Hepatology Publish Ahead of Print
DOI:10.1097/HEP.0000000000000941

OPEN

Physical Exercise in Liver Diseases

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Author Contributions: Yunwei Zhang and Chunyan Cao wrote the manuscript and prepared figures. Chaofan Li, Russell G Witt, Hai Huang, and Allan Tsung helped with manuscript revision. Hongji Zhang provided supervision, manuscript review, and editing. [#]Yunwei Zhang and Chunyan Cao have contributed equally to this work.

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Financial Support and Sponsorship: This work was supported by the National Institutes of Health R01-CA214865 and R01-GM95566 to AT, National Institutes of Health R01-GM137203 to HH, and state funds within the UVA Comprehensive Cancer Center "IDEA-Cancer pilot award" and "Cancer Therapeutics (CRX) pilot award" to HZ.

Conflicts of Interest: The authors have no conflicts to report.

Keywords: Exercise; Liver; Lipid metabolism; Insulin sensitivity; Immune response.

List of Abbreviations: Liver I/R, liver ischemia/reperfusion; MASLD, metabolic dysfunction-associated steatotic liver disease; PH, portal hypertension; DALYs, disability-adjusted life-years; IHGT, intrahepatic triglycerides; HIIT : high-intensity interval exercise; MET, metabolic equivalent of task; TLR-4, toll-like receptor 4; ERK, extracellular signal-regulated kinase; AMPK, AMP-activated protein kinase; HFD, high-fat diet; TAK1, TGFβ-activated kinase 1; USP4, ubiquitin-specific protease 4; DUSP14, dual-specificity phosphatases 14; JNK1, c-Jun N-terminal kinase 1; IRS1, insulin receptor substrate 1; ASK1, apoptosis signal-regulated kinase 1; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; Akt, protein kinase B; FAM3A, Family with sequence similarity 3 member A; PPAR-α, proliferator-activated receptor alpha; PPAR-γ, proliferator-activated receptor gamma; miRNA, microRNA; FoxO1, forkhead box O1; MASH, metabolic dysfunction-associated steatohepatitis; FFAs, free fatty acids; HMGCS2, hydroxy-3-methylglutaryl-CoA synthase 2; ADAR2, adenosine deaminases acting on RNA 2; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; SCD1, stearoyl-CoA desaturase 1; SREBP-1, sterol regulatory element-binding protein 1; FA, fatty acid; TG, triglyceride; HSL, hormone-sensitive lipase; ATGL, adipose triglyceride lipase; SIRT1, silent information regulator T1; KC, Kupffer cells; NETs, neutrophil extracellular traps; GalN, N-galactosamine; LPS, lipopolysaccharide; CPT-1, carnitine palmitoyl transferase-1; MCAD, medium-chain acyl-CoA dehydrogenase; MAIT, mucosa-associated invariant T cells; IL-6, interleukin-6; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1; IL-10, interleukin-10; NK cells, Natural Killer cells; IL-15, Interleukin-15; RAE-1, retinoic acid early inducible gene 1; AICAR, AMPK activator 5-aminoimidazole-4-

carboxamide ribonucleotide; RCTs, randomized controlled trials; HRQOL, health-related quality of life; FNDC5, fibronectin type III domain-containing protein 5; FBG, fasting blood glucose; HOMA-IR, homeostatic model assessment of insulin resistance; IHTG, intrahepatic triglyceride; HVPG, hepatic venous pressure gradient; CSPH, clinically significant portal hypertension; TIPS, transjugular intrahepatic portosystemic shunt; HMGCS2, 3-hydroxy-3-methylglutaryl-CoA synthase 2; MGAT1, monoacylglycerol O-acyltransferase 1; MoMFs, myeloid cell monocytes; 6MWD, 6-minute walk distance; HCC, hepatocellular carcinoma; TGF-β, transforming growth factor-beta; DRP1, dynamin-related protein 1; TME, tumor microenvironment; Aβ, amyloid-β peptide; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; APJ, apelin peptide jejunum; STAT3, signal transducer and activator of transcription 3; IGF-1, insulin-like growth factor 1.

Abstract

Liver diseases contribute to approximately 2 million deaths each year and account for 4% of all deaths globally. Despite various treatment options, the management of liver diseases remains challenging. Physical exercise is a promising non-pharmacological approach to maintain and restore homeostasis and effectively prevent and mitigate liver diseases. In this review, we delve into the mechanisms of physical exercise in preventing and treating liver diseases, highlighting its effects on improving insulin sensitivity, regulating lipid homeostasis, and modulating immune function. Additionally, we evaluate the impact of physical exercise on various liver diseases, including liver ischemia/reperfusion (I/R) injury, cardiogenic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), portal

hypertension (PH), cirrhosis, and liver cancer. In conclusion, the review underscores the effectiveness of physical exercise as a beneficial intervention in combating liver diseases[ak1].

Introduction

Liver diseases have become a major health concern and highly impact young individuals, ranking as the 12th leading cause of disability-adjusted life-years (DALYs) among those aged 25 to 49(1). MASLD, the most prevalent form of liver diseases, impacts approximately 25% of the global adult population(2, 3). The major causes of mortality related to liver diseases are cirrhosis and hepatocellular carcinoma(4, 5). With a deep understanding of the pathophysiological mechanisms of liver diseases, the medical community's choice of therapeutic approaches has been evolving(6).

Due to its beneficial effects on metabolism regulation, physical exercise has been extensively validated as an effective strategy in preventing and treating metabolic syndrome, including MASLD(7). Additionally, recent studies underscored its potential value in managing other liver diseases, such as cirrhosis and hepatocellular carcinoma(8, 9). Bed rest was once considered the cornerstone of the treatment of most liver diseases, such as viral hepatitis and cirrhosis(10, 11). This approach stems from the research that less physical exercise reduces metabolic demands on the liver and lowers the risk of complications(12) and that an upright posture further increases plasma renin levels(10). However, recent studies revealed the adverse consequences of prolonged inactivity, including muscle atrophy(13), deep vein thrombosis(14), and elevated risk of fibrosis(15). As a result, the prescription of bed rest has been critically reevaluated. Physical exercise is an effective measure for managing cirrhosis-related complications, including hepatic encephalopathy and sarcopenia(16, 17). Beyond that, regular physical exercise has also been linked to the reduced risk of liver cancer(18). Furthermore, studies demonstrated that regular exercise not only diminishes the likelihood of MASLD but also elevates the overall

quality of life for individuals afflicted with chronic liver diseases and liver transplantation(19, 20). Physical exercise also ameliorates systemic metabolic disorders like obesity and type 2 diabetes, both of which can exacerbate liver injury(21, 22).

