Review

From Liver to Muscle: Crosstalk Mechanisms and Interventions in Sarcopenia

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Received: 27 March 2025; Revised: 25 April 2025; Accepted: 23 May 2025; Published: 17 July 2025

Abstract: Aging is a complex and multifactorial process, characterized by a gradual decline of multiple organ systems. Increasing evidence suggests that organ crosstalk plays a crucial role in aging. It is particularly important in the development of age-related diseases like sarcopenia. The liver significantly impacts skeletal muscle health by influencing metabolic health, inflammatory signals, and the secretion of hepatokines. Chronic liver diseases, including non-alcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma (HCC), exacerbate sarcopenia by disruptiong the liver-muscle interactions. Recent studies have demonstrated that liver-derived metabolites, including ketone bodies, can modulate the skeletal muscle function. Notably, beta-hydroxybutyrate (BHB), a key liver-derived metabolite, has been shown to mediate post-translational modifications (PTMs) in muscle, reversing sarcopenia through beta-hydroxybutyrylation. This review explores the relationship between liver aging, chronic liver diseases, and sarcopenia. It focuses on mediators of liver-muscle crosstalk, including metabolic integration, hepatokines, and miRNAs in extracellular vesicles (EVs). We highlight the impact of liver-derived metabolites on skeletal muscle post-translational modifications, particularly the role of BHB in muscle rejuvenation and sarcopenia reversal. Understanding these mechanisms provides new insights into potential therapeutic strategies for mitigating sarcopenia via living aging intervention.

Keywords: skeletal muscle aging; liver aging; sarcopenia; organ crosstalk; liver-muscle axis; chronic liver diseases; hepatokines

1. Introduction

1.1. Organ Crosstalk Is Essential in Aging and Aging-Related Diseases

Aging is a complex, multifactorial process characterized by a gradual decline in the function of multiple organ systems. As individuals age, the homeostasis of various organs becomes increasingly disrupted, leading to a rise in chronic conditions and degenerative diseases [1]. Traditionally, aging and age-related diseases were studied in isolation, with a focus on specific organs. However, recent aging research has increasingly performed in a multi-organ scale, and recognized that different organs and systems may age at distinct rates, and their biological ages can predict organ-specific disease risks [2]. Furthermore, inter-organ communication, or crosstalk, is crucial for maintaining metabolic balance during aging and plays a key role in both aging onset and potential interventions [3].

Organ crosstalk refers to the communication between different organs in the body through signaling molecules such as cytokines, hormones, metabolites, and microRNAs. This bidirectional and multi-directional interaction enables organs to coordinate systemic adaptation to metabolic demands, immune challenges, and environmental stressors [3]. It is critical for maintaining homeostasis in metabolism, immunity, and tissue repair [4].

During aging, dysregulated crosstalk has been implicated in various age-related diseases. For example, impaired signaling between the brain, gut, and immune system exacerbates neuroinflammation and cognitive decline in Alzheimer's disease [5]. Dysregulated bone-muscle-endocrine networks drive sarcopenia and osteoporosis via imbalanced myokine and osteokine secretion [6]. Cardiometabolic diseases, such as diabetes and

atherosclerosis, are also linked to adipose-liver-pancreas crosstalk dysfunction mediated by lipotoxic metabolites and adipokines [7]. Chronic kidney disease exemplifies systemic dysregulation, as uremic toxins impair cardiac and skeletal muscle function through inflammatory pathways [8,9]. These findings highlight the necessity of preserving inter-organ communication to mitigate age-related decline, offering organ crosstalk as a novel aging and age-related disease intervention target [3].

1.2. Sarcopenia Is the Pathological Endpoint of Muscle Aging

While inter-organ communication is essential for maintaining systemic homeostasis, aging-related changes in skeletal muscle are particularly impactful, leading to conditions like sarcopenia. According to the consensus from the Aging Biomarker Consortium, skeletal muscle aging refers to the structural and functional changes that occur in skeletal muscle as an individual ages [10]. This process involves the reduction of muscle mass, loss of muscle fiber number, a decrease in the cross-sectional area of muscle fibers, changes in muscle fiber structure [11], increased fat deposition within muscle tissue [12], and fibrosis [13]. Functionally, skeletal muscle aging is characterized by impaired muscle contraction, impaired satellite cell function, and regeneration capabilities [14], reduced secretion functions, and disruptions in metabolic processes. Mechanically, human skeletal muscle aging atlas reveals that skeletal muscle aging is characterized by changes in muscle stem cell function, denervation and compensatory re-innervation at the neuromuscular junction, compensation for fast-twitch fiber loss, and immune cell attraction to the muscle microenvironment by single cells and single nuclei analysis of human skeletal muscle [15].

Skeletal muscle aging is a gradual and universal process, but it becomes clinically significant when it progresses to sarcopenia, the age-related loss of muscle mass and strength. Sarcopenia was defined in 1989 for the first time by Rosenberg [16]. It is characterized by muscle wasting, weakness, and impaired mobility, increasing the risk of falls, fractures, and mortality. Over time, the definition has evolved to include both muscle mass and strength as key indicators, with resistance exercise emerging as a potential intervention [17]. Although interrelated, skeletal muscle aging and sarcopenia represent distinct concepts in muscle biology and clinical pathology. Skeletal muscle aging is a universal, gradual process characterized by structural and functional changes, such as myofiber type transition, muscle stem cell (MuSC) depletion, and microenvironmental alterations (e.g., immune cell senescence, vascular dysfunction). While contributing to mild fat infiltration and reduced regeneration capacity, these changes may not always lead to significant functional decline [15,18]. In contrast, sarcopenia is a clinically significant syndrome defined by the accelerated loss of muscle mass, strength, and function, resulting in disability and increased mortality. It represents the pathological endpoint of skeletal muscle aging, driven by exacerbated aging mechanisms (e.g., chronic inflammation, hormonal imbalance) and systemic dysregulation (e.g., disrupted liver-muscle crosstalk) [19]. While skeletal muscle aging is a continuum observed in all individuals, sarcopenia is a threshold-based condition requiring specific diagnostic criteria (e.g., grip strength, gait speed) and targeted interventions such as resistance exercise and nutritional support to mitigate adverse outcomes [20]. Understanding this distinction is crucial for developing stratified strategies—preserving muscle health in aging populations and aggressively treating sarcopenia to prevent disability.

1.3. Organ Crosstalk Is Pivotal in Sarcopenia

The onset of sarcopenia is not solely due to skeletal muscle aging. The European Working Group on Sarcopenia in Older People (EWGSOP) classified sarcopenia into “primary” and “secondary” subtypes. The “primary” subtype occurs when aging is the sole evident cause, whereas the “secondary” subtype arises when other underlying causes are present. Secondary sarcopenia can result from: (1) reduced physical activity due to bed rest, a sedentary lifestyle, deconditioning, or zero-gravity conditions; (2) malnutrition due to inadequate energy and/or nutrient intake, absorption dysfunction, gastrointestinal diseases, or medications that induce anorexia; and (3) disease-related conditions, including advanced organ failure, malignancy, inflammatory diseases, or endocrine disorders [21]. These classifications show that sarcopenia develops due to complex interactions among various organs and tissues, especially in cases of malnutrition and disease-related sarcopenia.

Several organs are reported to influence the occurrence of sarcopenia. Liver dysfunction disrupts metabolic regulation and promotes inflammatory cytokine secretion such as TNF-α, contributing to muscle degradation [22]. Conversely, the extent of muscle wasting serves as an independent predictor of prognosis in patients with cirrhosis [23]. Altered adipose tissue function, including the secretion of pro-inflammatory cytokines and lipotoxic metabolites, exacerbates muscle loss, particularly in obesity-related forms of sarcopenia. Neurodegeneration and changes in neuromuscular junctions in frailty-related and cancer-related sarcopenia further impair muscle function and contribute to atrophy [24]. In clinical practice, sarcopenia is commonly classified into additional subtypes

based on specific underlying conditions, such as chronic kidney disease (CKD)-related sarcopenia [25], obesity-related sarcopenia (or sarcopenic obesity) [26], diabetes-related sarcopenia [27], heart failure-related sarcopenia [28], and cancer-related sarcopenia (more often mentioned as cancer cachexia) [29]. Each of these subtypes is driven by complex interactions between the skeletal muscle and other organs. Considering the crucial role of organ crosstalk in both the onset and progression of sarcopenia, this review primarily focuses on the interactions between the liver and skeletal muscle. It explores how liver dysfunction, aging, and chronic liver diseases such as NAFLD, cirrhosis, and hepatocellular carcinoma (HCC) contribute to muscle degradation through various mechanisms, including metabolic integration, the secretion of hepatokines, miRNAs, and metabolites. Additionally, the review discusses the therapeutic potential of targeting liver-muscle crosstalk to prevent or mitigate sarcopenia, considering interventions like exercise, nutrition, and pharmacological strategies. This comprehensive approach is visually summarized in Figure 1, which illustrates the key molecular and cellular pathways involved in liver-muscle interactions and their impact on sarcopenia development.

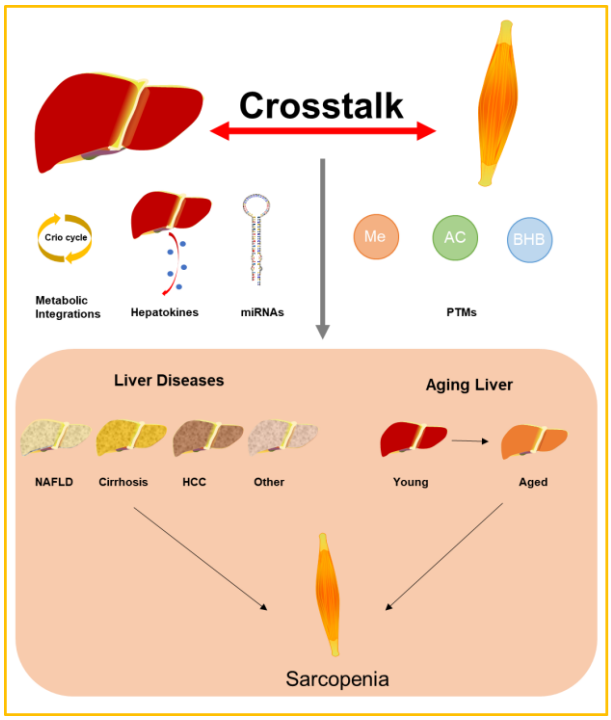

Figure 1. Liver-Muscle Crosstalk and Its Role in Sarcopenia. A schematic representation of the liver-muscle crosstalk, illustrating the key mechanisms involved in sarcopenia. The diagram depicts the metabolic integrations (e.g., Cori cycle), hepatokines, miRNAs, and PTMs that mediate the interaction between the liver and skeletal muscle. It also highlights how liver diseases such as NAFLD, cirrhosis and hepatocellular carcinoma (HCC), along with the effects of aging on liver function, contribute to muscle degradation and the progression of sarcopenia.

1.4. Skeletal Muscle Modulates Hepatic Function

Skeletal muscle and the liver engage in dynamic bidirectional communication through metabolic exchange, endocrine signaling, and energy regulatory networks to orchestrate systemic metabolic homeostasis. During physical activity, lactate generated by muscle glycolysis is transported to the liver via the Cori cycle, where it serves as a precursor for gluconeogenesis. This process not only sustains blood glucose stability but also enhances hepatic metabolic adaptability by modulating substrate flux [30]. Additionally, muscle-derived glutamine supports hepatic detoxification mechanisms by fueling the urea cycle and glutathione synthesis, critical for ammonia clearance and redox balance [31]. As endocrine organs, muscles secrete myokines that exert direct hepatic effects. Interleukin-6 (IL-6) suppresses hepatic glucose production and stimulates fatty acid oxidation via AMP-activated protein kinase (AMPK) activation, thereby ameliorating insulin resistance [32]. Irisin, another exercise-induced myokine, drives adipose tissue browning to lower systemic free fatty acid levels and attenuate hepatic lipotoxicity [32]. Fibroblast growth factor 21 (FGF21), synthesized in muscle during metabolic stress, fine-tunes hepatic glycolipid partitioning and ketogenesis, ensuring efficient energy distribution during fasting or exercise [33].

