highlight its molecular and clinical benefits, and explore its benefits and safety in the stage of cirrhosis.

Methods: Evidence from pre-clinical and clinical studies was reviewed to evaluate the impact of exercise on SLD (mainly MASLD), advanced chronic liver disease stages, and its relevance in the context of evolving therapies such as Resmetirom and incretin-based anti-obesity medications.

Conclusion: Exercise remains a cornerstone intervention in the management of MASLD, with suggested benefits even for patients who have progressed to cirrhosis. Personalized exercise regimens should be prioritized for all patients, including those receiving pharmacotherapy. Further research is needed to refine exercise protocols and investigate their impact on histologic and clinical outcomes, as well as their potential synergistic effects with emerging treatments.

1 | Introduction

Routine physical activity and exercise provide well-established health benefits, and their role is becoming increasingly crucial in combating the modern rise of sedentary lifestyles. This shift toward inactivity has been strongly linked to an increase in various physical and mental illnesses, including conditions such as obesity, type 2 diabetes mellitus (DM) and hypertension, which are also closely associated with liver disease [1, 2]. Physical activity refers to any movement that increases energy expenditure, while exercise is a subset of physical activity that is planned, structured and repetitive, with a specific goal in mind [3]. Regular exercise plays a crucial role in both the prevention and management of chronic conditions like liver disease and cardiovascular diseases by improving insulin sensitivity, enhancing anti-inflammatory and paracrine actions of myokines, supporting immune function and more [2, 4, 5].

Summary

- Increased physical activity, mainly with exercise, is associated with reduced liver disease incidence and better outcomes.
- Exercise is a cornerstone in managing metabolic dysfunction-associated steatotic liver disease (MASLD), offering benefits independent of weight loss such as reducing liver fat, improving inflammation biomarkers and enhancing cardiovascular health.
- Exploring the role of exercise in alcohol-related liver disease and metabolic dysfunction-associated alcohol-related liver disease (MetALD) is warranted.
- The benefits of exercise extend to advanced stages of steatotic liver disease, including portal hypertension and cirrhosis.
- Adopting an evidence-based, systematic approach to prescribing exercise for MASLD patients is of paramount importance.

Recent evidence suggests that physical activity is a protective factor not only for metabolic dysfunction-associated steatotic liver disease (MASLD) but also for the broader spectrum of chronic liver diseases (CLD), independent of other metabolic risk factors, age, or diet [2]. Nevertheless, most existing research focuses on the impact of exercise in MASLD, consistently demonstrating significant positive effects. Notably, much of the existing literature refers to MASLD by its previous name, non-alcoholic fatty liver disease (NAFLD). However, given the nearly complete overlap between the two [6, 7], MASLD will be used throughout. In 2023, the American College of Sports Medicine (ACSM) summarised the beneficial role of physical activity in MASLD at both the pathogenic and clinical levels, based on an extensive review of primary literature by international experts. They concluded that a minimum of 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week is recommended for all MASLD patients [8].

However, several barriers hinder the effective prescription and implementation of exercise as a therapeutic intervention in liver disease. First, tailoring exercise regimens to a diverse patient population with varying physical and psychosocial factors is challenging. Second, variations in both the populations studied and the exercise interventions used in MASLD research make it difficult to establish clear, case-specific exercise recommendations [8]. Third, the widespread use of incretin-based anti-obesity medications (AOMs) and their potency in promoting weight loss may reduce patients' motivation to engage in exercise, even though these medications are recommended for those already participating in physical activity [9]. This reduced engagement could further amplify recent concerns about AOM-related muscle mass loss, as resistance training is key for preserving lean body mass, even in a state of caloric restriction [10, 11]. Therefore, it is essential to refine our approach to recommending exercise for patients with or at risk of liver disease. In light of the recent classification of a broad range of liver diseases under the umbrella term 'steatotic liver disease (SLD)', we aim to provide an updated perspective on the role of exercise in SLD, particularly in the most prevalent forms—MASLD and alcohol-associated liver disease (ALD)—as well as in patients with cirrhosis [12].

2 | The 'Hepatoprotective' Effect of Exercise

Several recent studies have focused on examining the relationship between physical activity and liver health [2, 13–15]. Reports from animal models demonstrate the benefits of physical activity on liver histology [16, 17]. With respect to human studies, a survey-based study of over 26 000 Chinese adults found that moderate-to-vigorous physical activity was associated with reduced serum levels of alanine aminotransferase (ALT), a marker of hepatocellular injury [1]. Furthermore, Ye et al. showed that objective indicators of physical fitness might play a role in predicting liver chemistry results [18]. For instance, male body fat and lung vital capacity were positively correlated with ALT and serum albumin, respectively. In females, body fat percentage and VO_2 max (maximal oxygen consumption) were important predictors of abnormal liver function tests [18].