In this review, we summarize the protective roles of physical exercise in liver diseases. We discuss physical exercise modalities and how physical exercise prevents and manages liver diseases. Furthermore, we delve into physical exercise's role in mitigating acute and chronic liver inflammation and its potential in managing liver cancer. This exploration underscores the vital role of physical exercise in liver diseases and advocates for its incorporation into liver disease prevention and management strategies.

Physical Exercise Modality, Intensity and Duration

Physical exercise is mainly comprised of aerobic and resistance training, each with different benefits and precautions for liver diseases. Aerobic exercise effectively reduces body weight, glycosylated hemoglobin A1c, blood pressure, and serum cholesterol levels(23-25). However, it can induce fatigue and discomfort, potentially leading to poor long-term compliance, especially for individuals with lower cardiorespiratory fitness levels(26). Resistance exercise, which entails muscle contractions against external resistance to boost muscle strength, bone density, and endurance, has been shown to provide significant benefits in addressing dyslipidemia, hypertension, and insulin resistance(27, 28), offering metabolic advantages with relatively lower energy expenditure; however, limited access to appropriate equipment and facilities can pose a barrier to engaging in effective resistance exercise.

No particular liver disease has been exclusively linked to a specific exercise modality for treatment or management(29). A comparative randomized controlled

trial investigated the effects of moderate-intensity aerobic exercise versus resistance exercise on patients with MASLD, finding both regimens equally effective in reducing intrahepatic triglycerides (IHGT) and improving insulin resistance(30). In patients with cirrhosis, aerobic exercise enhances cardiopulmonary function and overall fitness, while resistance exercise is highly effective against sarcopenia(31). Combining these two forms of exercise can significantly improve hepatic complications and prognosis(8).

In mouse models focusing on liver diseases, physical exercise interventions primarily involve aerobic exercises such as treadmill running(32), voluntary wheel running(33), and swimming(34). Resistance exercise models include weightlifting(35), high-intensity interval exercise (HIIT)(36), and ladder climbing(37). These exercise models offer valuable insights into the effects of physical exercise on liver health, metabolism, and the potential for treating liver diseases. Understanding the impacts of different exercise modalities on liver disease is crucial for developing effective therapeutic strategies and promoting overall liver well-being.

The intensity of physical exercise is assessed through absolute and relative intensity. Absolute intensity is measured in Metabolic Equivalent of Task (MET) units, representing the energy expended during the exercise. Moderate-intensity activities range from 3 to 5.9 MET, while vigorous-intensity activities are 6 or higher(38). In contrast, relative intensity assesses effort to an individual's capacity. Intensity is a critical factor when considering physical exercise for patients with liver diseases(39). For instance, Keating *et al.* showed that the minimum effective dose of exercise to improve hepatic steatosis was 135 minutes of moderate-intensity aerobic exercise per week, and that increasing the intensity of exercise (including HIIT approaches) had no additional benefit for hepatic steatosis(40). It is essential to tailor physical

exercise considering absolute and relative intensity to maximize benefits based on individual fitness levels.

Determining the appropriate exercise duration is equally important. Our group found that liver I/R injury decreased with exercise duration and was lowest after 4 weeks of preoperative exercise compared with sedentary mice. However, extended pre-operative exercise periods beyond 4 weeks up to 16 weeks offered no further hepatic protection(32). Moreover, for those in poor physical condition, the recommendation is to initiate exercise with 20 minutes sessions and progressively increase the duration by 5-10 minutes every 1-2 weeks(41).

In conclusion, careful selection of physical exercise modality, intensity, and duration is essential for effectively managing liver diseases. A personalized physical exercise plan tailored to the individual's health needs and capabilities is recommended to ensure improved adherence and optimal health outcomes(29, 42).

The Mechanism of Physical Exercise in Protecting Against Liver Diseases

Improve Insulin Sensitivity

Physical exercise effectively improves insulin sensitivity, which is critical to regulating glucose and lipid metabolism(43). Insulin resistance is characterized by impaired responsiveness to insulin, leading to elevated insulin levels in the liver. This promotes MASLD through mechanisms that increase lipids' synthesis and accumulation. High levels of insulin resistance are a significant predictor of MASLD(44).

The positive effect of exercise on insulin sensitivity is attributed to its modulation of molecular pathways associated with insulin resistance (**Table 1**). For instance, Wang *et al.* found that treadmill running for 60 minutes per day, 5 days per week for 10 weeks, significantly improved the function of islet β-cells and effectively reduced insulin resistance in mice. These improvements were associated with the activation

of the toll-like receptor 4 (TLR-4)-mediated extracellular signal-regulated kinase (ERK)/AMP-activated protein kinase (AMPK) signaling pathway, which plays a crucial role in regulating insulin sensitivity and glucose metabolism(45). The research conducted by Zhang *et al.* demonstrated that 60 minutes per day, 5 days per week for 8 weeks of swimming training effectively improved hepatic insulin resistance induced by a high-fat diet (HFD) in male Sprague-Dawley rats through TGF-β-activated kinase 1 (TAK1)-dependent signaling. The improvement in insulin sensitivity was attributed to multiple factors, including the enhancement of proteins ubiquitin-specific protease 4 (USP4), dual-specificity phosphatases 14 (DUSP14) and a reduction in the phosphorylation of critical signaling molecules such as TAK1, c-Jun N-terminal kinase 1 (JNK1), and insulin receptor substrate 1 (IRS1)(46). Furthermore, this beneficial effect was associated with reduced apoptosis signal-regulated kinase 1 (ASK1) phosphorylation(47). Similarly, studies by Marinho *et al.* and Zhang *et al.* indicate that an identical regimen of swimming enhances insulin signaling through adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1 (APPL1) / protein kinase B (Akt) signaling pathway and the family with sequence similarity 3 member A (FAM3A)/ATP/Akt pathway, respectively(48, 49). AKT signaling plays a crucial role in insulin sensitivity, and disturbances in AKT signaling pathways may result in insulin resistance(50-52). Moreover, Diniz *et al.* have shown that treadmill running for 60 minutes per day, 5 days per week for 8 weeks, can attenuate the progression of HFD-induced hepatic steatosis and inflammation. This improvement is achieved through activating the AMPK-peroxisome proliferator-activated receptor alpha (PPAR-α) signaling pathway and PPAR-gamma (PPAR-γ) signaling pathways, leading to the amelioration of insulin resistance in obese mice(53).