In energy homeostasis, skeletal muscle functions as a primary glucose reservoir. Reduced muscle insulin sensitivity paradoxically alleviates hepatic gluconeogenic demand, curbing excessive glucose output and mitigating NAFLD progression [34]. Furthermore, muscle-mediated uptake and mitochondrial oxidation of free

fatty acids reduce lipid overflow to the liver, preventing ectopic lipid accumulation [35]. Regular exercise amplifies these benefits by stimulating muscle release of antioxidant enzymes (e.g., superoxide dismutase, SOD) and anti-inflammatory cytokines (e.g., IL-10), which collectively dampen hepatic oxidative stress and inflammatory cascades. Muscle-derived exosomes further contribute to liver repair by shuttling autophagy-inducing miRNAs, enhancing hepatocyte resilience [36]. Clinically, integrative exercise regimens combining resistance and aerobic training synergistically augment muscle mass and hepatic function [37]. Nutritional strategies, such as leucine or omega-3 fatty acid supplementation, bolster muscle protein synthesis while indirectly improving hepatic lipid metabolism [38–41]. A large number of studies have found that sarcopenia is closely related to chronic liver disease, alcoholic liver disease and non-alcoholic liver disease. The risk of NAFLD in patients with sarcopenia is still significantly increased [42]. Sarcopenia seriously affects the development of chronic liver disease due to its imbalance of protein balance [43]. Sarcopenia is significantly associated with the long-term survival of patients with liver cirrhosis [44]. Although the regulatory role of skeletal muscle in liver metabolism has been widely acknowledged, this review centers on the hepatic impact on skeletal muscle aging and sarcopenia. Accordingly, the muscle-to-liver axis is briefly outlined and not explored in depth.

2. Liver Aging and Aging-Related Liver Diseases Contribute to Skeletal Muscle and Sarcopenia

Liver function on skeletal muscle health has long been realized in pathological conditions such as NAFLD, cirrhosis, and HCC. The impact of aging-related liver function decline on sarcopenia has become increasingly recognized over the past decades.

2.1. Liver Diseases Exacerbate Sarcopenia

Liver diseases, including NAFLD, cirrhosis, significantly affect skeletal muscle health. These conditions contribute to muscle wasting and dysfunction, making it essential to understand the mechanisms linking liver diseases with sarcopenia.

2.1.1. NAFLD

NAFLD, characterized by excess fat accumulation in the liver, progresses through stages like nonalcoholic steatohepatitis (NASH) and metabolic-associated steatohepatitis (MASH) [45]. Research has consistently shown a strong association between NAFLD, NASH, and sarcopenia. Notably, the prevalence of sarcopenia tends to increase with the progression of liver disease. For example, a study conducted in a cohort of 75 American adults with NASH found that the prevalence of sarcopenia increased as liver disease progressed—from controls to NASH and subsequently to NASH cirrhosis. The study also reported that sarcopenia was more prevalent in NASH patients compared to those with non-alcoholic fatty liver (NAFL) or healthy controls [46]. Similarly, a large-scale cross-sectional analysis from the Korean National Health and Nutrition Examination Survey (KNHANES 2008-2011), which included 15,132 Korean adults, demonstrated that sarcopenia was independently associated with NAFLD, with individuals having a 2.3 to 3.3-fold increased risk of developing NAFLD, regardless of obesity or insulin resistance. This study further emphasized that sarcopenia was linked to more advanced liver fibrosis [47]. Another study of 2761 Korean adults also reported that sarcopenia was associated with significant liver fibrosis independent of obesity and insulin resistance, reinforcing the association between low muscle mass and advanced liver disease [47]. A separate study in 225 Italian adults further illustrated that sarcopenia prevalence increased with the severity of liver fibrosis in NAFLD patients. In individuals without significant fibrosis, 22% had sarcopenia, whereas 67% of patients with advanced fibrosis (≥F3) were found to have sarcopenia. This study confirmed that the presence of sarcopenia was independently associated with a two-fold increased risk of liver fibrosis, highlighting a potential association, but whether there is causality remain to be determined [48]. A study in 3602 Chinese adults showed that the skeletal muscle index decreased progressively with the increasing severity of hepatic steatosis and fibrosis, demonstrating that reduced muscle mass is independently associated with more advanced NAFLD in a Chinese cohort, although causality was not established [49]. A bidirectional Mendelian randomization study provides evidence for a causal relationship between NAFLD and sarcopenia. Genetic variants associated with increased muscle mass are linked to a reduced risk of developing NAFLD, while genetic predisposition to NAFLD is, in turn, associated with reduced muscle mass, supporting a causal effect in both directions [50]. Collectively, these studies consistently highlight the increasing risk of sarcopenia as liver disease progresses.

In animal models, robust evidence supports a causal link between NAFLD/NASH and sarcopenia. For instance, dietary interventions using the American lifestyle-induced obesity syndrome (ALIOS) diet in rodents induce hepatic steatosis, inflammation, and fibrosis. Moreover, these interventions cause significant muscle atrophy [51]. Mechanistic investigations in both human and animal studies reveal that overlapping pathways

contribute to the progression of both liver disease and sarcopenia. These pathways include insulin resistance, which enhances lipolysis and free fatty acid flux, leading to hepatic fat accumulation and muscle protein breakdown. Chronic inflammation with elevated cytokines such as TNF-α and IL-6 also plays a role. Impaired secretion of beneficial myokines and hormonal disturbances, including reduced growth hormone/IGF-1 signaling and vitamin D deficiency, further contribute to the progression. Oxidative stress and mitochondrial dysfunction are additional factors. Together, these factors establish a direct causal link between NAFLD/NASH and sarcopenia [45].

2.1.2. Cirrhosis

While NAFLD represents an early-stage liver disease closely associated with sarcopenia, the progression to cirrhosis exacerbates these effects, leading to more severe muscle wasting and dysfunction. Cirrhosis represents the final common pathway of chronic liver diseases and is characterized by diffuse hepatic fibrosis and nodular regeneration, which ultimately leads to portal hypertension and complications such as ascites, variceal bleeding, and hepatic encephalopathy [52,53]. A large body of clinical evidence shows that sarcopenia is highly prevalent among cirrhotic patients, with reported rates ranging from 40% to 70% in various cohorts [54]. A recent meta-analysis demonstrated that sarcopenia is highly prevalent in patients with cirrhosis, with an overall pooled prevalence of 37.5% (95% CI: 32.4–42.8%). Sarcopenia was independently associated with a significantly increased risk of mortality, with an adjusted hazard ratio (aHR) of 2.30 (95% CI: 2.01–2.63), and this association remained consistent across subgroups stratified by sex, liver disease etiology, and severity of hepatic dysfunction. The study emphasized the importance of recognizing sarcopenia as a critical prognostic factor in cirrhosis management [44].

Animal models have also provided substantial support for the link between liver cirrhosis and muscle wasting. In rodent models using bile duct ligation (BDL) or alcohol-induced liver injury, decreased protein synthesis, increased proteolysis, and elevated markers of inflammation were also observed, leading to significant muscle atrophy [55]. The underlying mechanisms linking cirrhosis to sarcopenia are multifactorial. One key factor is the imbalance in protein metabolism: cirrhosis is associated with impaired hepatic protein synthesis and accelerated muscle protein breakdown, a phenomenon partly driven by hyperammonemia and malnutrition [56]. Chronic systemic inflammation, characterized by elevated cytokines such as TNF-α and IL-6, further contributes to proteolysis and disrupts muscle regeneration [57]. Endocrine dysregulation also plays a role, with increased expression of myostatin—a potent inhibitor of muscle growth—observed in cirrhotic patients with sarcopenia [58]. Moreover, mitochondrial dysfunction, impaired energy metabolism, and disturbances in the gut–liver–muscle axis (including altered gut microbiota and increased endotoxin levels) further exacerbate muscle wasting [43].

Several interventional studies in both human and animal models provide evidence that targeted approaches can mitigate sarcopenia. For instance, resistance training and nutritional supplementation—such as branched-chain amino acids—have been shown to improve muscle strength and quality in cirrhotic patients, although their effects on clinical endpoints vary [59]. Furthermore, procedures like transjugular intrahepatic portosystemic shunt (TIPSS) not only alleviate portal hypertension but have also been associated with improvements in muscle mass, underscoring the dynamic interplay between liver function and muscle health [60].

2.1.3. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and often arises in the context of chronic liver disease, such as cirrhosis triggered by hepatitis B or C, alcoholic liver disease, or nonalcoholic fatty liver disease. Early-stage HCC typically remains asymptomatic, and many patients receive their diagnosis when the tumor is already advanced, limiting therapeutic options and resulting in generally poor outcomes. Despite progress made in surgical resection, transcatheter arterial chemoembolization, targeted therapies, and immunotherapies, HCC-related mortality remains high in most regions worldwide [61,62].

Population-based studies have investigated the association between sarcopenia and HCC outcomes. A systematic review and meta-analysis of 13 studies involving over 3000 HCC patients showed that sarcopenia significantly correlates with reduced overall survival and higher recurrence rates compared to non-sarcopenic individuals [63]. Likewise, single-center retrospective data have demonstrated that sarcopenic HCC patients undergoing transarterial chemoembolization experience shorter survival times [64], while advanced HCC patients with sarcopenia receiving immunotherapy also show worse prognoses [62]. Taken together, sarcopenia is viewed as a critical indicator of poor clinical outcomes in HCC management.

Emerging evidence suggests a potential causal relationship between lower muscle mass and HCC risk. A Mendelian randomization study of European data indicated that genetically predicted lower skeletal muscle levels may contribute to heightened HCC incidence, independent of reverse causality [65]. Additionally, animal

investigations have shed light on the biological interplay between HCC and muscle wasting. In mouse models, pro-inflammatory signals from the tumor environment accelerate both muscle and adipose tissue depletion [66]. Dietary interventions that induce NASH and HCC in rodents have also illustrated parallel declines in skeletal muscle, reflecting the metabolic disturbances and chronic inflammation frequently observed in human disease [51].

The biological mechanisms linking HCC and sarcopenia involve persistent inflammation, hormonal and growth factor imbalances, as well as altered autophagy and proteolysis. Chronic inflammatory mediators, including IL-6 and TNF-α, can upregulate pathways that degrade muscle proteins. Other evidence suggests that hyperammonemia and mTOR pathway dysregulation may further exacerbate muscle loss, particularly when nutritional intake is insufficient, leading to cirrhosis [56,57]. Ultimately, these multifactorial processes not only highlight HCC's capacity to promote muscle wasting, but also underscore sarcopenia as an important prognostic marker in HCC management. Further clarifying the interplay between them will be crucial for developing effective interventions and improving outcomes in patients at risk of or already experiencing muscle loss.

2.1.4. Other Liver Diseases

A range of chronic liver diseases and related conditions besides NAFLD, cirrhosis, and HCC can also influence skeletal muscle health and exacerbate sarcopenia. Although each condition has distinct pathophysiological features, they share common pathways—such as malnutrition, chronic inflammation, and hormonal dysregulation—that compromise muscle mass and strength.