The link between physical activity and liver disease was elucidated by two recent British studies [2, 15]. The first is a prospective study that involved 96 688 participants, whose physical activity levels were measured using wrist-worn accelerometers set to detect three-dimensional acceleration at a sampling rate of 100 Hz [2]. The outcomes of interest, including the incidence of any type of liver disease or progression of an existing liver disease, were identified using relevant families of International Classification of Diseases 10th edition (ICD-10) codes. The authors found that physical activity, in a dose-dependent manner, was associated with a reduced risk of developing liver disease over an average follow-up period of 5.5 years [2]. Specifically, when participants in the top quartile of physical activity were compared to those in the bottom quartile, a 59% decrease in liver disease development was observed. This protective effect was more pronounced in the presence of risk factors like obesity, DM, older age, or regular alcohol consumption, yet it remained independent of body mass index (BMI) and trunk fat content. For participants with pre-existing liver disease, a 10 milligravity/h increase in average physical activity was associated with a 44% lower risk of disease progression and a 68% reduction in liver-related mortality [2].

The second study is a cross-sectional analysis utilising data from the UK Biobank, aimed at exploring the relationship between physical activity and hepatic fibro-inflammation in 840 individuals aged 55–70 years, who had no diagnosed CLD at baseline [15]. Physical activity was measured in a manner like the first study, while hepatic fibro-inflammation was assessed using magnetic resonance imaging (MRI)-based iron-corrected T1 (cT1) scores. The authors found that all levels of physical activity (light, moderate, vigorous and moderate-to-vigorous) were inversely associated with hepatic fibro-inflammation [15]. The strongest association with hepatic cT1 was seen with vigorous level of physical activity suggesting a dose–response relationship, in line with prior data shown by Van Kleef et al. [19]. When the sample was split by median liver or body fat, significant inverse associations appeared only in the higher median groups. This suggests that the greatest

liver-related benefit of physical activity is possibly experienced by individuals with a baseline degree of metabolic dysfunction. While these results support the potential liver health benefits of physical activity, randomised controlled trials are necessary to confirm causality.

Although metabolic differences between men and women in response to exercise—particularly in terms of free fatty acid metabolism—have been shown, it is unclear whether these differences extend to liver protection [20]. However, a large epidemiological study found that, compared to men, women with higher levels of physical activity had a stronger association with risk reduction of MASLD [21]. One possible explanation for this difference is women's higher capacity for muscle-mediated lipid oxidation during exercise [20]. These findings highlight the need for dedicated studies to evaluate whether women may gain greater MASLD-protective benefits from exercise.

Regarding ethnic differences, the higher prevalence of MASLD among Hispanics and the lower prevalence among African Americans, compared to Whites, appears to be partly driven by the prevalence of high-risk gene alleles in these groups [22]. Using a subset of these genes, Ge et al. applied a validated MASLD-specific polygenic risk score to categorise individuals into low, medium and high risk. They found that individuals with high genetic susceptibility to MASLD experienced the greatest reduction in risk for incident MASLD when combining moderate-to-high physical activity with low sedentary behaviour, compared to those with low or intermediate genetic risk [23]. Based on these data, although it may be plausible to extrapolate an ethnic benefit of exercise correlating with MASLD prevalence, studies examining the differential impact of exercise on liver disease incidence by race are needed.

3 | MASLD

3.1 | Pathophysiology

MASLD is the most common cause of CLD worldwide, with a rapidly rising incidence linked to obesity epidemics and sedentary lifestyles [24, 25]. MASLD, and its related spectrum of liver damage, carry an increased risk of both liver-related and all-cause mortality [26]. This is driven by greater rates of cardiovascular disease, extrahepatic cancer, cirrhosis and hepatocellular carcinoma [27].

The pathophysiology of MASLD involves a complex interplay between adipose tissue, skeletal muscle and the liver. At the core of its pathogenesis is insulin resistance in these tissues, leading to increased circulating fatty acids that subsequently accumulate in the liver, resulting in hepatic lipotoxicity, local inflammation and consequent liver fibrosis [28, 29]. This process drives the progression from hepatic steatosis to steatohepatitis to cirrhosis [28] and could be mitigated by exercise. Improvement in insulin resistance in response to exercise is repeatedly demonstrated in both MASLD and non-MASLD contexts [13, 30]. This improvement is considered a key mechanism in counteracting the pathophysiological processes of MASLD, given the role of insulin in maintaining intrahepatic lipid homeostasis [31].