HIIT has been shown to reduce insulin resistance and hepatic glucose production. Castaño *et al.* revealed that HIIT can alter the microRNA (miRNA) profile of

circulating exosomes in mice. This alteration leads to increased expression of miR-133a and miR-133b in plasma, which, in turn, upregulates the insulin-regulating transcription factor forkhead box O1 (FoxO1) in the liver, ultimately contributing to the attenuation of insulin resistance(54). These findings underscore exercise-induced molecular adaptations' significance in alleviating hepatic insulin resistance.

Table 1. Molecular pathways involved in the improvement of hepatic insulin sensitivity by physical exercise

Reference	Exercise modeling	Exercise Intervention	Molecular pathways
Marinho *et al.*, 2013(49)	Aerobic exercise	Swimming, 60 min per day, 5 days per week for 8 weeks	Improved the APPL1/TRB3/Akt signaling pathway
Tsuzuki, *et al.*, 2015(52)	Aerobic exercise	Voluntary wheel running for 20 weeks	Suppressed the iNOS expression and S-nitrosylation of Akt
Zhang, *et al.*, 2018(48)	Aerobic exercise	Swimming, 60 min per day, 5 days per week for 8 weeks	Reduced the NFE2/miR-423-5p and increased FAM3A/ATP/Akt pathway
Wang, *et al.*,2018(45)	Aerobic exercise	Treadmill running, 60 min per day, 5 days per week for 10 weeks	Improved the TLR-4-mediated ERK/AMPK signaling pathway
Zhang, *et al.*, 2019(46)	Aerobic exercise	Swimming, 60 min per day, 5 days per week for 8 weeks	Suppressed hepatic TAK1/JNK/IRS1 signaling
Castaño, *et al.*, 2020(54)	Aerobic exercise	Treadmill running, 60 min per day, 3 days per week for 5 weeks	Increased the miR-133a, miR-133b and FoxO1

Diniz, *et al.*,2021(53)	Aerobic exercise	Treadmill running, 60% of maximum speed, 7 days per week for 8 weeks	Improved the AMPK-PPAR-α/ PPAR-γ signaling pathway
Rodrigues, *et al.*, 2021(51)	Resistance exercise	20 climbing series per day, 5 days per week for 3 weeks	Increased the IRS-1/2 and AKT tyrosine phosphorylation
Zhang, *et al.*, 2021(47)	Aerobic exercise	Swimming, 60 min per day, 5 days per week for 8 weeks	Decreased the ASK1 phosphorylation and improved JNK1/IRS1/Akt signaling pathway
Vieira, *et al.*, 2022(50)	Aerobic exercise	Treadmill running, 30-60 min per day, 7 days per week for 10 weeks	Improved the IRS1/AKT signaling pathway

Regulate Lipid Homeostasis

The liver is vital in regulating lipid homeostasis and is the primary organ for fatty acid metabolism(55). Excess glucose ingested is converted into fatty acids by hepatocytes through a series of enzymatic reactions collectively known as de novo lipogenesis(56). These newly synthesized fatty acids can be stored in the liver as triglycerides or transported to adipose tissue for long-term storage. Failure to transport or utilize these fatty acids promptly can result in their accumulation in the liver, leading to the development of metabolic dysfunction-associated steatohepatitis (MASH).

Physical exercise involves the complex physiological process significantly affecting lipogenesis and lipolysis (**Figure 1**). Increasing energy expenditure is one of the primary mechanisms through which exercise influences this process(57). During aerobic exercise, lipase enzymes in the body are activated, leading to the hydrolysis of triglycerides into glycerol and free fatty acids (FFAs)(58). Hormones, such as epinephrine and norepinephrine, further stimulate lipolysis(58). This process increases the release of FFAs into the bloodstream, serving as an energy source. Hepatic lipolysis is a complex metabolic process that relies on several critical regulatory enzymes to control the release of fatty acids from stored triglycerides. Additionally, fatty acid oxidation and autophagy are involved in this intricate cellular mechanism(59). Physical exercise can decrease de novo lipogenesis and increase the fatty acid β-oxidation and autophagy. In addition, exercise can further regulate lipid metabolism by enhancing insulin sensitivity(59).

AMPK-dependent pathway plays a central role in exercise-mediated lipid metabolism. Zou *et al.* demonstrated that swimming exercise for 4 hours per day, 5 days per week for 12 weeks decreased de novo lipogenesis and promoted liver

lipophagy and fatty acid β-oxidation by activating AMPK/Sirtuin 1 signaling in MASLD Zebrafish(60). Qian *et al.* noted that swimming training for 45 minutes per day, 5 days per week for 8 weeks induced hepatoprotection in HFD-fed mice was achieved by inhibiting the upregulation of hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2), which serves as the key rate-limiting enzyme in ketogenesis(61). Another study showed that treadmill running for 60 minutes per day, 7 days per week for 12 weeks, induced hepatic adenosine deaminases acting on RNA 2 (ADAR2), which protect against lipogenesis during MASLD by decreasing the level of miR-34a(62). In addition, exercise regulates hepatic lipid metabolism by modulating gut microbiota(63).