Alcoholic Liver Disease (ALD): Excessive alcohol intake induces hepatocellular damage and fibrosis, potentially leading to cirrhosis. During ALD progression, nutritional deficiencies, particularly in protein and micronutrients, and oxidative stress are frequent, heightening muscle protein catabolism and reducing muscle regeneration [67]. Several cohorts have reported that sarcopenia prevalence aligns with the severity of ALD: advanced stages often show higher rates of muscle wasting, worse functional performance, and poorer clinical outcomes. Nutritional support, alongside strict abstinence from alcohol, has been shown to improve muscle parameters in ALD patients [68].

Cholestatic Liver Diseases (PSC and PBC): Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are immune-mediated, cholestatic disorders characterized by chronic inflammation and fibrotic changes in the bile ducts. Bile salt retention impairs absorption of fat-soluble vitamins (including vitamin D), potentially disrupting both skeletal and muscle metabolism. Malabsorption and persistent inflammation further exacerbate proteolysis and hinder myocyte repair [52]. Clinical data have revealed that PSC and PBC patients with advanced disease frequently exhibit diminished muscle mass and strength, highlighting the importance of monitoring for sarcopenia in this population [69].

Autoimmune Hepatitis (AIH): AIH arises from aberrant immune-mediated targeting of hepatocytes, resulting in sustained liver inflammation and, in many cases, progression to cirrhosis [70]. In AIH, elevated circulating pro-inflammatory cytokines (e.g., TNF-α, IL-6) and potential nutritional insufficiencies can drive muscle atrophy. In pediatric patients with AIH, sarcopenia is highly prevalent. This condition is closely associated with increased visceral fat and negatively influences parent-perceived general health [71].

Liver Transplantation (LT): Many patients with end-stage liver disease (ESLD) secondary to ALD, PSC/PBC, AIH, or other etiologies undergo liver transplantation. Pre-transplant sarcopenia has consistently been identified as a predictor of increased postoperative complications, prolonged hospital stays, and reduced survival rates [72]. After transplantation, some patients experience partial recovery of muscle mass, yet factors such as chronic immunosuppression, persistent malnutrition, or lack of structured rehabilitation can maintain or worsen muscle wasting. Targeted physical therapy regimens and individualized nutritional strategies have shown promise in improving musculoskeletal outcomes post-transplant, underscoring the dynamic interplay between restored hepatic function and skeletal muscle health [73].

In summary, various liver diseases, including NAFLD/NASH, cirrhosis, HCC, and others, contribute to the development and progression of sarcopenia through mechanisms like chronic inflammation, nutritional deficiencies, endocrine imbalances, and mitochondrial dysfunction. Understanding these liver-muscle interactions is essential for early risk identification and treatment planning, including nutritional support, exercise programs, and potential pharmacological interventions. Such an integrated approach can significantly improve patient outcomes and quality of life. It is of note that skeletal muscle and liver engage in bidirectional communication, which is disrupted in various liver diseases. While aforementioned liver diseases contribute to the development of sarcopenia, skeletal muscle also significantly impacts liver function. Muscle health influences liver metabolism, including lipid and glucose homeostasis and insulin sensitivity. The risk of NAFLD in patients with sarcopenia is still significantly increased [42]. Sarcopenia seriously affects the development of chronic liver disease due to its

imbalance of protein balance [43]. Sarcopenia is significantly associated with the long-term survival of patients with liver cirrhosis [44]. However, this review primarily focuses on the impact of liver dysfunction on skeletal muscle health, and while the role of skeletal muscle in regulating liver function is important, it will not be explored in detail here.

2.2. Aging Liver Drives Liver Pathologies and Muscle Wasting

While it is well-established that chronic liver diseases can directly lead to sarcopenia (secondary sarcopenia), as mentioned above, the impact of aging—often considered a suboptimal health state or pre-disease condition—on sarcopenia remains less clear. However, accumulating evidence suggests that liver aging is directly associated with sarcopenia. For example, our recent study demonstrated that the expression of key enzymes involved in ketone body production, especially HMGCS2, in the liver is positively correlated with skeletal muscle mass, while the capacity for ketone body synthesis declines with age [74]. This finding indicates that, even in the absence of overt liver disease, the suboptimal state of the aging liver can be sufficient to induce muscle mass loss. Thus, liver aging not only increases the risk of chronic liver diseases but also directly contributes to muscle atrophy, with some pathological processes potentially occurring concurrently with chronic liver disease.

2.2.1. Liver Aging as a Risk Factor for Chronic Liver Pathologies

Based on the consensus statement by the Aging Biomarker Consortium, liver aging can be defined by a multidimensional framework that includes: (1) structural and cellular remodeling, where despite continuous hepatocyte renewal, aging is accompanied by reduced liver volume, diminished regenerative capacity, increased polyploidy, and alterations in sinusoidal architecture; (2) functional decline, as evidenced by impaired metabolic processes such as cholesterol and drug metabolism, decreased protein synthesis, and lower detoxification ability; and (3) increased inflammatory and fibrotic responses, which elevate the risk for chronic liver diseases like NAFLD, cirrhosis, and hepatocellular carcinoma while also contributing to systemic metabolic disturbances [75]. It emphasized that the evaluation should extend beyond merely the liver's regenerative capacity—as illustrated by a retrospective radiocarbon (14C) birth-dating study demonstrating that hepatocytes maintain an average age of about three years regardless of the donor's age [76]—to also include other critical aspects, particularly metabolic function.

Several clinical studies have demonstrated that aging significantly impacts the progression and outcomes of chronic liver disease. Early clinical data indicated that familial diabetes and aging contribute to glucose intolerance and diabetes in chronic liver disease patients, highlighting metabolic disturbances linked to age [77]. In patients with non-B, non-C, and non-alcoholic liver diseases, increased hepatocellular aging—measured as an increased relative nuclear size—has been identified as an independent risk factor for hepatocellular carcinoma, particularly in individuals over 50 [78]. Moreover, the rise in acute-on-chronic liver failure among NAFLD patients, especially those aged 60 and above, underscores the severe clinical impact of aging, with these patients experiencing higher waitlist mortality and poorer outcomes [79]. Clinical findings such as telomere dysfunction further reinforce the link between aging and adverse liver disease outcomes [80].

Studies on animal models have provided valuable insights into how aging exacerbates liver pathology. In rodent models of advanced chronic liver disease, aged animals develop more severe portal hypertension and liver fibrosis, which are associated with marked deregulations in hepatocyte function, capillarization of liver sinusoidal endothelial cells, and overactivation of hepatic stellate cells [81]. Additionally, a mouse liver cancer model induced by high-fat diets and nano-nitrosamines demonstrated that aging accelerates the progression from fatty liver disease to hepatocellular carcinoma. This model revealed that age-related changes in the liver's cellular and microvascular architecture create a tumor-promoting microenvironment [82].

Several key mechanisms explain the interplay between aging and chronic liver disease. Cellular senescence, while initially acting as a safeguard by arresting the proliferation of damaged cells, eventually creates a pro-inflammatory and fibrotic environment that can promote malignant transformation [83]. Disruption of the AMPK signaling pathway leads to mTOR activation. This can contribute to energy metabolism disorders, chronic inflammation, and hypoxia, thereby accelerating the transition from fatty liver to cancer [82]. Aging induces endothelial dysfunction in liver sinusoidal endothelial cells. This is marked by the loss of fenestrations, increased oxidative stress, and reduced nitric oxide production. These changes impair hepatic blood flow. They also promote the activation of hepatic stellate cells, which further drive liver fibrosis [84]. Telomere dysfunction also plays a crucial role by linking genomic instability with cellular senescence in chronic liver disease [80]. These shared aging mechanisms suggest that liver aging may also contribute to skeletal muscle aging and sarcopenia.

2.2.2. Direct Effects of Liver Aging on Skeletal Muscle Mass and Function

Although it is plausible to hypothesize that liver aging contributes to skeletal muscle aging and may ultimately lead to sarcopenia, research on how liver aging affects muscle function is relatively limited, particularly in the absence of overt liver disease. Based on a comprehensive analysis using plasma proteomic profiles and a bagged LASSO regression approach to model organ-specific biological age, researchers discovered that the aging processes across different tissues are moderately correlated, with an average pearson correlation coefficient of about 0.29. Notably, the liver and skeletal muscle showed stronger association with this average level, suggesting that these two organs may share more common underlying mechanisms or be similarly influenced by systemic factors during aging [85]. Based on data from the National Health and Nutrition Examination Survey (NHANES) conducted between 2017 and 2018, including 1756 adult participants, a significant negative association between the sarcopenia index and abnormal liver function was established. The adjusted odds ratio (OR) was 0.73, with a stronger association observed in females (OR = 0.61) compared to males (OR = 0.80), indicating that abnormal liver function is more closely linked to sarcopenia in women [86].

Liver aging is a multifaceted process that involve structural and functional changes, significantly affecting its ability to regulate metabolism and detoxify harmful substances. One of the key functional declines observed with liver aging is the decrease in regenerative capacity, which impairs the liver's ability to repair itself and maintain its critical functions. Structural changes, such as reduced liver size and hepatic blood flow, further exacerbate this decline [87,88]. This reduction in regenerative capacity is accompanied by a diminished ability to regulate glucose and lipid metabolism, contributing to systemic metabolic dysfunction [89]. These metabolic changes—impaired glucose regulation, insulin resistance, and altered lipid metabolism—contribute to skeletal muscle aging and may accelerate the development of sarcopenia in vulnerable individuals [90]. For instance, the liver's inability to regulate glucose and lipid availability leads to muscle energy deficits, particularly during physical activity [91]. The increased accumulation of intramuscular fat further exacerbates insulin resistance, impairing muscle function and accelerating muscle wasting [92].

Liver aging biomarkers such as IGF-1, albumin, and certain inflammatory markers such as CRP have been consistently linked to sarcopenia in older adults. IGF-1, synthesized predominantly by the liver, plays a pivotal role in muscle protein synthesis and regeneration. Although mechanistic and preclinical studies have established its causal role in promoting muscle mass, lower circulating levels in humans are mostly correlated with muscle loss, and the extent of causality in clinical settings remains to be fully elucidated [93]. Likewise, albumin is a key indicator of hepatic synthetic function and nutritional status; studies have shown that reduced albumin levels correlate with poorer muscle outcomes and increased frailty risk, though causality remains to be confirmed [94]. Inflammatory markers, particularly CRP, are also produced (or modulated) by the liver; elevated CRP reflects a state of chronic inflammation that exacerbates muscle protein breakdown and insulin resistance, thereby potentially contributing to sarcopenia through associative pathways [95]. Other novel biomarkers, including PCSK9, fibrinogen, and liver enzymes (ALT, ALP, GGT), may indicate broader aspects of hepatic aging or metabolic dysregulation, and the evidence linking them specifically to sarcopenia is still emerging. For instance, while PCSK9 is primarily studied for its role in lipid metabolism and cardiovascular risk, recent findings suggest that its inhibition is associated with reduced muscle mass, potentially increasing the risk of sarcopenia [96]. While fibrinogen is primarily associated with coagulation processes and cardiovascular events, elevated fibrinogen levels are associated with sarcopenia in hospitalized elderly patients, suggesting its potential as a biomarker for sarcopenia risk [97].

In summary, liver and skeletal muscle aging share key features, such as chronic inflammation and disrupted metabolic function, exacerbating conditions like sarcopenia. The liver's decline not only contributes to chronic liver diseases but also directly influences muscle health. Understanding the mediators involved in liver-muscle crosstalk is essential for addressing sarcopenia (Figure 2 and Table 1).