3.2 | Exercise as a Treatment for MASLD: A Brief Mechanistic Overview

Many cellular and metabolic pathways implicated in MASLD pathogenesis are favourably affected by exercise [32]. Those pathways have been the subject of intensive research attempting to develop medications to treat MASLD. In their review, Heinle et al. identify 10 distinct mechanisms or cellular targets through which exercise exerts a therapeutic effect on MASLD [32]. Collectively, these mechanisms improve insulin sensitivity and fatty acid metabolism which in turn prevents hepatic steatosis and its related inflammation and fibrosis. A noteworthy example is the impact of exercise on glucagon-like peptide-1 (GLP-1), a gut-derived incretin involved in enhancing glucose and lipid metabolism. A short term, high intensity exercise program was shown to reduce the GLP-1 resistant state of MASLD [33]. This could have an important therapeutic effect, particularly considering recent trials that investigated GLP-1 receptor agonists as potential therapeutic agents for MASLD [34, 35].

The relationship between thyroid function and MASLD is well established [36]. Exercise is known to impact the levels and turnover of thyroid hormones. Thyroid hormone receptor-beta (THR-β), present in the liver, is closely linked to multiple metabolic pathways often disturbed in patients with MASLD. The significance of thyroid-liver relationship on MASLD is highlighted by recent phase 3 clinical trial results, which demonstrate the efficacy of Resmetirom, a selective THR-β agonist, in resolving non-alcoholic steatohepatitis (NASH) and improving liver fibrosis [37]. As such, Resmetirom has been officially approved by the FDA for use in patients with MASH and stage 2 or 3 level of fibrosis [38]. Further research is needed to explore the potential synergistic effects of combining exercise with Resmetirom, and other potential future candidates, in the treatment of MASLD, with a particular attention on how physiologic adaptation can change drug delivery to the liver owing to changes in hepatic blood flow and metabolism over time.

3.3 | Exercise and MASLD: Clinical Implications

To date, the mainstay treatment for MASLD revolves around regular exercise and a Mediterranean-informed diet [39]. The benefit of exercise in preventing and treating MASLD has been demonstrated in numerous human studies and across different patient populations, including those with lean MASLD [8, 40, 41].

A large retrospective study evaluated the impact of exercise on the development of incident hepatic steatosis and resolution of baseline hepatic steatosis at 5-year follow-up. It showed that engaging in moderate-to-vigorous exercise ≥ 5 times per week (lasting at least 10 min on each occasion) was associated with a reduced risk of developing incident hepatic steatosis and a higher likelihood of resolving existing hepatic steatosis, independent of change in body mass index (BMI) [42]. The direct effect of exercise on improving hepatic and metabolic outcomes in MASLD has been demonstrated in multiple clinical trials [41, 43–47], despite variations in the type, frequency and intensity of exercise interventions across and within different studies. For instance, Zhang et al. demonstrated both moderate exercise (brisk walking

for 150 min per week over 12 months) and vigorous-moderate exercise (jogging 150 min per week at 65%–80% of maximum heart rate for 6 months and brisk walking 150 min per week for another 6 months) were equally effective in lowering intrahepatic triglyceride levels in patients with MASLD [41]. A recent meta-analysis examined the role of different exercise interventions in achieving a clinically meaningful reduction in MRI-measured liver fat (≥30% relative reduction) in patients with MASLD. Pooled data from seven randomised controlled trials (RCTs) showed that exercise is more likely to result in this reduction (odds ratio 3.51, 95% confidence interval 1.49–8.23, $p = 0.004$) compared to standard care, independent of weight loss [48].

Given the impact of genetic factors on MASLD incidence and outcomes [49, 50], understanding the role of lifestyle modification in those with a genetic predisposition is crucial [51]. The PNPLA3 rs738409 variant, characterised by a C-to-G mutation resulting in the I148M substitution, is a major genetic factor linked to MASLD onset and progression [52]. A post hoc analysis of a 12-month RCT found that MASLD patients with the G allele experienced greater intrahepatic triglyceride reduction in response to a lifestyle modification program focused on diet and exercise compared to those with the CC genotype [53, 54]. More recently, and similarly, Harris et al. demonstrated that MASLD patients who completed 20 weeks of moderate-intensity exercise had a higher rate of clinically significant ALT reduction (≥17 IU/L) compared to those receiving standard care (53% vs. 13%, $p < 0.001$), and this reduction was strongly correlated with the presence of the PNPLA3 G allele [55]. Therefore, the observed higher effectiveness of exercise in genetically predisposed individuals should prompt case-specific emphasis and increase patient awareness of the importance of adherence to this intervention.