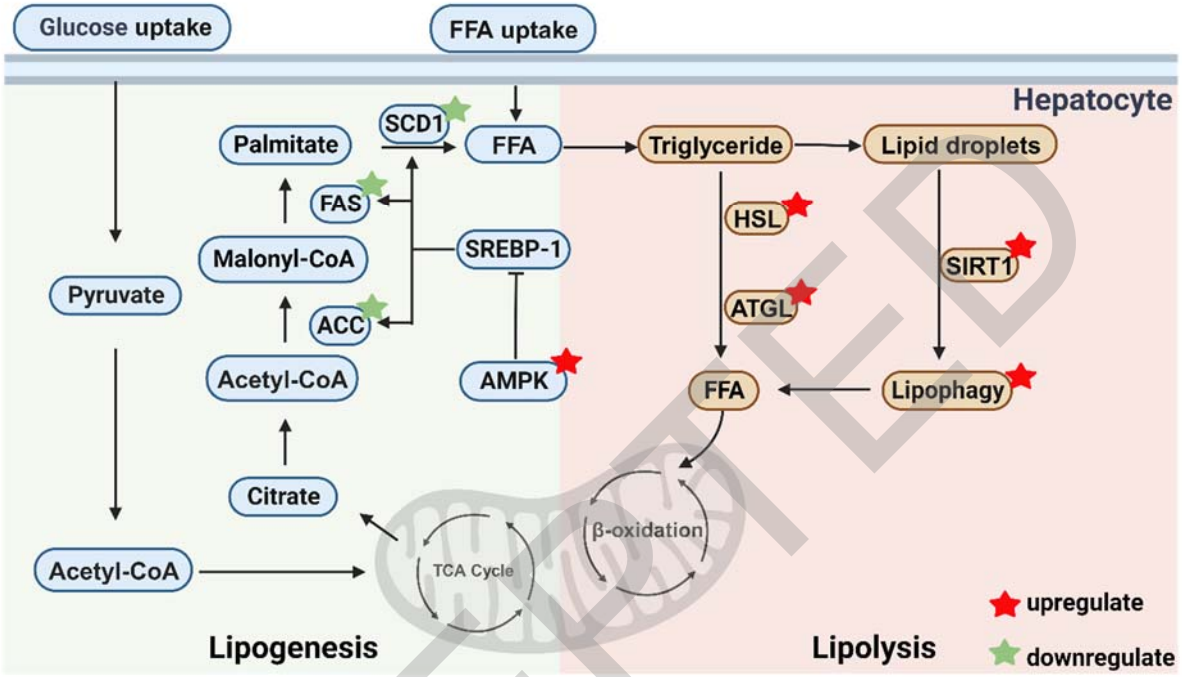

Figure 1. Physical exercise on hepatic lipogenesis and lipolysis. Physical exercise suppresses hepatic lipogenesis and promotes liver triglyceride breakdown, enhancing lipolysis. FFA: free fatty acid; ACC: acetyl-CoA carboxylase; FAS: fatty acid synthase; SCD1: stearoyl-CoA desaturase 1; SREBP-1: sterol regulatory element-binding protein 1; FA: fatty acid; TG: triglyceride; HSL: Hormone-Sensitive Lipase; ATGL: Adipose Triglyceride Lipase; SIRT1: silent information regulator T1.

Skeletal muscle is critical in absorbing and utilizing FFAs for energy during exercise(64). Physical exercise enhances FFA utilization by skeletal muscle and promotes mitochondrial energy production, leading to more efficient utilization of FFAs. Exercise improves muscle cells' responsiveness to insulin, leading to more efficient absorption and utilization of glucose for energy production(65). This process, coupled with the indirect effects on FFA metabolism, contributes to the burning of stored fat. Consequently,-physical exercise improves the body's overall energy metabolism efficiency(66).

Immunomodulation

Hepatic inflammation is a critical factor in the development and progression of liver diseases(67). Physical exercise is pivotal in regulating the hepatic inflammatory response by modulating key cytokines and signaling pathways(68), which emerges as a potent modulator of immune cell infiltration within the liver and the tumor immune microenvironment(69-71), effectively reducing hepatic inflammatory response (**Figure 2**).

In the acute hepatic injury model, our group has shown that 60 minutes per day, 5 days per week for 4 weeks of aerobic pre-operative exercise regimen significantly attenuates liver injury and inflammation from ischemia and reperfusion in mice. We found that exercise specifically drives Kupffer cells (KC) toward an anti-inflammatory phenotype with trained immunity via metabolic reprogramming(32). In the context of acute liver injury induced by N-galactosamine (GalN) and lipopolysaccharide (LPS), a median of 45 days of voluntary long-distance running has been found to alter the intrahepatic immunophenotype, which reduces the number of intrahepatic CD4+ T cells, B lymphocytes, and macrophages, thereby

leading to a change of hepatic microenvironment that is less susceptible to acute liver injury in mice(72).

In MASH, treadmill training for 60 minutes per day, 5 days per week for 12 weeks has shown the capacity to attenuate hepatic inflammation, liver steatosis, and fibrosis by inhibiting the hepatic accumulation of bone marrow-derived macrophages and PD-1+ CD8+ T cells in mice(73). Additionally, the study by Cai *et al.* revealed that swimming training for 60 minutes per day, 7 days per week for 12 weeks, down-regulated the expression of key markers associated with insulin resistance, including PPAR-γ, carnitine palmitoyl transferase-1 (CPT-1), and medium-chain acyl-CoA dehydrogenase (MCAD), ultimately leading to improved insulin sensitivity in HFD-induced MASLD mice(74). A randomized clinical trial including 60 minutes per day, 3-5 times per week for the 12-week aerobic exercise regimen, has been shown to elevate the levels of the apoptotic marker CD95 in mucosa-associated invariant T cells (MAIT) cells, both in the blood and within the liver in patients of MASLD. Additionally, this exercise regimen leads to decreased intrahepatic MAIT cells and notable histological improvements(75). Exercise also hinders the activity of hepatic bone marrow-derived macrophages, thereby reducing the accumulation of inflammatory macrophages stemming from monocytes and bone marrow precursors in mice(71). Moreover, a specific subset of KC known as CD206+ ESAM+ KC has been identified to promote oxidative stress through the scavenger receptor CD36, a pivotal factor in MASH progression(76). Treadmill running for 60 minutes per day, 5 days per week for 16 weeks, can reduce the expression of CD36 in KC(77), thereby decelerating the progression of MASH by altering the phenotype of these cells in mice.

Through targeted alterations in hepatic mRNA expression, exercise effectively suppresses the production of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and monocyte

chemoattractant protein-1 (MCP-1)(78), and elevates the expression of anti-inflammatory mediators, such as interleukin-10 (IL-10)(79). Remarkably, this suppression is accompanied by a reduction in infiltrating macrophages, distinctly mitigating immune cell-driven inflammation characteristic of MASH(71). In addition to immunomodulatory effects, push-ups and set squats for 20-30 minutes per day, 3 days per week for 12 weeks, reduce hepatocyte apoptosis, specifically involving cytokeratin 18 in MASLD patients(80). Additionally, treadmill running for 50 minutes per day, 5 days per week for 12 weeks, effectively inhibits the hepatic TLR4-mediated NF-κB pathway through apolipoprotein A5, further enhancing its protective effects on the liver(81). The level of physical exercise is inversely related to hepatic fibro inflammation, as measured by iron-corrected T1, underscoring its pivotal role in maintaining liver health and mitigating inflammation-associated liver diseases(82).