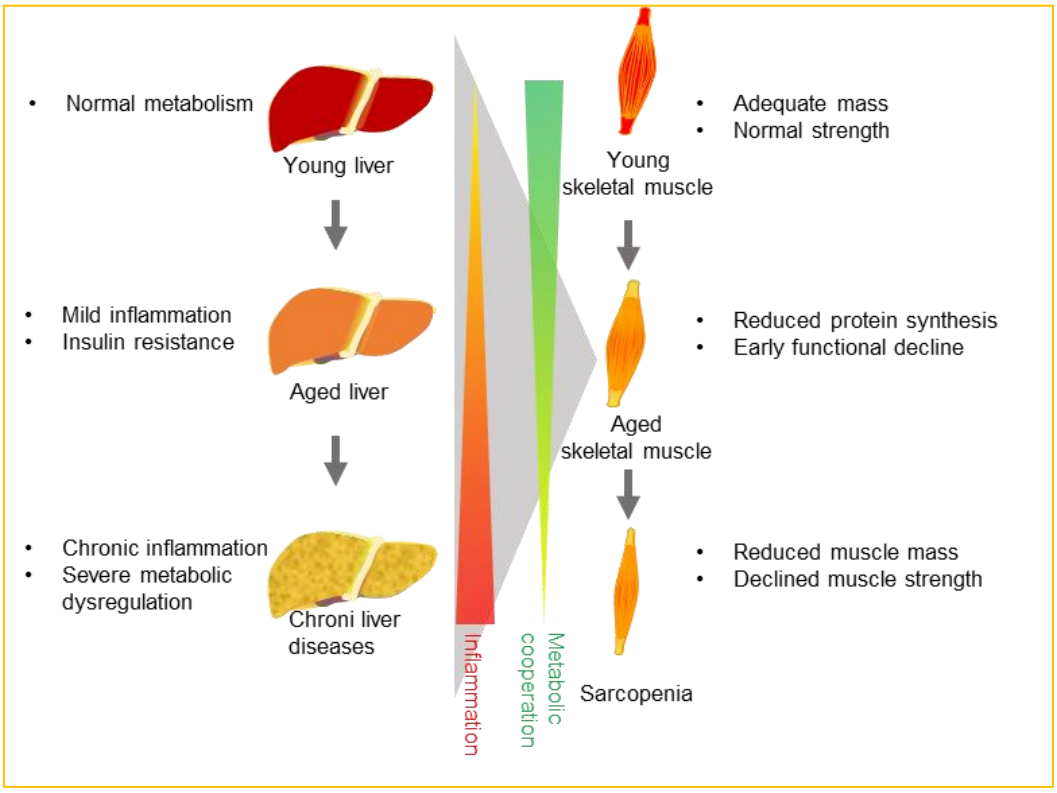

Figure 2. Parallel progression of the liver and skeletal muscle from young, healthy states to advanced age and diseases. Initially, both organs function with minimal inflammation and robust metabolic coordination, but during aging, chronic inflammation intensifies while metabolic regulation deteriorates. This reciprocal decline fosters a vicious cycle that ultimately contributes to sarcopenia and other age-related pathologies.

Table 1. The incidence of sarcopenia in liver diseases and its impact on muscle function.

Liver Diseases	Probability of Sarcopenia	Mechanisms Related to Sarcopenia
NAFLD	↑ (2.3–3.3 fold risk)	Insulin resistance [45]; Changes in cytokines [51]; Chronic inflammation [46]; Oxidative stress [51]; Inflammation [45,47,51]
NASH	↑	Inflammation [45]; Mitochondrial dysfunction [45]
Cirrhosis	↑ (40–70%)	Chronic inflammation [46]; Mitochondrial dysfunction [58]; Endocrine Dysfunction [57]; Dysregulation of proteostasis [43,55,58]
Hepatocellular Carcinoma	↑	Chronic Inflammation [65]; Dysregulation of autophagy and proteostasis [56,57]
Alcoholic Liver Disease (ALD)	↑	Protein and micronutrient deficiencies [67,68]; Oxidative stress [67]
Cholestatic Liver Diseases (PSC and PBC)	↑	Malabsorption [69]; Chronic inflammation [70]; Vitamin D deficiency [69,70]
Autoimmune Hepatitis (AIH)	↑	Chronic inflammation [70,71]
Liver Transplantation (LT)	↑	Chronic immunosuppression [72]; Persistent malnutrition [72,73]

3. Mediators for the Interactions between the Liver and Skeletal Muscle

The liver and skeletal muscle are both essential organs for maintaining metabolic homeostasis, and their interactions influence multiple aspects of human health. The liver serves as the body's metabolic hub, regulating

blood glucose levels, storing and releasing glycogen, synthesizing proteins, and breaking down fats and toxins. The liver is also responsible for maintaining systemic energy balance, coordinating nutrient sensing pathways that control the allocation of energy resources to various organs [98]. On the other hand, skeletal muscle is the largest organ in the body and is responsible for generating movement and maintaining body posture. Muscle tissue accounts for a significant portion of the body's energy expenditure, particularly during physical activity [99]. In addition to its role in locomotion, skeletal muscle is also a major source of protein synthesis, contributing to the maintenance of muscle mass and function [91].

Despite their distinct roles, the liver and skeletal muscle are deeply interconnected through a variety of metabolic, hormonal, and inflammatory signaling pathways. Their interactions generally occur through the following mechanisms: (1) Metabolic integration; (2) organ-secreted factors, including hepatokines and myokines; (3) MicroRNAs and microvesicles (Figure 3 and Table 2).

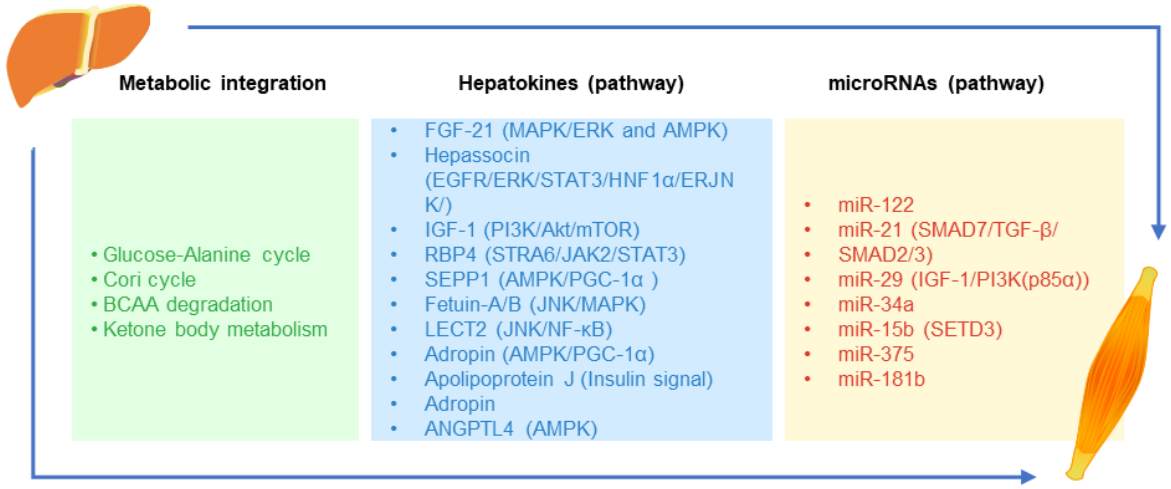

Figure 3. Schematic depiction of key mechanisms in liver–muscle crosstalk. The green text indicates principal metabolic pathways shared by the liver and skeletal muscle (glucose–alanine cycle, Cori cycle, branched-chain amino acid degradation, and ketone body metabolism). The blue text lists liver-derived proteins and growth factors (IGF-1, RBP4, SEPP1, Fetuin-A/B, FGF-21, Adropin, Apolipoprotein J, ANGPTL4, Hepassocin, and LECT2) that modulate muscle metabolism and function. The red text highlights liver-derived microRNAs (miR-122, miR-21, miR-29, miR-34a, miR-15b, miR-375, miR-181b) implicated in muscle atrophy and sarcopenia.

Table 2. Mediators of liver-muscle crosstalk in sarcopenia.

Molecule	Type	Involved Pathway/Mechanism	Role in Sarcopenia
Adropin	Hepatokine	Regulates energy homeostasis and lipid metabolism [100].	Low levels correlate with muscle weakness and metabolic diseases [101].
ANGPTL4	Hepatokine	Regulates lipid metabolism, inhibits lipoprotein lipase activity [102].	Elevated levels may contribute to muscle atrophy via lipid metabolism disruption [103].
Fetuin-A	Hepatokine	It interferes with the insulin receptor and activates TLR4 [104]. Impair insulin signaling and activate inflammatory pathways [105].	Promotes insulin resistance and inflammation [104], may exacerbate sarcopenia.
Fetuin-B	Hepatokine	Impair insulin signaling and promote insulin resistance [106].	Contributes to insulin resistance and glucose intolerance [107].
FGF-21	Hepatokine	Promotes fatty acid oxidation, mitochondrial biogenesis, and insulin sensitivity via FGFR1 and β-Klotho [108].	Elevated levels lead to muscle wasting by enhancing mitophagy during fasting [109]; Protective for muscle in obese mice [110].
Hepassocin	Hepatokine	Adversely influence metabolic regulation, and promote insulin resistance [111,112].	Impair insulin signaling, MAY contribute to muscle atrophy in metabolic diseases.
LECT2	Hepatokine	Involved in insulin resistance and inflammation regulation via NF-kB activation [113,114].	Contributes to muscle atrophy and sarcopenia via systemic inflammation [113,114].

RBP4	Hepatokine	Activate STRA6-JAK2/3 [115].	promote denervation-induced muscle atrophy[115]; elevated serum RBP4 levels in sarcopenic patients [116].
Selenoprotein P	Hepatokine	impair insulin signaling [117]; blunte AMPK and PGC-1α [118]; inhibition of skeletal muscle differentiation [119].	"exercise-resistant" phenotype [118]; protective for its deficiency in immobilizeation-induced muscle atrophy model [120].
Apolipoprotein J	Hepatokine	Activate LRP2 to improve insulin sensitivity [121].	improve muscle insulin sensitivity [121].
IGF-1	Hepatokine	Regulates muscle growth, regeneration, and repair via Akt/Pkb [122].	Contributes to muscle regeneration, decline with aging leads to sarcopenia [123].
miR-122	miRNA	Targets SCD-1, SREBP1, IGF-1R, SIRT1; are involved in NAFLD, insulin resistance, hepatic fibrosis [124,125].	Promotes skeletal muscle proteolysis in cancer cachexia; plays a role in muscle wasting [126].
miR-21	miRNA	Targets SMAD7, TGF-β/SMAD2/3 pathway; activates muscle atrophy and fibrosis [127,128].	Promotes muscle atrophy and fibrosis; involved in sarcopenia development [127,128].
miR-29b	miRNA	Targets IGF-1, PI3K(p85); contributes to muscle atrophy [129].	Contributes to skeletal muscle atrophy through inhibition of anabolic signaling [129].
miR-375	miRNA	Downregulated in cachexia; correlates with body weight loss severity [130].	Potential role in cachexia-induced muscle wasting [130].
miR-181b	miRNA	Upregulated in cancer cachexia; linked to tissue wasting [130].	Contributes to muscle wasting in cancer cachexia [130].
miR-33	miRNA	Regulates muscle metabolism and function [125].	Regulates muscle metabolism, potentially affecting sarcopenia [125].
miR-34a	miRNA	Increases frailty and diabetes; contributes to sarcopenia [131].	May contribute to muscle loss in frailty and diabetes [131].
miR-15b	miRNA	Targets SETD3; represses muscle cell differentiation [132].	Inhibits muscle regeneration, contributing to sarcopenia [132].
miR-181a	miRNA	It regulates muscle atrophy pathways and is linked to various types of muscle wasting [130].	Linked to various types of muscle wasting and sarcopenia [130].
Beta-hydroxybutyrate (BHB)	Metabolite	Produced by the liver during fatty acid oxidation, regulates histone modifications (Kbhb), promotes muscle rejuvenation by enhancing mitochondrial function [74].	Promotes muscle rejuvenation by improving mitochondrial function, and helps reverse sarcopenia [74].
Ammonia	Metabolite	Increased levels contribute to muscle wasting, particularly in cirrhosis-induced sarcopenia [133].	Elevated levels contribute to muscle wasting in cirrhosis-induced sarcopenia [133].
Acetoacetate	Metabolite	Produced alongside BHB, contributes to muscle function but not as potent as BHB [134].	Less potent than BHB in muscle rejuvenation but plays a role in energy homeostasis [134].
Isobutyrylation	Metabolite	Involved in BCAA metabolism, generated from leucine catabolism, impacts muscle function [135].	Influences muscle function and metabolism, linked to sarcopenia through BCAA metabolism [135].
2hydroxyisobutyrylation	Metabolite	Involved in BCAA metabolism, generated from leucine catabolism, impacts muscle function [136].	Similar to isobutyrylation, affects muscle function and sarcopenia development through metabolic intermediates [136].
Glutathione (GSH)	Metabolite	Produced by the liver, protects proteins from oxidative damage, modulates function during oxidative stress, and affects muscle function under stress [137].	Participates in muscle redox signaling, and helps protect against muscle function loss due to oxidative stress [137].