Federal guidelines recommend that adults engage in at least 150 min of moderate-intensity physical activity, 75 min of vigorous-intensity activity, or a combination of both per week to improve and maintain health [56]. Current evidence suggests that higher exercise intensity may be necessary to improve more advanced or active stages of MASLD [39]. For instance, Kistler et al. found that MASLD patients who reported engaging in ≥75 min of vigorous exercise per week were less likely to have NASH compared to those performing low or moderate levels of exercise. Moreover, only those who reported ≥150 min of vigorous exercise per week had lower odds of advanced fibrosis [57].

In light of this, current American Association for the Study of Liver Diseases (AASLD) guidance advocates tailoring the duration and intensity of exercise to individual needs of MASLD patients, while emphasising that all patients should be encouraged to exercise as much as possible [39]. Correspondingly, the European guidelines recommend 150–200 min/week of moderate-intensity aerobic physical activity in 3–5 sessions [58]. Recommendations based on different societal guidelines are summarised in Table 1.

3.4 | Exercise in MASLD: Barriers to Implementation and Insights Into Solutions

Despite the well-documented benefits of exercise for patients with MASLD, most do not meet the minimum weekly PA recommendations outlined by societal guidelines [63]. In a study of 87 adult patients with MASLD, the three most commonly reported barriers to exercise were a lack of exercise resources and education from healthcare providers, physical discomfort during exercise and time constraints [63]. To address the first barrier, clinicians can follow the Screening, Brief Intervention and Referral to Treatment (SBIRT) framework proposed by the ACSM [8]. This approach helps healthcare providers assess a patient's baseline activity status, identify specific barriers when the patient falls below the recommended levels, provide evidence-based, patient-centred counselling on the benefits of exercise in MASLD, and either prescribe an exercise regimen or refer the patient to an expert professional.

The second and third barriers can perhaps be best addressed by providing a personalised exercise prescription. Using the four

TABLE 1 | Exercise recommendations for MASLD patients.

Society	Exercise recommendations
American Association for the Study of Liver Diseases (AASLD) [39, 59]	• Moderate-intensity exercise at least five times per week for a total of 150 min per week or an increase in activity level by more than 60 min per week • 2023 Update: Patients with MASLD should be strongly encouraged to increase their activity level to the extent possible. Individualised prescriptive exercise recommendations may increase sustainability and have benefits independent of weight loss
European Association for the Study of the Liver (EASL) [60]	• Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients' preferences to be maintained in the long term • 150–200 min per week moderate intensity in 3–5 sessions • Resistance training to promote musculoskeletal fitness and improve metabolic factors
American College of Sports Medicine (ACSM) [8]	• At least 150 min per week of moderate OR 75 min per week of vigorous-intensity physical activity, plus two sessions a week of resistance training
American Gastrological Association (AGA) [61]	• 150–300 min of moderate-intensity or 75–150 min of vigorous-intensity aerobic exercise per week • Resistance training exercise can be complementary to aerobic exercise and can have independent effects on MASLD
Exercise and Sport Science Australia (ESSA) [62]	• 150–240 min per week of at least moderate-intensity aerobic exercise to improve hepatic steatosis. However, as little as 135 min per week may also be effective

components of exercise prescription—Frequency, Intensity, Time and Type (FITT)—a wide range of exercise combinations can be tailored to achieve the recommended weekly physical activity goals. Frequencies ranging from 3 to 7 days per week, types varying from aerobic only (running, cycling, swimming) to a combination of aerobic and resistance training, and session durations from 10 to > 60 min have been studied, showing positive effects in MASLD [64–66]. This flexibility allows providers and patients to jointly choose a prescription tailored to patient-specific factors or barriers, such as perceived discomfort, time constraints, comorbidities, fitness level and preferences. Finally, engaging related disciplines in the appropriate setting is crucial. For example, referring patients with certain comorbidities or those struggling to meet their exercise prescriptions to an exercise specialist is important [8]. Additionally, when psychosocial barriers are prominent, referral to a health psychologist has been shown to be effective [39].