Natural Killer (NK) cells are vital component of the innate immune system, primarily responsible for immunosurveillance and eliminating cells with low expression of major histocompatibility complex class I(83). Interleukin-15 (IL-15) is a critical activator of NK cells and enhances their anti-tumor responses(84). A cross-sectional study of 133 medical students indicated that regular endurance training increases serum IL-15 expression(85). Also, treadmill running for 60 minutes per day, 5 days per week for 12 weeks, increases the expression of NK cell ligands retinoic acid early inducible gene 1 (RAE-1) in the liver tissue of tumor-bearing mice, thereby enhancing the cytotoxic capabilities of NK cells(86). The efficacy of T cells in recognizing and eliminating cancer cells is paramount in preventing tumor growth and forms the basis of current immunotherapy(87). During exercise, higher levels of metabolites such as lactate released into the bloodstream from skeletal muscle enhance the effector profile of CD8+ T cells. In response to exercise, activated CD8+ T cells in mice adapt their central carbon metabolism.

Transferring trained mouse CD8+ T cells into untrained tumor-bearing animals produces a more potent antitumor effect(88).

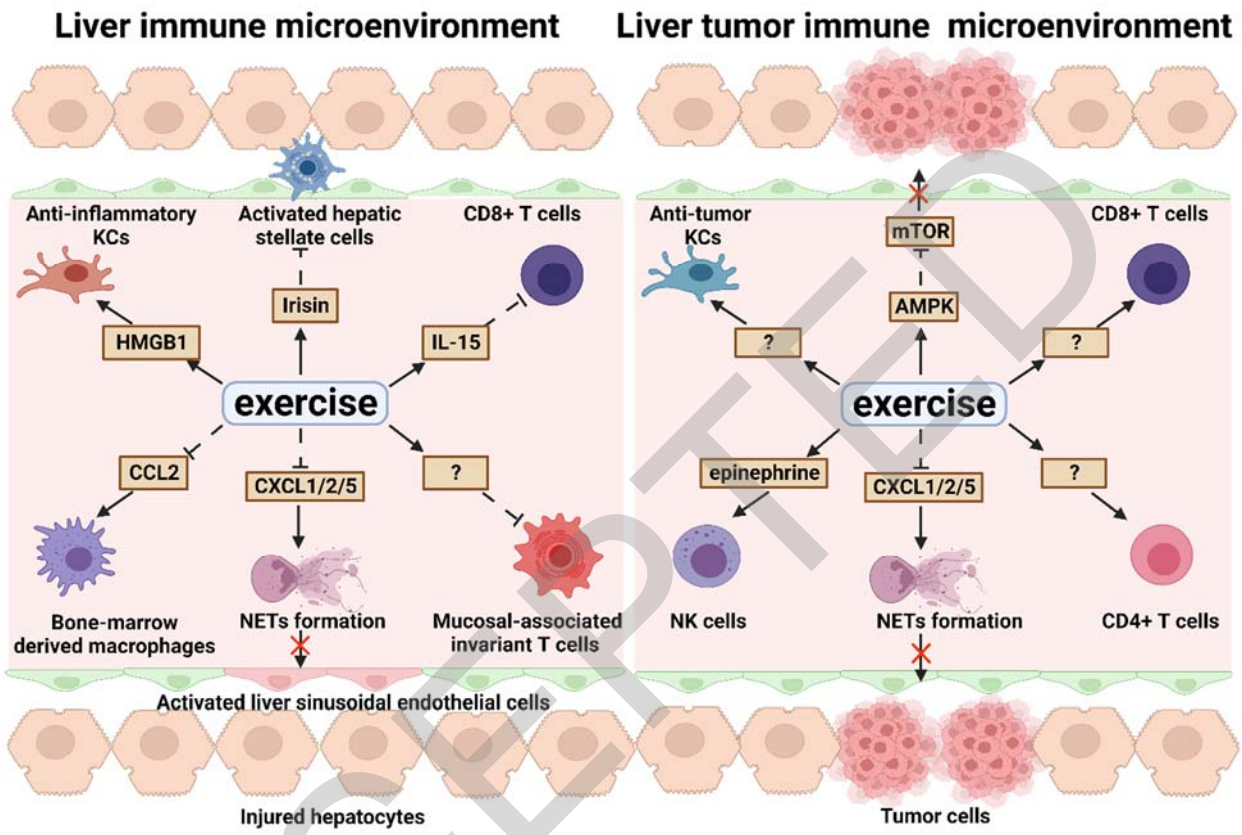

Figure 2. Physical exercise on liver/tumor immune microenvironment in liver diseases. Physical exercise inhibits the infiltration of pro-inflammatory immune cells into the liver in benign liver diseases (left) while recruiting anti-tumor immune cells to both the liver and tumor microenvironment in malignant liver diseases(right).

Exercise in Liver Ischemia/Reperfusion (I/R) Injury

Liver I/R injury is a complex and multifaceted acute inflammation liver disease that occurs when the blood supply to the liver is temporarily interrupted and restored(89). This process may occur in various clinical situations, such as liver surgery, trauma, or liver transplantation(90). Ischemia is the initial phase that leads to hypoxia in liver tissue, resulting in cellular damage and metabolic disturbances. Subsequently, during the reperfusion phase, tissue damage is exacerbated due to the release of ROS and inflammatory mediators. This phenomenon leads to severe hepatic dysfunction and, in extreme cases, multi-organ failure(91). The pathophysiology of hepatic I/R injury involves a complex interplay of various cellular and molecular mechanisms(92). It is, therefore, an essential area of research for developing therapeutic strategies to mitigate its harmful effects.

Exercise activates AMPK, an intracellular sensor that plays a role in metabolic reprogramming(93). The AMPK activator 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) enhances ischemic tolerance and fatty liver regeneration after hepatic I/R in diet-induced hepatic steatosis mice(94). Another key player in the liver I/R process is irisin, a hormone-like molecule released from muscle tissue during physical exercise(95). Irisin's ability to attenuate hepatic I/R injury by binding to the αVβ5 integrin receptor in hepatocytes has significant implications(96). Administering irisin at the onset of reperfusion has been shown to improve mitochondrial function, reduce oxidative stress, and alleviate endoplasmic reticulum stress in HFD mice, ultimately mitigating liver injury(97).

In liver transplantation, exercise plays a distinct role in enhancing the overall well-being of individuals undergoing this life-transforming procedure. Both pre- and post-transplant exercise training are recognized as safe and highly beneficial(98, 99).

A meta-analysis including 8 randomized controlled trials (RCTs) indicates that exercise training improves liver transplantation candidates' physical function and health-related quality of life (HRQOL), furthering their cardiorespiratory and muscle health(100). It optimizes their post-transplant recovery, ultimately contributing to an improved long-term quality of life following transplantation.

