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Review Article

Sarcopenia in Chronic Liver Disease: A Metabolic Perspective

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Abstract

Sarcopenia, a condition of low muscle mass, quality, and strength, is commonly found in patients with chronic liver disease (CLD) and is associated with adverse clinical outcomes including reduction in quality of life, increased mortality, and complications. A major contributor to sarcopenia in CLD is the imbalance in muscle protein turnover wherein changes in various metabolic factors such as hyperammonemia, amino acid deprivation, hormonal imbalance, gut dysbiosis, insulin resistance, chronic inflammation, etc. have important roles. In particular, hyperammonemia is a key mediator of the liver-gut axis and is known to contribute to sarcopenia by various mechanisms including increased expression of myostatin, increased phosphorylation of eukaryotic initiation factor 2a, cataplerosis of α-ketoglutarate, mitochondrial dysfunction, increased reactive oxygen species that decrease protein synthesis and increased autophagy-mediated proteolysis. Skeletal muscle is a major organ of insulin-induced glucose metabolism, and sarcopenia is closely linked to insulin resistance and metabolic syndrome. Patients with liver cirrhosis are in a hypermetabolic state that is associated with catabolism and depletion of amino acids, particularly branched-chain amino acids. Sarcopenia can have significant implications for nonalcoholic fatty liver disease, the most common form of CLD worldwide, because of the close link between metabolic syndrome and sarcopenia. This review discusses the potential metabolic derangement as a cause or effect of sarcopenia in CLD, as well as interorgan crosstalk, which that might help identifying a novel therapeutic strategies.

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Abbreviations: AAAs, aromatic amino acids; ATF4, transcription factor 4; BCAAs, branched-chain amino acids; CLD, chronic liver disease; DM, diabetes mellitus; GLUTs, glucose transporters; GH, growth hormone; HD, hepatogenous diabetes; HE, hepatic encephalopathy; ISR, integrated stress response; IL6, interleukin-6; IR, insulin resistance; IGF-1, insulin-like growth factor-1; LC, liver cirrhosis; MHE, minimal hepatic encephalopathy; mTOR, mammalian target of rapamycin; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; TNF, tumor necrosis factor; TCA, tricarboxylic acid; TIPS, transjugular intrahepatic portosystemic shunt; UPP, ubiquitin-proteasome pathway.

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Introduction

Skeletal muscle is one of the largest organs in the body. It is not just a part of our locomotor system; but is also, an important secretory organ.[1] Muscle fibers produce and release a variety of cytokines and other peptides known as myokine that which have autocrine, paracrine, and endocrine effects. Myokines regulate metabolism in organs including the liver and adipose tissues, in addition to maintaining muscle mass and strength.[2,3] Myokines affect glucose and lipid metabolism as well as systemic inflammation.[2] Crosstalk between myokines and other organokines, such as hepatokines and adipokines, has a critical role in orchestrating systemic metabolic alterations that lead to insulin resistance (IR), diabetes mellitus (DM), obesity, and metabolic syndrome (MetS).[2,4] Because both the liver and the muscles are involved in metabolism, simultaneous loss of muscle and liver function can have a major influence on overall metabolism. In patients with chronic liver disease (CLD), loss of skeletal muscle mass, quality, and strength, defined as sarcopenia, is being increasingly recognized.[5,6] Sarcopenia is thought to affect between 25% and 70% of CLD patients, with higher rates in men and in Western populations.[6] In patients with liver cirrhosis (LC), sarcopenia causes significant clinical complications and has been linked to higher mortality, lower quality of life, longer hospital stays, and the development of complications such as infections, hepatic encephalopathy (HE), and hepatogenous diabetes (HD), putting a significant financial burden on the patient.[7–11]

A common link between sarcopenia and CLD is metabolic imbalance (Table 1). In fact, MetS is a key risk factor for sarcopenia, and nonalcoholic fatty liver disease (NAFLD), also known as metabolic associated fatty liver disease, the most prevalent cause of CLD worldwide.[12,13] Skeletal muscle is a major organ of insulin-induced glucose metabolism, and thus sarcopenia is closely linked to IR and MetS.[14] Sarcopenia is caused by a complex equilibrium between protein synthesis and breakdown. Hyperammonemia, amino acid deficiency, hormone imbalance, chronic inflammation, and other metabolic variables all appear to play a part in the pathophysiology.[15,16] Patients with LC are in a hypermetabolic state characterized by catabolism and amino acid

Table 1. Metabolic alterations involved in the pathogenesis of sarcopenia in liver cirrhosis