4 | The Role of Exercise in ALD and MetALD

Regarding the effect of exercise on alcohol-associated liver disease (ALD), evidence is limited to murine models. In one such study, Mikami et al. evaluated the effects of a 4-week treadmill exercise regimen on liver response to acute alcohol exposure. The study revealed a smaller increase in liver transaminases in the exercised mice compared to the sedentary mice [67]. In another mice experiment, Cui et al. showed that, during the recovery phase of ALD, 6 weeks of exercise ameliorated the oxidative-stress mediated hepatocyte damage. However, the study also showed that alcohol exposure during exercise exacerbated markers of liver inflammation [68]. These findings underscore the complex interplay between exercise, alcohol consumption and liver inflammation. Considering the prevalence of ALD, human studies investigating how exercise influences the natural history of ALD are needed. In addition, given the recognition of the overlap between MASLD and ALD as a distinct continuum known as metabolic and alcohol-related liver disease (MetALD), further research is needed to investigate the impact of exercise on this new category of SLD [12].

5 | The Role of Exercise in Cirrhosis

Exercise capacity is significantly diminished in individuals with cirrhosis, a consequence of several factors. These include disturbances in carbohydrate metabolism, protein-energy malnutrition, fatigue, physical deconditioning and sarcopenia, a lowered maximum oxygen uptake (VO_2 max) and reduced ventilatory capacity [5, 69]. Furthermore, reduced muscle strength and function worsens sarcopenia and frailty [70]. This reduction in exercise capacity is exacerbated by an associated cardiac dysfunction from hyperdynamic circulation with splanchnic vasodilation [71]. A study involving 74 cirrhotic patients and 27 healthy volunteers revealed that, based on accelerometer measurements, cirrhotic patients had significantly fewer average daily steps and lower exercise levels compared to the healthy group [72]. Another study showed that those with cirrhosis wait-listed for transplantation were sedentary 75.9% of the time, in contrast to 62% for the general population aged 60–69 [73]. Finally, cirrhotic patients consistently demonstrate a shorter 6-min walk distance (6MWD), a standard measure of physical capacity, compared to healthy subjects [71, 74].

Considering the established benefits of exercise for older adults and patients with certain chronic conditions, recent evidence suggests that physical activity may also carry benefits for patients with cirrhosis.

5.1 | Effect on Physical Function, Frailty and Sarcopenia

In the context of cirrhosis, frailty and sarcopenia are major predictors of adverse patient outcomes, both before and after liver transplantation [75]. Unfortunately, about 50% of patients with cirrhosis have frailty and/or sarcopenia [75, 76]. Although current research shows promising results for exercise in preventing or alleviating the effects of frailty and sarcopenia, a definitive assessment of its impact on clinical outcomes remains to be elucidated [77].

Randomised trials on patients with cirrhosis show that exercise can improve physical function indices, including increases in six-minute walk distance, thigh circumference and peak VO_2 [70, 78–80]. These findings highlight the potential of exercise to reduce frailty and sarcopenia in cirrhosis, supporting current AASLD recommendations for exercise-based interventions to enhance muscle mass in these patients [81].

5.2 | Effect on Portal Hypertension

Portal hypertension is the key pathophysiological factor leading to cirrhosis decompensation and the consequent drastic increase in morbidity and mortality [82]. Decompensation most commonly occurs when hepatic venous pressure gradient (HVPG) is at 10 mmHg or more, a threshold referred to as clinically significant portal hypertension (CSPH) [83]. Few studies explore the effect of exercise on portal pressure with potentially promising results. Macias-Rodriguez et al. randomised 25 subjects with cirrhosis (MELD 7–14) to either three times weekly exercise (cycle ergometry/kinesiotherapy) or standard of care, along with nutritional therapy for both groups. At 14-week follow-up, HVPG was reduced in the exercise group, while it unexpectedly rose in the control group ($p = 0.009$) [84]. Of note, all patients were on a non-selective beta blocker (NSBB) [84]. In a following single arm study, 50 patients with compensated cirrhosis (MELD 6–12), 72% of whom had CSPH, completed a 16-week program of personalised hypocaloric diet and exercise (60 min/week of gym-based exercise plus an unsupervised increase in baseline physical activity). A significant reduction in both HVPG (from 13.9 ± 5.6 to 12.3 ± 5.2 mmHg) and body weight was observed [85]. Notably, a 10% weight loss was associated with a greater reduction in HVPG. In this study, being on NSBB did not mediate the impact of the intervention on HVPG [85]. In a more recent trial, 27 cirrhosis patients (MELD 8–10) were randomised into exercise plus nutritional therapy or nutritional therapy alone for 12 weeks. The exercise consisted of device-monitored walking four times a week at a moderate intensity. In the exercise group, the number of steps increased from 9667 ± 3008 to $11\,931 \pm 4463$ ($p = 0.002$), compared to a lesser increase in the control group.