Exercise in Cardiogenic Liver Disease

Other conditions leading to liver injury, including cardiogenic liver disease triggered by myocardial infarction, may benefit from exercise. Treadmill running for 60 minutes per day, 5 days per week for 6 weeks has the potential to effectively mitigate liver injury by promoting the anti-inflammatory phenotype of hepatic macrophages, attenuating myocardial infarction-induced hepatic inflammation, enhancing the expression of fibronectin type III domain-containing protein 5 (FNDC5) protein, and activating the PI3K/protein kinase B signaling pathway in the liver of myocardial infarction-afflicted mice(101).

Exercise in MASLD

MASLD is indeed one of the most prevalent chronic liver disorders worldwide, affecting up to 25% of the global population(102). This condition encompasses a range of histological features, including hepatic steatosis, hepatocyte ballooning, hepatic lobular inflammation, and liver fibrosis. Approximately 4% of individuals with simple steatosis and over 20% of those with MASH are expected to develop cirrhosis during their lifetime(103). MASLD is a complex multifactorial disease whose exact pathogenesis is not fully understood. Insulin resistance and liver steatosis may represent the first hit for the liver(104). However, it's important to note that steatosis, or fat accumulation in the liver, is typically an early event in MASLD and doesn't necessarily progress to MASH. Additional stresses are required to induce

MASH onsets, such as oxidative stress, lipotoxicity, inflammation, subsequent stimulation of hepatocyte death, tissue regeneration, and fibrogenesis(104).

A large amount of evidence derived from clinical studies of MASLD supports the vital role of physical exercise in improving histological parameters and decelerating the progression of the disease. This includes its ability to enhance insulin resistance, reduce hepatic steatosis, and attenuate hepatic inflammation(30, 105). For instance, a randomized clinical trial conducted by Charatcharoenwitthaya *et al.* reported moderate-intensity aerobic exercise or resistance training for 60 minutes per day, 5 times per week for 12 weeks, coupled with dietary modifications equally reduced intrahepatic fat and substantially improved underlying insulin resistance in individuals diagnosed with MASLD(30). It is worth noting that the effectiveness of exercise in combating hepatic insulin resistance varies based on the duration of the intervention. Hari *et al.* discovered that short-term (7d) treadmill training consists 60 minutes per day at 80%-85% of maximal heart rate increased peripheral insulin sensitivity by 34% in radiographically-confirmed MASLD (>5% intra-hepatic lipid content) patients(106). Another meta-analysis that included 26 randomized clinical trials showed that short-term exercise interventions, lasting less than 12 weeks, have shown efficacy in reducing specific insulin resistance markers such as fasting blood glucose (FBG) and the homeostatic model assessment of insulin resistance (HOMA-IR)(107). Interestingly, a randomized controlled trial indicated that combining moderate-intensity aerobic exercise (60 minutes per day, 5 times per week for 12 weeks) with alternate-day fasting has been shown to reduce insulin resistance in adults with MASLD. However, this combined approach does not significantly enhance insulin resistance improvements compared to exercise alone(108). These clinical findings underscore the therapeutic potential of physical exercise as a potent tool in combatting insulin resistance in MASLD.

Several clinical studies demonstrate that physical exercise reduces intrahepatic triglyceride (IHTG) levels, which is independent of weight loss(24, 108-110). A systematic review has compared the therapeutic effects of aerobic and resistance exercises on hepatic steatosis in MASLD. They found that both aerobic and resistance exercise improved hepatic steatosis to a similar extent, with common parameters of duration, frequency, and training period (40-45 minutes/session, 3 times/week for 12 weeks)(7). However, resistance exercise may be more feasible for MASLD patients with poor cardiorespiratory fitness because it improves MASLD with lower intensity and less energy consumption(7). Additionally, a meta-regression analysis from 17 studies (373 exercising participants) revealed a significant negative correlation between the duration of exercise and the reduction in IHTG (β = -0.27 [95% CI: -0.35 to -0.19], $p < 0.001$). This suggests that as the duration of exercise increases, the reduction in IHTG becomes more pronounced. Specifically, compared with shorter high-intensity exercise, continuous moderate-intensity protocols commonly exhibit a more significant decrease in IHTG in those MASLD patients(111). The study revealed no statistically significant distinctions among the three levels of aerobic exercise regimens regarding reducing intrahepatic lipid content. The results demonstrated that even minimal engagement in exercise led to a noticeable reduction in intrahepatic lipid levels(111). These findings highlight the importance of developing individualized sustainable exercise interventions that may yield the most significant benefits for IHTG reduction in patients with MASLD.

Although the FDA has approved Rezdiffra (resmetirom) as the first drug treatment for MASH patients with moderate to advanced liver scarring (fibrosis), lifestyle modification, including physical exercise, remains generally recommended as a first-line therapy for all patients with MASLD(112). In line with this recommendation, the American Gastroenterological Association recommends that

all patients with MASLD should engage in regular physical activity with a target of 150-300 minutes of moderate-intensity (3–6 MET) or 75-150 minutes of vigorous-intensity (more than 6 MET) aerobic exercise per week. Resistance training can be complementary to aerobic exercise but not a replacement (**Figure 3**)(112).

Exercise in Portal Hypertension (PH)

PH is defined as abnormally high blood pressure within the portal vein system, primarily caused by cirrhosis and other portal vein obstruction, such as portal vein thrombosis(113). PH can lead to serious complications such as ascites, variceal bleeding, splenomegaly and an elevated risk of spontaneous bacterial peritonitis or other infections, hepatic encephalopathy, hepatorenal syndrome, and liver failure(114). The gold standard for the diagnosis of PH is the hepatic venous pressure gradient (HVPG). An HVPG value exceeding 5 mmHg indicates the presence of PH, while a value above 10 mmHg denotes clinically significant portal hypertension (CSPH). This latter threshold is considered clinically significant because it marks the point at which complications of PH begin to develop(115). Treatment of PH focuses on reducing portal pressure, preventing complications, and managing symptoms. This approach mainly includes the medication (non-selective beta-blockers), the transjugular intrahepatic portosystemic shunt (TIPS), and pericardial devascularization(116).