S-adenosylmethionine (SAM)	Metabolite	Changes during aging, influences methylation processes and muscle repair [138].	Impairs muscle regeneration, low levels in aging contribute to sarcopenia [138].
Lactate	Metabolite	Produced during anaerobic exercise, modulates hepatic function, regulates liver-muscle interactions in the Cori cycle [139].	It is a key regulator in liver-muscle coordination and impacts skeletal muscle during anaerobic exercise [139].

3.1. Metabolic Integrations

The liver and skeletal muscle work together to maintain energy balance. During physical activity or fasting, the liver releases glucose, fatty acids, and ketone bodies that fuel muscle contraction, while also producing essential nutrients like amino acids for muscle protein synthesis. Conversely, impaired liver function (due to disease or aging) can weaken muscle responsiveness and lead to wasting. What is more important is that several metabolic processes depend on the collaboration of both organs to manage key substrates such as glucose, amino acids, and fatty acids. Some critical metabolic pathways involving the liver and skeletal muscle include the glucose-alanine cycle (coupled with ammonia metabolism and the urea cycle), Cori cycle, branched-chain amino acid (BCAA) metabolism.

The glucose-alanine cycle plays a crucial role in maintaining glucose homeostasis during exercise and periods of fasting [140]. Through the glucose-alanine cycle, pyruvate from muscle glycolysis and ammonia from protein breakdown combine to form L-alanine, which is transported to the liver. In the liver, alanine is converted into pyruvate and glutamate; the glutamate yields urea, while the pyruvate is used for gluconeogenesis. This cycle detoxifies ammonia, generates ATP, and is essential for maintaining glucose levels and sustaining muscle energy, particularly during increased activity or carbohydrate scarcity. Although the glucose–alanine cycle was discovered in the 1970s, recent metabolomics research has revealed an enrichment of its metabolites in many age-related diseases. Trans-omic analysis of liver and skeletal muscle reveals that glucose-ananine cycle is involved in obesity-associated dysregulation of inter-organ metabolic cooperation [141]. A two-month ketogenic diet in middle-aged mice significantly alters metabolites in the glucose-alanine cycle across muscle, serum, and liver, suggesting that modulation of this cycle may contribute to the diet's systemic anti-aging effects including mitigating possible sarcopenia in senior individuals [142]. In diabetic kidney disease, especially in patients with moderately increased albuminuria, disturbances in the glucose–alanine cycle can be found, though whether it will contribute to muscle wasting is still unknown [143]. Mechanistically, a recent study found that the strength of the glucose–alanine cycle directly determines hepatic mitochondrial oxidation efficiency, as reduced alanine turnover during prolonged fasting leads to significantly diminished oxidation rates [144,145]. Research focusing on skeletal muscle is limited. However, during prolonged running, calf muscles deplete glycogen more than thigh muscles. The soleus also uses intramyocellular lipids. During recovery, glycogen redistributes from nonexercising to exercising muscles via the glucose–lactate (Cori cycle) and glucose–alanine cycles [146]. These studies suggest that the glucose–alanine cycle plays a crucial role in liver–skeletal muscle crosstalk under both physiological and pathological conditions. The glucose-alanine cycle is linked to changes in ammonia metabolism, causing increased blood ammonia levels, which contribute to muscle wasting, particularly in cirrhosis-induced sarcopenia [133]. However, the impact of other metabolic intermediates on skeletal muscle atrophy and sarcopenia remains to be further explored.

The Cori cycle, also known as the lactate shuttle, was originally described in 1929, and is a hepatic gluconeogenic pathway that uses lactate—produced by non-hepatocyte cells such as skeletal muscle and erythrocytes via glycolysis during anaerobic exercise—as its substrate. This lactate is transported to the liver, where it is converted back into glucose through gluconeogenesis and then released into circulation to be used by muscle cells for further energy production. This process not only provides an efficient means to recycle lactate but also prevents its accumulation in muscles, thereby reducing fatigue [147]. The Cori cycle plays a role in liver-muscle communication and the regulation of whole-body metabolism. Deletion of the mitochondrial pyruvate carrier (MPC) in skeletal muscle leads to increased conversion of pyruvate to lactate, enhancing the Cori cycle and elevating whole-body energy expenditure [148]. Several skeletal muscle or liver-related disease condition or animal model are involved in the altered Cori cycle. In cancer related sarcopenia, known as cachexia, the Cori cycle becomes more active, leading to increased energy expenditure. This cycle involves the conversion of lactate produced by tumors and muscles into glucose in the liver, consuming significant energy. This process contributes to the weight loss observed in cachexia patients [149]. Primary nonfunction in fatty liver allografts results from a dysfunctional Cori cycle—marked by complete loss of the lactate transporter SLC16A1—which impairs lactate reutilization for gluconeogenesis, leading to hyperlactatemia, lactic acidosis, and increased susceptibility to ischemia/reperfusion injury [150]. Under type 1 diabetes conditions, excess L-lactate disrupts the normal Cori

cycle, and this disruption contributes to hepatic oxidative stress and apoptosis. FGF21 intervenes by upregulating MCT2 protein translation, thereby enhancing L-lactate uptake and stabilizing the Cori cycle, which in turn mitigates liver damage [151]. Muscle-specific deletion of Arid5b in mice led to increased glucose uptake in skeletal muscle, where it was converted into lactate through glycolysis and released into the bloodstream, thereby fueling the Cori cycle and linking the metabolic activities of the liver and skeletal muscle [152]. In addition to serving as an energy substrate, lactate functions as a signaling molecule through lactylation modifications—a mechanism that is crucial for liver-muscle crosstalk. Lactate treatment increased H3K9 lactylation in myoblasts during differentiation, resulting in upregulation of Neu2 levels and inhibition of H3K9 lactylation or Neu2 blocked lactate-induced myogenesis [153]. Although some studies have already uncovered the relationship between the Cori cycle and skeletal muscle function and sarcopenia, further detailed research—especially into its molecular mechanisms—is warranted.

In fact, the glucose-alanine cycle and the Cori cycle mentioned above are relatively simple because they involve fewer metabolites. In contrast, another key metabolic process involving both the liver and skeletal muscle is the metabolism of branched-chain amino acids (BCAAs), including leucine, isoleucine, and valine. They play much broader roles in metabolic regulation. The initial step in the breakdown of BCAAs occurs in the skeletal muscle, because the liver lacks the corresponding transaminases for BCAAs; in skeletal muscle, they are transaminated into keto acids that can be used for energy production [154]. These keto acids are then transported to the liver for further metabolism or are further metabolized in the skeletal muscle. These keto acids are metabolized into glucose via propionyl-CoA (to succinyl-CoA) or into fatty acids and ketone bodies (via acetyl-CoA or acetoacetyl-CoA). BCAA metabolism is particularly important during exercise and fasting, as it provides muscles with an alternative energy source to glucose [155]. Assay of plasma amino acid among young, elderly and centenarian subjects revealed a decreased concentration of BCAAs, especially leucine and valine [156]. A population-based cohort study of over 100,000 UK adults demonstrated that higher circulating BCAA levels—especially valine—are associated with increased muscle mass and strength, with muscle mass mediating the relationship and reducing sarcopenia risk [157]. Supplementation with branched-chain amino acids (BCAAs) and their corresponding branched-chain α-keto acids has been demonstrated to improve sarcopenia and is now incorporated into clinical guidelines [158]. The mechanisms underlying these benefits appear to be multifaceted. On one hand, BCAAs provide essential substrates for muscle protein synthesis, thereby directly supporting anabolic processes. BCAAs make up approximately 35–40% of the dietary essential amino acids incorporated into body proteins and account for about 14–18% of the total amino acids in muscle proteins [159]. BCAAs and their metabolites act as signaling molecules. Leucine binds to leucyl-tRNA synthetase (LRS), activating Rag GTPases and promoting mTORC1 localization to the lysosomal surface for activation [160]. Additionally, leucine binds to Sestrin2, relieving its inhibition of mTORC1 and enabling the GATOR2 complex to activate mTORC1 [161]. Leucine can also regulate mTORC1 signaling via SAR1B, a newly identified leucine sensor. Under conditions of leucine deficiency, SAR1B inhibits mTORC1 by physically targeting its activator GATOR2. In contrast, when leucine levels are sufficient, leucine binds to SAR1B, causing a conformational change that allows SAR1B to dissociate from GATOR2, resulting in the activation of mTORC1 [162]. Additionally, the leucine bypass metabolite β-hydroxy β-methylbutyrate (HMB), which is produced from only about 5% of leucine catabolism under normal conditions, has been identified as a potent agent in improving muscle mass and strength in sarcopenic individuals [163]. These signals can all activate the anabolism of skeletal muscle.

The metabolic processes described above are typical examples of those that rely on the cooperative functioning of the liver and skeletal muscle. In fact, nearly all metabolic processes, including glucose and lipid metabolism, depend on the interplay between the liver, muscle, and adipose tissue. The intermediate metabolites involved in these interactions are particularly important in the context of skeletal muscle aging and sarcopenia.

3.2. Hepatokines

Beyond direct metabolic exchange, the liver and skeletal muscle also communicate dynamically through secreted proteins that function in autocrine, paracrine, or endocrine modes. This protein-mediated crosstalk is essential for systemic metabolic regulation. Hepatokines are liver-secreted proteins that influence other organs; the term ‘hepatokine’ was first introduced by Stefan and Häring in 2008 to describe α2-HS-glycoprotein (fetuin-A), the production of which increases in steatotic and inflamed livers [98,164]. They play an important role in regulating metabolism, energy balance, and inflammation. Some well-known hepatokines include Adropin, ANGPTL4, Fetuin-A, Fetuin-B, FGF-21, Hepassocin, LECT2, RBP4, Selenoprotein P and Apolipoprotein J. These molecules can affect various physiological functions by acting locally (autocrine), on the same organ (paracrine), or distantly (endocrine). Although myokines—such as IL-6 and irisin—mediate reciprocal signaling

from skeletal muscle, they are not discussed in detail here [165]. Hepatokines regulate skeletal muscle at a distance through four main mechanisms: (1) modulation of insulin resistance and glucose metabolism, (2) regulation of oxidative stress and mitochondrial function, (3) control of muscle atrophy and regeneration, and (4) responses to exercise and nutritional signals.