Notably, exercise led to a decrease in HVPG from 11 (range 8–14) to 8 (range 6–11) mmHg ($p = 0.032$), with no significant change in the control group. There was no significant change in BMI in either group. Finally, the study observed an improvement in cerebral hemodynamics, cognitive function and overall quality of life in the exercise group [86]. No adverse events were observed in any of the three aforementioned studies.

Although these results are encouraging, the extent to which they can be applied to patients with higher MELD scores or HVPG levels, regarding safety and efficacy, is uncertain, although in earlier stages of cirrhosis exercise training appears both safe and efficacious.

5.3 | Decompensated Cirrhosis: Safety Versus Benefits of Exercise

In patients with decompensated cirrhosis, the benefits of exercise should be weighed against the potential risk of further decompensation, given certain physiological effects of exercise. From a hemodynamic standpoint, exercise results in increased systemic vascular resistance; reduced perfusion of splanchnic organs and kidneys; and activated renin-angiotensin-aldosterone and sympathetic systems. These changes can perpetuate the vicious cycle of portal hypertension increasing the risk of cirrhosis complications [87]. An early study by Garcia-Pagan et al. on eight patients with cirrhosis and oesophageal varices revealed that acutely, a single session of mild to moderate exercise reduced hepatic blood flow and increased HVPG. This was attributed to neurohumoral vasoconstrictive factors triggered by increased sympathetic activity. Although this effect was short-lived, lasting for 5 min, this was thought to be clinically relevant given the degree of HVPG increase (up to 21% from baseline). Of note, no bleeding events were reported [88]. In a subsequent study by the same group, pre-exercise propranolol administration prevented HVPG elevation. It is important to contrast these acute effects with the impact of regular exercise training over time, which has been shown to safely reduce HVPG [85].

Regarding volume status, Salo et al. observed differences in the baseline activities of the renin-angiotensin and sympathetic systems among patients with cirrhosis and ascites. Patients with normal or slightly overactive systems had no significant changes in renal function in response to exercise. However, those with highly overactive systems at baseline experienced marked reductions in renal function and sodium excretion after the same level of exercise [89]. The authors concluded that these findings are important for managing diuretic-resistant cirrhosis with ascites [89].

Attenuating skeletal muscle loss and improving nutritional status may be key to minimising the risk of hepatic encephalopathy (HE) in cirrhosis. This stems from the role of skeletal muscle in ammonia metabolism, especially in the context of portal hypertension, which depends on an adequate supply of branched-chain amino acids (BCAAs) [90]. Clinically, HE is more prevalent in patients with cirrhosis and concomitant muscle wasting or malnutrition [91, 92]. Given the known impact of exercise on preserving muscle mass and function, exercise interventions may help prevent HE. This was demonstrated in an animal study, where exercise combined with leucine supplementation, a BCAA, increased muscle mass, reduced brain oedema and improved cognitive function in cirrhotic rats compared to controls [93]. However, to date, no human studies have evaluated the effect of exercise interventions on HE.

6 | Prescribing Exercise for Steatotic Liver Disease Management: A Modern Approach

This review highlights the critical role of exercise in the prevention and treatment of SLD, namely MASLD. These benefits seem to encompass the whole spectrum of disease severity. Hence, it is imperative for health care professionals to consistently promote regular physical activity, not only as a preventive tool but also to minimise potential complications for those with SLD. This is especially crucial when MASLD is suspected as the primary or a co-existing liver disease [39].

It is not uncommon for patients with SLD to be prescribed AOMs to treat accompanying metabolic syndrome disorders. While AOMs are highly effective in inducing weight loss and have shown liver-specific benefits in MASLD, such as improved NASH histology [35, 94], it is crucial to emphasise the importance of incorporating an adequate exercise regimen [95]. This is especially relevant in advanced liver disease, where using AOMs without concurrent exercise may have significant consequences. Firstly, AOM-induced weight loss has been linked to a loss of lean muscle mass, which can impair functional capacity and worsen sarcopenia, particularly in patients with cirrhosis or even those in earlier stages of MASLD where sarcopenic obesity is common [96, 97]. Secondly, using AOMs alone can lead to rebound weight gain upon treatment cessation, a critical issue for MASLD patients that may be mitigated by incorporating supervised exercise [98]. Importantly, weight gain after stopping AOMs is likely to be exclusively due to an increase in fat mass, potentially recreating metabolic dysfunction, possibly at levels exceeding those before AOMs were initiated. Lastly, the long-term safety of AOMs in cirrhosis has not yet been evaluated [99], and concerns about worsening sarcopenia with weight loss > 10%–20% must be taken into account. Therefore, AOMs should be prescribed as adjunctive treatments alongside exercise.