Research on the impact of physical exercise on PH is limited and has historically raised concerns about the potential for exacerbating complications such as hepatic encephalopathy or bleeding post-exercise(117). Initial studies indicated that 8-10 minutes of cycling at 30% and 50% of peak workload increased HVPG(117). In a randomized controlled trial, 40 patients with compensated cirrhosis of Child-Pugh A were recruited to evaluate the effects of a 12-week home-based exercise program. The regimen included moderate- intensity aerobic/isotonic continuous training

exercises, lasting 40 minutes per session, conducted at least 4 times weekly. This study reported no adverse events such as gastrointestinal bleeding, ascites, or musculoskeletal injuries, yet it did not find any beneficial impact on PH(118). Conversely, another pilot randomized clinical trial involving 29 patients with cirrhosis and PH (average HVPG > 10 mm Hg) who participated in a 14-week supervised exercise program showed significant benefits. The regimen, which consisted of physical exercises performed for 40 minutes, 3 times a week at an intensity of 12-14 on the Borg Rating of Perceived Exertion scale, led to an average reduction in HVPG of 2.5 mm Hg, with no episodes of variceal bleeding or hepatic encephalopathy observed(119). Additionally, a prospective, multicenter, uncontrolled pilot study focused on the effects of an intensive lifestyle intervention on patients with compensated cirrhosis and PH (HVPG ≥ 6 mmHg). Participants were engaged in a 16-week intensive lifestyle modification program, which included a personalized hypocaloric normoproteic diet and 60 minutes of supervised physical activity (10 minutes of warm-up, 40 minutes of aerobic and strength exercising routine, and 10 minutes of cooling down) each week. Results showed a significant reduction in HVPG, decreasing from an average of 13.9±5.6 mmHg at baseline to 12.3±5.2 mmHg post-intervention, with 42% of participants achieving an HVPG decrease of ≥ 10%. However, the study's design does not confirm whether the observed reductions in PH were due to exercise, diet, or a combination of both(120). Current research on PH is primarily focused on cirrhosis-induced cases, with other causes of PH have not been well studied. Additionally, there is a lack of comprehensive data on the appropriate intensity, duration, and type of exercise required for effective treatment and prevention of PH, and thus no consensus has been reached in this area.

Exercise in Cirrhosis

Cirrhosis, primarily caused by MASLD, viral hepatitis, and alcohol consumption, accounts for 2.4% of global deaths in 2019(121, 122). Cirrhosis manifests as extensive fibrosis, resulting in nodular changes in liver structure. Portal hypertension in combination with cirrhosis can lead to severe complications such as ascites, variceal bleeding, and hepatic encephalopathy(113). The liver's ability to synthesize and metabolize is impaired in cirrhosis, and the risk of hepatocellular carcinoma is elevated(3).

Physical exercise has been demonstrated to diminish hepatic inflammation and fibrosis by influencing different signaling pathways. The mechanisms are primarily associated with the regulation of several related signaling pathways, including the AMPK signaling pathway(123), the 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2)-regulated Wnt3a/β-catenin pathway(61), monoacylglycerol O-acyltransferase 1(MGAT1) pathway(124), and MD2-TLR4 pathway(125), etc. In addition, these mechanisms encompass the inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation(126), modulation of myeloid cell monocytes (MoMFs) infiltration in the liver(127), and restoration of gut microbiota(128).

Numerous clinical studies have highlighted the advantageous effects of exercise for individuals in the early stages of cirrhosis. Aamann *et al.* found a regimen of resistance training for 1 hour, 3 times weekly for 12 weeks, not only diminished the risk of initial hospitalization and mortality among patients with cirrhosis classified as Child-Pugh class A/B three years post-trial entry but also resulted in increased muscle strength and size(31, 129). Sirisunhirun *et al.* implemented a 12-week program of aerobic moderate-intensity continuous training exercises, lasting 40 minutes per session, at least 4 times a week, in compensated cirrhotic patients(118). This program significantly ameliorated the fatigue domain of the quality-of-life index without inducing adverse reactions. However, no benefits were observed in

thigh muscle mass, liver stiffness, or spleen stiffness. Moreover, a meta-analysis of randomized controlled trials by Kawaguchi *et al.* discovered that a median protocol of aerobic exercise for 30 minutes per session, 3 times a week for 12 weeks, in combination with a resistance exercise protocol of 60 minutes per session, 3 times a week for 10 weeks, significantly reduced the incidence of serious events in patients with liver cirrhosis and enhanced the 6-minute walk distance (6MWD), an independent prognostic factor for these patients(8, 130).

Given the heterogeneity of disease progression and variable clinical presentations in cirrhosis, standardized exercise guidelines, particularly for resistance exercise, remain elusive(131). Nonetheless, there are established recommendations for the prescription of aerobic exercise in patients with cirrhosis. Before initiating an exercise regimen in cirrhotic patients, a comprehensive medical assessment is imperative. This assessment should encompass an evaluation of cardiopulmonary function, concurrent pathologies, and musculoskeletal constraints. Following this, it is crucial to delineate exercise objectives and modalities, adhering to the FITT (Frequency, Intensity, Time, and Type) principle, tailored to the patient's unique health condition. The clinical practice recommendations for patients with cirrhosis advocate for the engagement in physical exercise of mild to moderate intensity for 30-60 minutes per session, 5 days per week (cumulatively ≥ 150 minutes per week) through an activity such as walking or cycle ergometry. The intensity should be calibrated to 30-40% of heart rate reserve or within a range of 10-14 on the Borg scale (**Figure 3**)(41).

Exercise in Liver Cancer

Liver cancer represents a significant global health challenge and the third leading cause of cancer death worldwide, accounting for approximately 7.8% of total cancer deaths in 2022(132). The impending burden of liver cancer is expected to affect over

one million individuals by 2025(133). Notably, physical exercise is emerging as a particularly promising strategy. Studies suggest that physical exercise might play a role in various aspects, including reducing the risk of developing liver cancer(134-136), controlling liver cancer progression[111], enhancing efficacy, and reducing the side effects of anti-cancer treatments(137, 138). This growing evidence suggests that physical exercise could be an effective component in combating liver cancer.

The accumulating epidemiological evidence supports the potential protective role of physical exercise against liver cancer, particularly hepatocellular carcinoma (HCC). In the United States, a study revealed a moderate inverse correlation (r=-0.40, p=0.004) between state-level physical exercise and the incidence of HCC(9). This is further supported by comprehensive research from over 44 million participants across the US and Europe, revealing that higher levels of leisure-time physical exercise reduce liver cancer risk by over 20%(139). Another cohort study, quantifying the dose-response relationship between leisure-time physical exercise and liver cancer showed that engagement in 7.5-15 hours per week of leisure-time physical exercise was associated with an 18%-27% lower risk of liver cancer(134). However, the study also identified a nonlinear association between the risk of liver cancer and activity levels, implying a limit beyond which additional exercise does not further decrease liver cancer risk. This finding raises important questions about the optimal amount and intensity of physical exercise for liver cancer prevention. While these studies are groundbreaking, they are limited by their failure to adjust for other potentially important confounding factors, including viral hepatitis, MASLD, cirrhosis, and alcohol consumption. A prospective multinational cohort study further explored this association, finding physical exercise associated with a lower risk of liver cancers. This relationship persisted even after adjusting for liver cancer risk factors like alcohol consumption, smoking, waist circumference, or body mass index(140). Moreover, a meta-analysis provided further evidence, demonstrating a

23% reduction in liver cancer risk and a 19% decrease in mortality among individuals who engaged in moderate physical exercise, reinforcing the potential protective impact of exercise against liver cancer(141).