Fibroblast Growth Factor 21 (FGF21) is a hormone-like hepatokine primarily produced in the liver in response to fasting, exercise, and metabolic stress. It regulates systemic energy homeostasis by promoting fatty acid oxidation, enhancing mitochondrial function, and modulating glucose metabolism. FGF21 acts via fibroblast growth factor receptors (mainly FGFR1) in complex with the co-receptor β-Klotho, triggering signaling pathways such as MAPK/ERK and AMPK to exert metabolic effects [108]. In skeletal muscle, FGF21 enhances insulin sensitivity and mitochondrial biogenesis through activation of PGC-1α [166]. Notably, FGF21 plays a dual role in muscle homeostasis. While it can suppress TNFα-induced inflammation and muscle atrophy in vitro [109], chronic elevation of FGF21 during fasting or metabolic stress promotes mitophagy through Bnip3, leading to muscle mass loss and weakness [109]. Mouse models show that overexpression of FGF21 induces muscle wasting, whereas FGF21 deficiency aggravates obesity-related muscle atrophy due to increased MuRF1/Atrogin-1 expression and reduced AMPK activity [110]. Although its exact role in sarcopenia is not fully defined, FGF21 represents a potential therapeutic target for metabolic muscle disorders.

Hepassocin (HPS/FGL1), a liver-secreted protein upregulated during regeneration [167,168], promotes hepatocyte proliferation via EGFR/ERK, STAT3, and HNF1α pathways while mitigating oxidative/ER stress [169–171]. Elevated circulating Hepassocin correlates with metabolic disorders (e.g., NAFLD, diabetes), suggesting biomarker potential [172,173]. Beyond hepatic roles, Hepassocin impairs skeletal muscle insulin sensitivity through EGFR/JNK signaling, contributing to insulin resistance—demonstrated in hyperlipidemia models where hepatic-derived Hepassocin compromises muscle glucose uptake [111,112]. Although its age-related changes remain underexplored, Hepassocin's dual involvement in liver metabolism and muscle insulin resistance implies a potential link to sarcopenia development, particularly given the muscle-liver metabolic crosstalk in aging. However, no direct evidence yet connects Hepassocin dysregulation to age-related muscle loss, highlighting a critical research gap. Targeting Hepassocin pathways may offer dual therapeutic strategies for liver repair and sarcopenia prevention, warranting mechanistic studies on its role in muscle atrophy during aging [168,170]. Insulin-like Growth Factor 1 (IGF-1) is a liver-derived anabolic hormone produced primarily in response to growth hormone stimulation. It is crucial for skeletal muscle development, hypertrophy, and regeneration, acting through the PI3K/Akt/mTOR signaling pathway to promote protein synthesis and inhibit degradation [122]. IGF-1 levels decline with age [174], contributing to the onset of sarcopenia through impaired muscle regeneration and reduced satellite cell activity [175,176]. Observational studies have shown that lower circulating IGF-1 levels are associated with decreased muscle mass, strength, and increased frailty in elderly individuals [123,177]. Despite being classified as a growth factor, IGF-1 is often regarded as a hepatokine due to its hepatic origin and systemic endocrine effects. Its central role in muscle maintenance makes IGF-1 one of the most promising targets for sarcopenia intervention, especially in age-related hormonal decline.

Retinol-Binding Protein 4 (RBP4) is a hepatokine primarily secreted by the liver and adipose tissue, responsible for transporting vitamin A (retinol) to peripheral tissues. Beyond this classical role, RBP4 has emerged as a key player in metabolic regulation. Elevated circulating RBP4 levels are linked to insulin resistance, hepatic steatosis, and metabolic syndrome [178,179]. Mechanistically, RBP4 disrupts insulin signaling in muscle by activating pro-inflammatory cytokines and impairing glucose uptake. Its levels are decreased in liver cirrhosis due to impaired hepatic synthesis [180]. It is increased in NAFLD, correlating with hepatic lipid accumulation [181]. Pharmacological reduction of RBP4 using pioglitazone improves insulin sensitivity and reduces liver fat [182]. Recent studies show that RBP4 promotes denervation-induced muscle atrophy via a STRA6–JAK2–STAT3 signaling axis [115]. Moreover, RBP4 levels are significantly associated with sarcopenia-related traits such as reduced grip strength and muscle mass in older adults [116], suggesting its utility as both a mechanistic mediator and a biomarker of sarcopenia progression.

Fetuin-A and Fetuin-B, two structurally related hepatokines, are glycoproteins predominantly secreted by the liver and are closely linked to insulin resistance and metabolic inflammation. Fetuin-A, the first protein classified as a hepatokine [98,164], promotes insulin resistance by binding to TLR4 and enhancing pro-inflammatory cytokine release, thereby disrupting insulin signaling in skeletal muscle and adipose tissue [104]. It also contributes to NAFLD through activation of hepatic stress kinases such as JNK [183]. Elevated Fetuin-A levels are observed in elderly individuals with obesity or type 2 diabetes, reflecting chronic low-grade inflammation [184], and have been associated with sarcopenia in older adults [185], although its direct role in muscle wasting remains unclear. Similarly, Fetuin-B is upregulated in metabolic diseases such as NAFLD, type 2 diabetes, and coronary artery disease [107,186,187]. It impairs insulin signaling in muscle and liver via MAPK activation and contributes to

systemic glucose intolerance [106]. While its impact on aging and sarcopenia is not fully established, Fetuin-B may exacerbate age-associated insulin resistance and metabolic dysfunction.

LECT2 is a multifunctional cytokine primarily synthesized by hepatocytes [188], with roles in immune regulation, metabolism, and inter-organ signaling. It enhances macrophage activation via CD209a and improves bacterial clearance in sepsis [188], while also impairing insulin signaling in skeletal muscle through JNK pathway activation [189]. LECT2 levels are dysregulated in liver cancer [190] and decrease during systemic inflammation [191]. It is implicated in systemic amyloidosis and chronic kidney dysfunction in aging, indicating systemic metabolic stress [192]. Although direct evidence linking LECT2 to sarcopenia remains limited, its ability to induce NF-κB activation, impair insulin sensitivity, and promote inflammation strongly suggests a potential role in muscle catabolism [113,114]. Further studies are needed to establish whether LECT2 acts as a causal mediator of age-related muscle loss or serves mainly as a biomarker of systemic dysfunction.

Selenoprotein P (SEPP1) is a selenium-rich plasma protein primarily synthesized in the liver, traditionally known for selenium transport and antioxidant functions [193]. Recent studies have identified SEPP1 as a hepatokine that impairs insulin signaling in hepatocytes and skeletal muscle, thereby contributing to insulin resistance and type 2 diabetes [117]. Elevated SEPP1 expression is linked to obesity and NAFLD, further implicating it in systemic metabolic dysregulation [194]. In skeletal muscle, SEPP1 inhibits exercise-induced ROS production and suppresses activation of AMPK and PGC-1α, leading to impaired mitochondrial adaptation and an "exercise-resistant" phenotype [118]. It also interferes with myogenesis through miR-181a–mediated signaling and promotes muscle degeneration [119]. In mouse models, SEPP1 deficiency protects against immobilization-induced muscle atrophy by reducing the expression of atrophy-related genes [120]. These findings suggest that SEPP1 may play a detrimental role in muscle aging and serve as a therapeutic target in sarcopenia.

Apolipoprotein J (Clusterin) is a multifunctional glycoprotein synthesized in the liver and widely expressed across tissues. Recent evidence has identified it as a hepatokine that regulates muscle glucose metabolism via LRP2-mediated insulin receptor internalization and signaling; loss of ApoJ or muscle LRP2 leads to insulin resistance and impaired glucose tolerance [121]. Additionally, clusterin levels are reduced in patients with alcohol-associated hepatitis and liver failure, suggesting a role in hepatic function and systemic metabolic stress [195]. Although its direct contribution to sarcopenia is not fully established, impaired ApoJ signaling may exacerbate muscle metabolic dysfunction, particularly in liver disease contexts.

Adropin is a hepatokine that links dietary macronutrient intake with energy homeostasis and lipid metabolism, showing protective effects against hepatic steatosis and insulin resistance in obesity [100]. Exercise, such as descending stair walking, has been shown to increase adropin levels, correlating with improved muscle strength and metabolic outcomes [196]. Although elevated adropin correlates with enhanced muscle function following exercise, there is limited evidence on whether adropin alone can directly reverse sarcopenia.

Angiopoietin-like protein 4 (ANGPTL4) is secreted by the liver and modulates lipid metabolism by inhibiting lipoprotein lipase (LPL) [102]. In skeletal muscle, ANGPTL4 can regulate fatty acid uptake and activate AMPK signaling, influencing insulin sensitivity and energy homeostasis [197,198]. Aging-related increases in ANGPTL4 are associated with chronic inflammation and metabolic stress, which may indirectly contribute to muscle atrophy [103]. However, causality remains unproven, and ANGPTL4 likely acts more as a metabolic regulator than a direct driver of sarcopenia.

The liver is the primary source of plasma proteins, synthesizing nearly all fibrinogen, albumin, and over 80% of plasma globulins [199]. Beyond these well-established proteins, the liver also produces a wide array of other bioactive factors—many of which remain underexplored—that could function as novel hepatokines, playing critical roles in inter-organ communication and metabolic regulation between liver and skeletal muscle.

3.3. miRNAs

In addition to metabolic and hepatocytes-mediated interactions, the liver and skeletal muscle communicate through miRNAs, which regulate gene expression and cellular function. miRNAs are a class of short, non-coding RNA molecules (typically 19–25 nucleotides long) that regulate gene expression at the post-transcriptional level [200]. By binding to complementary sequences—usually in the 3′ untranslated region (UTR) of target messenger RNAs—miRNAs can repress translation or promote mRNA degradation, thus fine-tuning protein production and cellular processes such as proliferation, differentiation, apoptosis [201], and metabolism [202]. According to data from the widely used miRBase database (https://www.mirbase.org/, accessed on 5th May, 2025), the human genome harbors approximately 1917 precursor miRNAs and about 2654 mature miRNAs, whereas in *Mus musculus* there are approximately 1237 precursor miRNAs and around 2009 mature miRNAs [203].

miRNAs play crucial roles in liver development [204], metabolism, aging [205], and the pathogenesis of liver-related diseases [206]. DICER1 and DGCR8 are essential for miRNA production; their disruption leads to a complete loss of miRNAs. In mice, DICER loss results in embryonic death at E7.5 due to impaired proliferation and loss of extraembryonic pluripotency. Conditional knockouts of DICER1 and DGCR8 in hepatoblasts/hepatocytes were generated to study the role of miRNAs in liver development [207,208]. Specific miRNA, such as miR-122, which accounts for more than a half of the total microRNA in the liver [124], is involved in NAFLD, insulin resistance, hepatic fibrosis, with upregulated level, targeting important protein such as SCD-1, SREBP1, IGF-1R, SIRT1 etc [125]. For skeletal muscle, miRNAs are also involved almost all aspect of its physiology and pathology. For instance, muscle-specific miRNAs such as miR-1, miR-133, and miR-206 are key to myogenesis and muscle regeneration, with their dysregulation linked to various myopathies and age-related sarcopenia [209]. miR-29b contributes to skeletal muscle atrophy by targeting IGF-1 and PI3K(p85α), and that its inhibition can attenuate atrophy induced by various stimuli [129].