Metabolic alteration	Implication
Decreased hepatic glycogen; Decreased body fat to muscles volume; Increased gluconeogenesis	Muscles protein breakdown
Muscle anabolic resistance; Altered lipid and amino acid metabolism; Reduced BCAA; Decreased bile production; Pancreatic insufficiency	Decreased muscles protein synthesis
Decreased anabolic hormones (IGF-1 and testosterone)	Decreased muscles protein synthesis; Muscles protein breakdown
Hyperammonemia: Increased myostatin expression; Cataplerosis of α-ketoglutarate; Increased phosphorylation of eukaryotic initiation factor 2a; Altered integrated stress response; Mitochondrial dysfunction	Decreased muscles protein synthesis; Muscles protein breakdown
Insulin resistance; Myosteatosis; Pro-inflammatory cytokines	Decreased muscles protein synthesis; Muscles protein breakdown

BCAA, branch chain amino acid; IGF-1, insulin-like growth factor-1.

deficiency. Reduced levels of branched-chain amino acids (BCAAs) are associated with sarcopenia in LC.[15,17] Despite the extensive data supporting the predictive relevance of sarcopenia in patients with LC, research on metabolic dysregulation as a cause or effect of sarcopenia in such patients is still evolving. The goal of this review is to summarize what is currently known about sarcopenia in cirrhotic patients, with a focus on metabolic dysregulation and its possible impact on clinical outcomes, molecular pathophysiology, and targeted therapeutic approaches.

Metabolic functions of skeletal muscles

Skeletal muscle is the largest metabolic organ in terms of size and is an important site of glucose, protein, and lipid metabolism.[18] In order to meet energy demands and maintain nutritional homeostasis, skeletal muscle alters metabolic pathways in response to varying physiologic needs.

Glucose metabolism

Skeletal muscle has a significant role in glucose metabolism and insulin sensitivity, clearing roughly 80% of postprandial glucose via insulin-dependent glucose uptake.[14,19] In a fed state, glucose is actively transported across the plasma membrane of skeletal muscle in an insulin-dependent manner by specialized carrier proteins known as glucose transporters (GLUTs). GLUT1 is primarily found on the plasma membrane and is involved in basal glucose absorption, whereas GLUT4 is found in intracellular vesicles and is transported to the plasma membrane in response to stimuli. GLUT4 is the most abundant and is also known as the insulin-regulated glucose transporter.[20] Inside the cell, hexokinase phosphorylates glucose, which is then be stored as glycogen, used as a substrate in glycolysis, used as a substrate for protein synthesis via the hexosamine pathway, or used as a substrate in the pentose phosphate pathway, depending on the metabolic demands of the cell.[21]

Protein metabolism

Muscle is important for whole-body protein metabolism because it serves as a primary storage site for amino acids, allowing protein synthesis in various tissues as well as providing precursors for hepatic gluconeogenesis.[22] The needs for amino acids in all tissues do not alter greatly from the post-absorptive to the fed stage because an excess of protein is stored. Ingested amino acids are mostly consolidated into muscle protein in order to replenish the amino acid reserves lost during fasting. Thus, gains in muscle protein mass in the fed state generally offset losses in protein mass in the post-absorptive state.[23]

Lipid metabolism

Skeletal muscle is also an essential regulator of lipid metabolism in the body. Individuals with skeletal muscle diseases including muscular dystrophy and sarcopenia have a much increased risk of developing NAFLD.[24,25] Increased intramyocellular triacylglycerol concentrations are linked to IR in skeletal muscle. This lipid accumulation is most likely caused by increased uptake and decreased mitochondrial oxidation of fatty acids in the muscle.[26] Increased fatty acid levels in obese subjects contribute to accumulation of toxic lipid molecules, oxidative stress, and muscle autophagy.[27]

Muscle protein homeostasis and interorgan crosstalk

Muscle mass homeostasis is tightly regulated, requiring a balance between muscle protein synthesis and proteolysis. The exercise-activated mammalian target of rapamycin (mTOR) pathway is the most important regulator of protein synthesis.[28] Variables that influence protein turnover, include cellular energy status, physical activity, substrate availability, insulin, insulin-like growth factor-1 (IGF-1), corticosteroids, testosterone, myostatin, and cytokines including interleukin-4 and interleukin-6 (IL6).[29] Muscle degradation is driven by three pathways, the ubiquitin-proteasome pathway (UPP), caspase-mediated protein cleavage, and the autophagy system.[30] the UPP is a key proteolysis process in which muscle protein is ubiquitinated and then degraded and eliminated by the 26S proteasome. Inactivity, glucocorticoids, tumor necrosis factor (TNF), and poor insulin/IGF-1 transmission can all activate UPP.[31] Autophagy involves removal of misfolded proteins and damaged organelles by the formation of autophagosome, with subsequent degradation by lysosomes. Muscle replacement requires the activation and recruitment of muscle satellite cells, which are adult stem cells found in skeletal muscle.