Emerging data suggest that unsupervised home-based exercise programs are both safe and effective, even in cases of CSPH or decompensated cirrhosis [100–102]. In the context of MASH with moderate-to-advanced fibrosis, combining an exercise regimen with FDA-approved therapies like resmetirom is expected to improve metabolic risk factors while providing targeted liver treatment.

In terms of recommending exercise to a patient with or at risk of liver disease, we suggest adopting the dose-effect relationship as a general paradigm. In line with public health guidelines and that from multiple leading hepatology and exercise societies, a foundational recommendation, barring contraindications, should include aiming for a minimum of 150 min per week of moderate-intensity physical activity, such as brisk walking, complemented by muscle-strengthening activities at least twice a week (Table 2) [56]. Vigorous-intensity activity of 75 min per week or more can be substituted in the correct setting as well for those individuals

TABLE 2 | Author recommendations for prescribing exercise regimens in steatotic liver disease.

General recommendations:

- When prescribing exercise, patient-specific factors (such as comorbidities, baseline level of physical activity, motivators, psychosocial barriers) should be taken into account to ensure safety and improve adherence [8, 39, 60].
- Dietary management is an important complementary component to exercise interventions [61].
- A multidisciplinary approach, inclusive of patient support systems, behavioural medicine specialists, physiotherapists and nutritionists, can optimise success of exercise interventions [8, 39].
- Using a pedometer or wrist accelerometer is an effective and inexpensive method of monitoring patients' physical activity levels [100, 102, 103].

Definitions:

- Progressive Resistance Training (PRT): Involves repeatedly lifting or moving heavy weights/loads in short bursts for all major muscle groups, progressively increasing the resistance to enhance muscular strength and endurance.
- American College of Sports Medicine (ACSM) Guidance on Exercise for MASLD Prevention and Management: At least 150 min per week of moderate (at 40%–60% of HR reserve) or 75 min per week of vigorous-intensity (at 60%–85% of HR reserve) physical activity are recommended [8].
- HR Reserve (HRR): Difference between the individual's maximum heart rate and resting heart rate.

Liver disease type/state	Exercise prescription
MASLD without cirrhosis	• 3–5 times per week of 30–60-min of moderate-intensity (40%–60% of HR reserve) aerobic exercise • For MASH: Moderate-to-vigorous-intensity (50%–70% of HR reserve) exercise is preferred • Consider adding twice weekly sessions of PRT
Compensated cirrhosis	• 120–150 min per week of aerobic exercise, preferably through a combination of supervised and unsupervised sessions • Dividing exercise session into 3 phases is recommended (warm-up phase, a main component phase and cool-down phase) to limit injuries • As tolerated light resistance and flexibility training
Decompensated cirrhosis or cirrhosis with CSPH	• Three sessions per week of supervised moderate-intensity aerobic training. Each session is 30–60 min long, achieving 40%–60% of HR reserve • Dividing exercise session into 3 phases is recommended (warm-up phase, a main component phase and cool-down phase) to limit injuries • Supervised light resistance/weight training • The addition of Kinesiotherapy including 30 min of rhythmic activities is recommended to improve muscle strength and elasticity, coordination and balance

Abbreviations: CSPH, clinically significant portal hypertension; HR, heart rate; MASLD, metabolic dysfunction-associated steatotic liver disease.

with less time or greater physical ability to complete higher intensity exercise. At a closer look, determining the ideal intensity, duration, frequency and specific goals of physical activity should be personalised. This tailored approach should take into account factors like the cause of liver disease, the stage of the disease, accompanying comorbidities and patients' personal preferences to ensure long-term adherence. Lastly, in certain scenarios, involving a multidisciplinary team including appropriately trained clinical exercise professionals can optimise outcomes [39].