Initially, it was thought that miRNAs acted solely within the cells that synthesized them. However, it is now widely recognized that extracellular vesicles, such as exosomes, can carry miRNAs and targeted to other organs and tissues [210]. Extracellular vesicles (EVs) are membrane-bound particles released by cells that transport a variety of molecular cargoes, serving as biomarkers and mediators of intercellular communication. They are traditionally classified as exosomes, microvesicles, and apoptotic bodies, with emerging subtypes including autophagic, stressed, and matrix vesicles [211]. In the context of organ-crosstalk, the source of EVs from a particular organ is important. Generally, EVs derived from platelets, erythrocytes [212], and immune cells [213] constitute the majority of circulating EVs—with platelet-derived EVs possibly accounting for 25% or more based on different assessment methods [214]. However, under pathological conditions, EVs from specific tissues or organs can increase dramatically. For example, during vascular injury, endothelial cell–derived EVs are significantly elevated [215]. Similarly, tumor-derived EVs can lead to the development of cachexia [216], and recent research has shown that amiloride, a drug that inhibits the release of tumor exosomes, can effectively alleviate muscle wasting [217]. As for the liver, although the proportion of hepatocyte- or stellate cell-derived exosomes in the bloodstream is low under normal physiological conditions, the liver can secrete a large number of EVs into the circulation under pathological circumstances such as in NAFLD [218]. In these circumstances, miRNAs can be delivered via EVs to other tissues and organs, such as skeletal muscle.

In normal human liver, nine highly expressed miRNAs are: miR-122 (52.0%), miR-192 (16.9%), miR-199a/b-3p (4.9%), miR-101 (3.7%), let-7a (3.3%), miR-99a (2.2%), let-7c (2.1%), let-7b (1.7%), and let-7f (1.5%). These miRNAs collectively account for approximately 88.2% of the entire miRNome [219]. The miRNA number expressed by the liver further expanded to 277 later including miR-16, miR-27b, miR-30d, miR-126 [220]. The miR-29a and miR-29b were also revealed to be expressed by the liver to suppress collagen deposition [221]. In addition, several miRNAs have been reported to be upregulated or downregulated under pathological conditions (refer to the review [125]). In NAFLD, miR-122, miR-34a, miR-21, miR-15b, miR-33, miR-375, miR-451, miR-190b, miR-181b were reported to be upregulated in the liver. And almost all these miRNAs can be found to be upregulated in the serum of NAFLD patients, suggesting their roles in organ crosstalk, apart from serving as biomarkers. Tumor cells can also secret miR-122 to suppress O-GlcNAcylation by targeting O-GlcNAc transferase (OGT), thus promoting skeletal muscle proteolysis [126]. The elevated levels of miR-122-3p in the reduced muscle strength group were identified by screening for differentially expressed miRNAs through miRNA sequencing [222]. Circulating miR-34a was upregulated and contributed to frailty and diabetes [131]. However, whether it directly contributes to the occurrence of sarcopenia remains unclear. miR-21 promotes skeletal muscle atrophy and fibrosis by targeting SMAD7 and activating the TGF-β/SMAD2/3 signaling pathway, which is essential for muscle atropy and sarcopenia [127], while miR-21 inhibition alleviates these pathological changes [223]. miR-21 can also impair myogenesis by modulating IL6R, PTEN, and FOXO3 signaling, reducing satellite cell viability and muscle regenerative capacity [128]. miR-15b was reported to inhibit SETD3 expression, thus repress muscle cell differentiation [132]. miR-375, together with miR-122, were consistently downregulated in cachectic tissues and showed a negative correlation with body weight loss severity, suggesting its potential role in contributing to tissue wasting in human cancer cachexia [130]. miR-29, which was thought to be expressed in liver, is involved in multiple types of muscle atrophy induced by dexamethasone, TNF-α, H_2O_2, denervation, and immobilization—by targeting IGF-1 and PI3K(p85α) [129]. Generally, several liver-derived miRNAs have been reported to be involved in muscle physiology and atrophy; however, whether they directly influence muscle tissue and serve as the primary mediators remains to be further investigated. In human liver tissues, 114 miRNAs were significantly upregulated and 72 were downregulated when transitioning from fetal to pediatric stages, while only 2 were upregulated and 3 downregulated from pediatric to adult stages [224]. This suggested a dynamic change of miRNA in liver tissue and the miRNAs profile change beyond 60 or 65 years old needing further investigation.

Altogether, the liver influences skeletal muscle through various mechanisms. However, skeletal muscle also exerts significant effects on the liver. For example, skeletal muscle-derived myokines, such as irisin, drive adipose tissue browning, reduce systemic free fatty acids, and alleviate hepatic lipotoxicity [32]. Muscle-derived lactate, produced during physical activity, is transported to the liver via the Cori cycle, where it serves as a precursor for gluconeogenesis, helping to sustain blood glucose levels and enhance hepatic metabolic adaptability [30]. Additionally, muscle-secreted glutamine supports hepatic detoxification and redox balance [31]. These factors highlight the bidirectional nature of liver-muscle communication. While this review focuses on the liver's impact on muscle health, the role of skeletal muscle in regulating liver function is equally important in understanding overall metabolic homeostasis and the progression of liver-related diseases.

4. The Role of Metabolites and Post-Translational Modifications in Liver-Muscle Crosstalk

Besides being the main energy substrates (glucose, fatty acids, and amino acids, provided largely by the liver), metabolites can also act as signaling molecules to regulate skeletal muscle function. Metabolites regulate cellular functions through various mechanisms, including binding to membrane receptors, activating intracellular signaling pathways, and modulating gene expression [225]. One of the most important roles of metabolites is their involvement in PTMs of proteins. PTMs involve the formation or cleavage of covalent bonds on protein backbones or amino acid side chains. PTMs represent a significant extension of the "central dogma" [226]. Although the central dogma describes the flow of genetic information from DNA to RNA to protein, metabolite-driven modifications both expand the diversity of proteins and influence DNA replication and transcription via histone modifications.

To date, more than 740 types of PTMs have been reported in UniProt (http://www.uniprot.org/docs/ptmlist.txt, accessed on 5 May 2025), compared to approximately 650 types reported in 2022 by Zhong et al. [227]. This remarkable increase suggests an explosion in the diversity of PTMs. In addition to the well-characterized modifications such as phosphorylation, acetylation, ubiquitination, and methylation, many novel PTMs are currently being discovered. For instance, even vitamin C can also modify proteins; it has been shown to induce "vitcylation" on lysine 298 (K298) of STAT1 [228]. Generally, PTMs can be broadly classified into three groups: one involving the addition of modifiers (e.g., phosphate, sugar, methyl, acetyl groups) to nucleophilic amino acid side chains like lysine and cysteine; another encompassing chemical alterations such as deamination, citrullination, and redox modifications (e.g., S-nitrosylation, S-glutathionylation); and a third involving the cleavage of the protein backbone via enzymatic or autocatalytic processes that regulate protein localization, activity, and turnover (Refer to [227]).

Numerous PTMs—including phosphorylation, acetylation, ubiquitination, SUMOylation, glycosylation, glycation, methylation, S-nitrosylation, carbonylation, and S-glutathionylation—have been identified in skeletal muscle, where they play critical roles in regulating muscle function, muscle aging, and sarcopenia [229]. It is noteworthy that these PTMs target some of the most critical genes, factors, and signaling pathways involved in muscle function. For instance, phosphorylation events in the PI3K/AKT/mTORC1 pathway and the acetylation of histones are essential for muscle regulation. A human cohort study revealed basal hyperphosphorylation of mTORC1 in elderly individuals, and is thought to contribute to both insulin resistance and the diminished anabolic response of skeletal muscle protein metabolism to nutrition and exercise [230]. Among molecular chaperones, phosphorylation of αB-crystallin is significantly elevated in aged muscle tissues [231]. As for methylation, G9a-mediated methylation of MyoD at lysine 104, plays a pivotal role during muscle development by restraining MyoD's transcriptional activity; mutation of lysine 104 renders MyoD unresponsive to G9a's inhibitory methyltransferase activity, thereby enhancing myogenic potential [232]. And MG53 functions as an E3 ubiquitin ligase targeting the insulin receptor and IRS1 for ubiquitin-dependent degradation, and its overexpression alone is sufficient to induce muscle insulin resistance and metabolic syndrome [233].

Although most PTMs in skeletal muscle are mediated by local substrates and modifying enzymes, liver–muscle crosstalk often involves metabolites that are predominantly produced by the liver, transported via the bloodstream, and absorbed by skeletal muscle to mediate post-translational modifications. This scenario primarily involves the first class of PTMs—that is, the addition of modifiers to nucleophilic amino acid side chains such as lysine and cysteine. Currently known liver-derived metabolites in such PTMs include ketone bodies (e.g., β-hydroxybutyrate and acetoacetate), liver-derived short-chain fatty acids, and urea. In addition, the liver serves as the primary site for glutathione synthesis and is responsible for homocysteine clearance.

Among the various lysine acylations, β-hydroxybutyrylation (Kbhb) stands out as almost exclusively hepatic in origin. Under prolonged fasting, caloric restriction, or low-carbohydrate intake conditions, the liver significantly upregulates β-oxidation of fatty acids. This process leads to the production of β-hydroxybutyrate (BHB), a key

ketone body that not only serves as an energy substrate for peripheral tissues but also acts as the acyl donor for Kbhb. Consequently, β-hydroxybutyryl-CoA generation is a liver-dominated process, making Kbhb a unique marker of hepatic ketogenesis [134]. Our recent study on aging muscles showed that providing exogenous BHB increases histone Kbhb in muscle, upregulating genes for mitochondrial function and improving muscle mass in old mice. Blocking histone β-hydroxybutyrylation abolished BHB's benefits, confirming that the ketone itself was being utilized by muscle to create a PTM that enhanced muscle function [74]. However, acetoacetylation (Kacac) has not yet been reported in skeletal muscle function and sarcopenia. Roles of other acylation in skeletal muscle function and sarcopenia need further research. Some clues have been proposed. For example, increased levels of malonyl-CoA in skeletal muscle have been reported in patients with type 2 diabetes [234]. Additionally, modifications related to branched-chain amino acid metabolism, such as isobutyrylation (Kib) [135] and 2-hydroxyisobutyrylation (Khib) [136], are reported. Isobutyrate and 2-hydroxyisobutyrate are produced by both liver and muscle, and whether they are involved in liver-muscle crosstalk, necessitating further investigation. Additionally, lactylation has recently been identified as a crucial PTM, which is predominantly derived from lactate produced by skeletal muscle during anaerobic exercise [139]. The absence of myristoylation of ARF mediates the sustained activation of the endoplasmic reticulum UPR caused by the down-regulation of fatty acid synthesis. Subsequently, it inhibits the translation of sarcomere structural protein UNC-97/PINCH through eIF2a, thereby causing sarcomere structural defects [235]. This modification, in turn, plays a significant role in regulating hepatic function. Notably, lactate is a key metabolite of the Cori cycle, underscoring the metabolic interdependence between the liver and skeletal muscle. This highlights the importance of investigating metabolic pathways that necessitate inter-organ coordination between the liver and skeletal muscle in the context of liver-skeletal muscle crosstalk.