The beneficial effects of physical exercise on liver cancer can be attributed to various systemic and local biological mechanisms. Obesity, an independent risk factor for mortality in primary liver cancer, can be significantly mitigated by physical exercise, reducing the associated risk[117]. Additionally, in patients with HCC, a decline in skeletal muscle mass is significantly associated with severe adverse events from chemotherapy, low tolerability, increased tumor recurrence, and all-cause mortality(142). Significantly, exercise intervention has improved skeletal muscle strength in these patients(143). This underscores the effective role of exercise in enhancing the management of liver cancer, potentially improving treatment outcomes and survival rates for affected individuals. The benefits of exercise on liver cancer can be elucidated through three fundamental mechanisms. Firstly, exercise regulates critical signaling pathways and modulatory proteins crucial in HCC progression. This includes the suppression of transforming growth factor-beta (TGF-β)(144), downregulation of dynamin-related protein 1(DRP1)(145), activation of p53(146), and modulation of the AMPK/mTOR signaling pathway(147). Secondly, exercise enhances anti-tumor immunity by increasing the CD8+ T cells infiltration into the tumor microenvironment (TME), creating a hostile environment for tumor growth and progression within the liver(148). Thirdly, exercise induces metabolic reprogramming of TME(149), forming an exercise-induced metabolic shield unfavorable for tumor cell colonization. This metabolic reprogramming underscores the role of exercise in reshaping the metabolic landscape of the TME to impede cancer progression and metastasis. Beyond these specific mechanisms, exercise also influences other critical factors, such as angiogenesis and oxidative stress, which can affect tumor growth and survival(150). However, it is essential to acknowledge that

current research on these mechanisms remains limited, necessitating further empirical investigation to substantiate these findings and fully elucidate their implications in the context of liver cancer management.

The American Society of Clinical Oncology and the American College of Sports Medicine actively endorse the integration of regular exercise into both cancer treatment regimens and post-treatment recovery(151, 152). During the second roundtable conference held in 2018, an updated consensus on exercise programs for cancer survivors, including those with liver cancer, was presented. The most effective exercise prescription for addressing health-related outcomes caused by cancer diagnosis and treatment includes engaging in moderate-intensity aerobic training at least 3 times per week, for at least 30 minutes each session, for at least 8-12 weeks. In addition to aerobic training, incorporating resistance training at least twice a week, with at least 2 sets of 8-15 repetitions, where each repetition is performed with at least 60% of the maximum weight that can be lifted once, appears to offer similar benefits (**Figure 3**)(153). This endorsement highlights the recognized importance of physical activity in enhancing the overall health and quality of life for individuals undergoing cancer therapy and those in the recovery phase post-treatment. Further evidence is needed to formulate individualized and realistic exercise programs, including the type, intensity, and duration of exercise, ensuring their effectiveness and feasibility for patients with liver cancer.

Figure 3. Aerobic exercise（upper）and resistance exercise（lower） are recommendations for normal-condition patients with MASLD, cirrhosis, and liver cancer.

Physical Exercise Indirectly Improves Liver Diseases through Other Organs

Physical exercise offers systemic benefits that improve health and disease resistance across various organs. In the brain, physical exercise enhances cognitive functions through multiple mechanisms: it increases the generation of new neurons in the hippocampus via brain-derived neurotrophic factor(154), suppresses neuroinflammation by up-regulating amyloid-β peptide (Aβ) transporter activity to clear Aβ(155), and promotes neuroplastic changes by altering the synaptic structure and function(156). Cardiovascular health benefits significantly from physical exercise, which promotes myocardial mitochondrial biogenesis and autophagy through the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)(157). Additionally, exercise attenuates myocardial inflammation and apoptosis by regulating the apelin peptide jejunum (APJ)/ signal transducer and activator of transcription 3 (STAT3) signaling pathway(158), and it improves heart function after myocardial infarction through the AMPK signaling pathway(159). For muscles, physical exercise increases the utilization of glucose and fatty acid(160), promotes the secretion of myokines that facilitate communication with other organs such as adipose tissue, liver, and pancreas(161), and reduces the risk of sarcopenia by maintaining muscle mass and strength(162). Moreover, physical exercise contributes to promoting adipose tissue utilization(163), boosts the anti-inflammatory gene expression in adipose tissue(164), and enhances paracrine and endocrine functions of adipose tissue by increasing the production of beneficial adipokines and extracellular vesicles(165). Exercise also benefits gut health by regulating the gut microbiota and increasing butyrate production(166), and restoring intestinal barrier integrity[(167)].

Physical exercise indirectly promotes liver health through its effects on other organs. For instance, physical exercise stimulates the brain to secrete insulin-like growth factor 1 (IGF-1)(168), which alleviates hepatic histologic lesions in MASH(169). Additionally, exercise enhances cardiopulmonary efficiency, which significantly improves overall well-being and quality of life in adult liver transplant recipients(100). Physical exercise also triggers the release of myokines such as Irisin, which can inhibit hepatic inflammation by competitively binding with MD2 to improve MASLD(170). Moreover, exercise helps reduce the accumulation of adipose tissue, addressing a key factor in the development of MASLD(109). It also regulates the gut microbiota, providing therapeutic benefits for liver diseases like MASLD and cirrhosis(171, 172). Through these indirect mechanisms, physical exercise substantially supports liver health, highlighting its wide-ranging impact.

Conclusion and Further Perspective

In summary, the existing literature demonstrates the impact of physical exercise on liver health, as it effectively improves critical factors such as insulin resistance, hepatic fatty acid metabolism, and the modulation of inflammatory cascades. These findings support the current guidelines recommending tailored exercise programs to enhance long-term adherence and promote an active lifestyle among patients with liver diseases. However, there remains a pressing need for multicenter clinical trials to establish exercise norms for different disease stages, thereby further enriching our understanding of the role of exercise in liver diseases management.

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