Despite the promising effects of physical activity on MASLD, a significant global health burden, key knowledge gaps remain in the area of exercise and SLD. These include, but are not limited to, the impact of exercise on liver histology and long-term clinical outcomes; its effects on patients with ALD and MetALD; strategies to improve patient adherence to recommended physical activity levels; the influence of gender, ethnicity and genetic polymorphisms on exercise response; and the potential role of artificial intelligence in optimising exercise prescriptions based on patient-specific factors and longitudinal feedback. Securing future grant funding is crucial to drive rigorous research and effectively address these knowledge gaps.

7 | Conclusion and Future Directions

Exercise will remain an essential intervention for the management of SLD, with the bulk of evidence supporting its benefits in MASLD. Regular physical activity improves insulin sensitivity, reduces hepatic fat accumulation and lowers biomarkers of liver inflammation. This evidence underscores the importance of integrating physical activity screening, counselling and recommendations into standard SLD patient care, even at the stage of cirrhosis. Figure 1 provides an overview of the established hepatic and systemic effects of exercise.

Informed by rigorous research, future practice should move toward personalised exercise protocols that account for patient demographics, clinical and behavioural determinants of exercise uptake and genetic predispositions to optimise treatment outcomes. Understanding these mediators of response can guide precise exercise prescriptions, ensuring that patients receive targeted, effective care. Moreover, exploring the potential synergy of combining exercise with dietary modifications and pharmacologic therapies—both approved and investigational—will be crucial. Such advancements will refine clinical guidelines, enhance

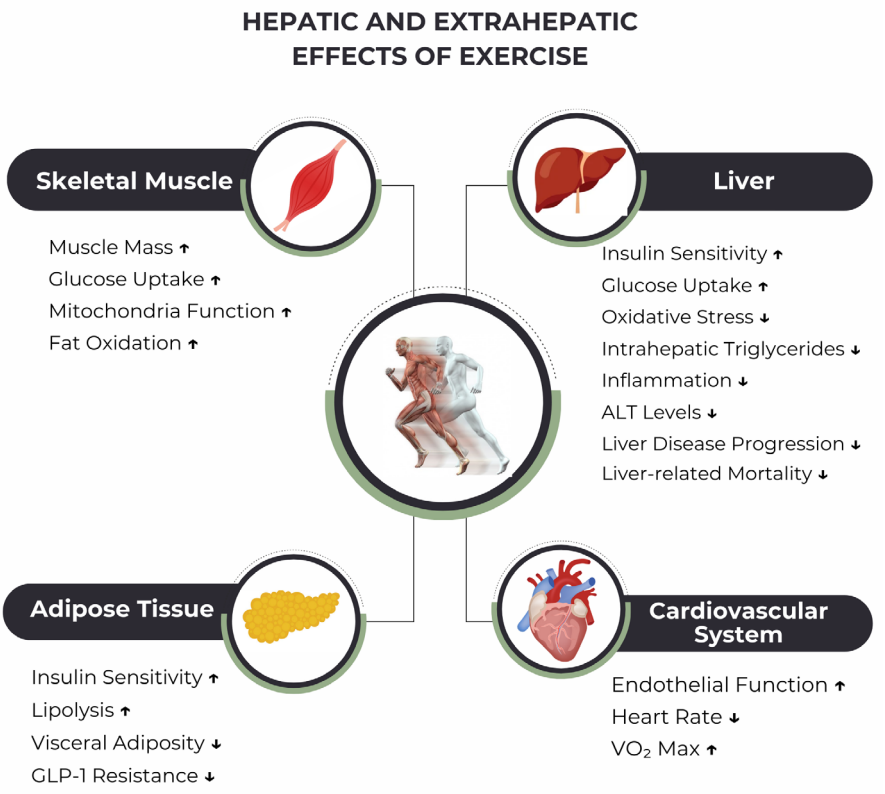

FIGURE 1 | Multi-system effects of exercise showing key physiological and metabolic benefits that counteract disturbances seen in metabolic dysfunction-associated steatotic liver disease (MASLD) and cirrhosis.

patient adherence and support a comprehensive, multidisciplinary approach to SLD management, ultimately improving patient outcomes.

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The authors have nothing to report.

Conflicts of Interest

Hirsh D. Trivedi serves as an advisor to Madrigal Pharmaceuticals and consults for Novo Nordisk. There are no other relevant disclosures or conflicts of interest for the creation of this manuscript. Dr. Jonathan Stine receives or has received research support from Astra Zeneca, Galectin, Kowa, Noom Inc., Novo Nordisk and Zydus Therapeutics. Dr. Stine consults for Novo Nordisk and Everyday Health.

Data Availability Statement

The authors have nothing to report.

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