In addition to acylation, other modifications—such as carbamylation, glutathionylation, and methylation—are also involved in liver–muscle crosstalk. Carbamylation is a nonenzymatic PTM mediated by cyanate, which reacts with protein amino groups—especially lysine side chains (homocitrullination) [236,237]. Cyanate forms via two pathways: slow decomposition of urea into cyanic acid and cyanate under normal conditions and increased production during inflammation when myeloperoxidase shifts the cyanate–thiocyanate balance [238]. Carbamylation disrupts ionic interactions, altering protein structure and function, which can impair normal protein assembly [227]. Protein carbamylation is implicated as a hallmark of aging. Measurements of homocitrulline—a key carbamylation product—in skin tissues from various mammals reveal that carbamylated protein accumulation increases with age and is inversely correlated with lifespan [239]. Role of carbamylation in skeletal muscle aging and sarcopenia, which need to be further investigated.

Glutathione (GSH) and S-adenosylmethionine (SAM), the donor molecules for S-glutathionylation and methylation respectively, are primarily synthesized in the liver. It is estimated that the liver contributes over 70% of the glutathione present in the bloodstream [240]. S-glutathionylation is a reversible PTM where glutathione (GSH) reacts with protein cysteine thiols, forming mixed disulfides (PSSG). This modification plays a crucial role in redox signaling, protecting proteins from oxidative damage and modulating their function. During oxidative stress, the GSH/GSSG ratio decreases, promoting non-enzymatic S-glutathionylation. In skeletal muscle, S-glutathionylation occurs on proteins like troponin I (TnI) in response to fatigue, potentially preserving muscle function under stress [137]. SAM levels exhibit notable changes during aging, with research indicating both decreases and increases depending on the tissue and species studied. In a study involving rats, tissue levels of SAM were measured in 30-month-old rats and compared to adult rats, revealing a significant decrease in SAM levels with age [241]. Conversely, research suggests that age-related increases in SAM levels may be causal factors that shorten lifespan in various species [242]. These contrasting findings highlight the complexity of SAM's role in aging, suggesting that its levels and effects may vary across different tissues and organisms. But we definitely find that supplementation of SAM improved the skeletal muscle repair post injury [138]. Further research is necessary to fully understand the implications of SAM in the skeletal muscle aging process and sarcopenia.In summary, metabolites and PTMs play pivotal roles in liver-muscle crosstalk, influencing skeletal muscle aging and sarcopenia (Figure 4).

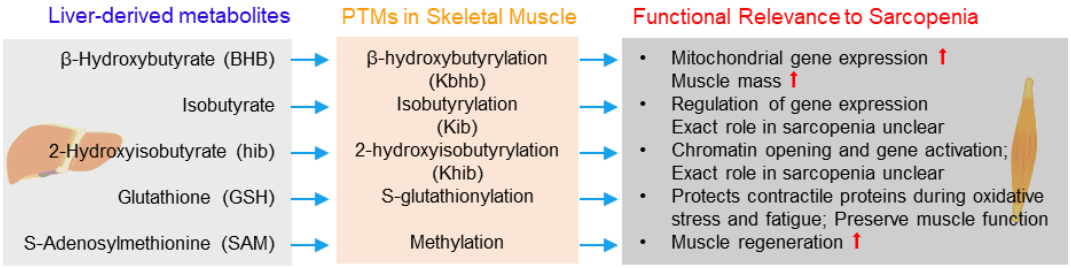

Figure 4. Liver-derived Metabolites and Their Functional Roles in Sarcopenia via PTMs. Metabolites produced by the liver—including β-hydroxybutyrate (BHB), isobutyrate, 2-hydroxyisobutyrate (2-HIBA), glutathione (GSH), and S-adenosylmethionine (SAM)—serve as donors for PTMs in skeletal muscle. These PTMs include β-hydroxybutyrylation (Kbhb), isobutyrylation (Kib), 2-hydroxyisobutyrylation (Khib), S-glutathionylation, and methylation. Some of these modifications (e.g., Kbhb and methylation) are known to enhance mitochondrial gene expression and muscle regeneration, while others are implicated in oxidative stress protection or chromatin remodeling. However, the roles of Kib and Khib in sarcopenia remain to be fully elucidated.

5. Liver-Muscle Crosstalk as Potential Biomarkers and Therapeutic Strategies for Sarcopenia

As a growing body of basic research unveils the underlying molecular mechanisms of liver–muscle crosstalk, clinical applications are gradually emerging. The following aspects illustrate the significant potential of these inter-organ interactions in preventing skeletal muscle aging and treating sarcopenia.

Firstly, it is critical to consider the role of comorbidities in the prevention and management of sarcopenia. The interaction between the liver and skeletal muscle plays a crucial role in muscle mass regulation and various metabolic disorders, including diabetes, obesity, and cardiovascular diseases. Abnormal liver function has been strongly associated with muscle wasting, with large-scale studies demonstrating that dysregulated liver parameters correlate with an increased risk of sarcopenia [86]. Although there is growing recognition of the need to monitor sarcopenia in patients with liver disease, current clinical guidelines have yet to incorporate liver function assessment and improvement into the evaluation and management of sarcopenia. This represents a potential area for future research and clinical intervention.

Secondly, liver-derived mediators involved in liver-muscle crosstalk are emerging as promising biomarkers for sarcopenia. Mediators such as FGF21, ANGPTL4, Fetuin-A, and RBP4 have been identified as key players in this process and show potential as biomarkers for sarcopenia. Elevated circulating levels of FGF21 have been linked to muscle loss and metabolic stress [243,244], while increased RBP4 levels correlate with decreased muscle mass and strength [116]. The development of sensitive assays to measure these mediators may offer non-invasive approaches for early diagnosis and monitoring of sarcopenia progression.

Thirdly, liver-muscle crosstalk is emerging as a key focus for potential therapeutic interventions for sarcopenia. For instance, exogenous administration of β-hydroxybutyrate (BHB) has been shown to increase histone β-hydroxybutyrylation in skeletal muscle, thereby upregulating genes involved in mitochondrial function and reversing sarcopenia [61]. BHB can also promote myoblast proliferation and differentiation through the activation of GPR109a [245]. Furthermore, BHB has been reported to alleviate disuse-induced muscle atrophy [246]. Evidence from multiple sources suggests that BHB is a promising molecule for improving sarcopenia, and gut microbiota producing BHB have been shown to mitigate tumor-induced cachexia [247]. Studies investigating ways to increase circulating BHB, including lifestyle modifications and exogenous supplementation, will be crucial for advancing its clinical application [248]. Another successful example is HMB, a byproduct of leucine metabolism bypass, which has been recommended as a supplement for the treatment of sarcopenia.

Fourthly, several pharmacological agents used to treat liver diseases have also shown benefits for skeletal muscle health. In patients with NAFLD, GLP-1 receptor agonists (e.g., liraglutide) reduce liver fat and alleviate muscle atrophy by inhibiting myostatin and enhancing myogenic signaling via GLP-1R pathways [249,250]. Vitamin E attenuates liver inflammation [251], reduces muscle oxidative stress, and improves motor function [252]. Empagliflozin, an SGLT2 inhibitor, improves liver fibrosis while reversing muscle dysfunction and fibrosis through modulation of AMPKα and the MMP9/TGFβ1/Smad pathway [253,254]. These findings highlight the dual potential of liver-targeted drugs in managing both hepatic and muscular dysfunctions. Further large-scale trials are needed to validate their efficacy in treating sarcopenia alongside liver disease.

Moreover, beyond pharmacological approaches, lifestyle-based interventions—including nutrition and exercise—are emerging as promising strategies specifically targeting the liver-muscle axis. Nutritional supplements such as branched-chain amino acids (BCAAs) and omega-3 fatty acids can modulate both hepatic

and muscular metabolism. BCAAs support muscle protein synthesis and have shown benefits in cirrhotic patients [255,256], while omega-3s improve liver function under stress and counteract age-related muscle decline [41,257]. Exercise also exerts dual effects on the liver and muscle. Resistance training enhances irisin secretion, promotes adipose tissue browning, facilitates muscle glucose uptake, and improves hepatic metabolic profiles [258,259]. Aerobic exercise reduces hepatic glucose output via the IL-6/AMPK pathway and mitigates NAFLD progression [260]. To maximize therapeutic outcomes, future interventions should integrate multi-omics profiling to define individual liver-muscle interaction patterns, enabling stratified intervention plans. Combining tailored nutrition, targeted drugs, and personalized exercise regimens may offer a new paradigm for managing metabolic liver disease and sarcopenia through precise modulation of the liver-muscle axis.

Overall, clinical applications targeting liver-muscle interactions are still in the early stages, and further research is needed to fully understand the underlying mechanisms and develop effective therapeutic strategies.

6. Conclusions and Future Perspective

In this review, we have highlighted the significant role of liver-muscle crosstalk in the progression from skeletal muscle aging to sarcopenia, with a focus on liver-derived metabolites, hepatokines, and signaling molecules that impact skeletal muscle function. While the current body of research demonstrates a strong association between liver dysfunction and muscle wasting, it is essential to shift from identifying correlations to establishing clear causal relationships between liver-muscle interactions and sarcopenia. The discovery of new key molecules involved in liver-muscle crosstalk will be crucial for advancing our understanding of sarcopenia and identifying novel therapeutic targets. Future studies should investigate the molecular mechanisms underlying these interactions, particularly regarding how liver-derived metabolites, such as β-hydroxybutyrate (BHB) and other signaling factors, regulate muscle health and contribute to sarcopenia.

As previously discussed, skeletal muscle aging is a gradual process that may or may not progress into clinically defined sarcopenia, one important note is that this review does not distinctly separate muscle atrophy from sarcopenia, as many of the underlying causes of muscle atrophy overlap with those contributing to sarcopenia. However, recognizing sarcopenia as a complex, multifactorial syndrome, further exploration of the specific molecular pathways that drive the progression from simple muscle atrophy to clinically relevant sarcopenia is needed. A more detailed understanding of these processes will allow for the development of targeted interventions for sarcopenia, which could significantly improve patient outcomes in aging populations and those with liver disease.

There are significant limitations in the methodology of studying the liver-muscle axis: Rodent models have difficulty simulating the chronic course of human diseases due to differences in metabolic rate, muscle composition and signaling pathways (such as FGF21); The in vitro model lacks a circulatory system and a dynamic metabolic environment, resulting in distorted results. Clinical studies mostly rely on cross-sectional data and heterogeneous muscle assessment tools to limit causal inference. In the future, it is necessary to integrate multi-species models, organoid chips and dynamic omics technologies to enhance the reliability of transformation.

Furthermore, while the liver-muscle axis holds promise for therapeutic strategies, additional research on clinical applications is required. For instance, studies exploring how to modulate liver function to prevent or reverse sarcopenia, such as with liver-targeted therapies or lifestyle interventions to increase circulating metabolites like BHB, will be pivotal. The integration of liver and muscle health in clinical practice could revolutionize the way sarcopenia is managed, ultimately offering a more holistic approach to treating this debilitating condition.

In summary, liver-muscle crosstalk is a vital aspect of sarcopenia development, and understanding its mechanisms will pave the way for innovative strategies to preserve skeletal muscle function during aging and to treat pathological sarcopenia. The discovery of new molecular mediators and therapeutic targets, along with a better understanding of the pathophysiological processes, will be key to advancing the field.

Author Contributions: Q.W., M.Y., X.W. and Y.X.: Writing—Original draft preparation. X.L., G.F. and Y.X.: Writing—Reviewing and Editing. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Key R&D Program, Ministry of Science and Technology of China (2023YFF1001000, 2023YFC3603300), the National Natural Science Foundation of China (81873814, 82330046), Jiangxi Province (20242BAB26156) and Nanchang University (NCUJCCX-2024-04 and 28740105).

Data Availability Statement: Not applicable

Conflicts of Interest: The authors declare no competing interests.

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