Skeletal muscle, liver, and adipose tissue all function as endocrine organs, releasing myokines, hepatokines, and adipokines to perform interorgan crosstalk via autocrine, paracrine, and endocrine pathways.[2,4] Myokines are peptides released by myocytes in response to muscle contraction.[32] There are around 600 myokines known to date, with myostatin being the first to be identified as a myokine. In

mature myofibers, myostatin forms complexes with Smad4 and activates protein degradation pathways such as UPP and autophagy while suppressing the Akt-mediated mTOR signaling pathway, resulting in suppression of protein synthesis and sarcopenia.[33] Myostatin also prevents myogenesis by blocking satellite cell activation.[34] In order to maintain muscle homeostasis, myostatin levels are regulated by follistatin, another glycoprotein. Follistatin promotes satellite cell recruitment while inhibiting Smad2/3, hence negating the action of myostatin. Follistatin infusions stimulate muscle protein synthesis in experimental models, resulting in muscle growth.[35] However, the follistatin was recently found to be increased in human NAFLD, where it induced lipolysis in adipose tissue, but was not associated with skeletal muscle mass.[36] Organokines are associated with obesity, IR, type 2 DM, MetS, and cardiovascular health. The presence of IL6-mediated muscle-liver crosstalk promotes glucose homeostasis during exercise, in which glucose absorption in muscle is followed by enhanced glucose release from the liver.[37] Hepatokines are novel hormones produced by the liver that have a stronger interaction with adipose and skeletal muscle tissue, indicating an endocrine dependent crosstalk linkage.[38,39] Among the hepatokines, fetuin-A was identified early on to be released from the fatty liver and found to induce subclinical inflammation and IR.[39] Adipokines are a type of cell signaling molecule produced by adipocytes and are involved in lipid metabolism, insulin sensitivity, hepatic steatosis, and fibrogenesis.[40]

Sarcopenia in CLD

According to several observational studies, sarcopenia and CLD have a significant association.[5–9] Sarcopenia appears early in the course of CLD and worsens as the disease progresses. Within CLD, NAFLD shares multiple risk factors with sarcopenia, and hence sarcopenia is linked to an increased risk of NAFLD and NAFLD progression, regardless of the presence of obesity, MetS, or IR.[41–43] Sarcopenia is one of the most common complications of LC and is associated with poor clinical outcomes as well as metabolic consequences.[7–11] The prevalence of sarcopenia ranges from 25–70% in cirrhotic patients.[3,6] The prevalence depends on ethnicity, severity of underlying liver disease, and diagnostic criteria and tools used to define sarcopenia. Indians are expected to have high prevalence of sarcopenia because the lean muscle mass is 15% lower compared with Western populations of the same height.[44] According to a meta-analysis conducted by Kim G *et al*.,[6] the global prevalence of sarcopenia in LC is 48.1%, with men being more commonly involved (61.6%) than women (36%).

Recently, the European Working Group on Sarcopenia in Older People has proposed a new definition of sarcopenia giving more importance to muscle function than muscle mass, which is difficult to screen in patients with sarcopenia.[5] The diagnosis of probable sarcopenia can be made when muscle strength is low. It is confirmed when there is additional documentation of low muscle quantity or quality. Severe sarcopenia is accompanied by low muscle strength, low muscle quantity/quality, and low physical performance.[5] Patients with sarcopenia in the presence of obesity, a body mass index of ≥2 5 kg/m^2, is defined as sarcopenic obesity. Sarcopenic obesity has greater metabolic implications than sarcopenia alone.[45]

Metabolic changes and pathophysiology of sarcopenia in CLD

Sarcopenia in CLD is a multifactorial disorder with a complex pathophysiology (Fig. 1). Its pathogenesis is more complex than simple protein and calorie malnutrition. Metabolic alterations in cirrhosis, such as depleted glycogen stores, hyperammonemia, and endocrine dysfunctions, cause excessive protein catabolism, increased UPP activation, inappropriate muscle autophagy, and diminished satellite cell proliferation. A combination of elevated myostatin levels, low IGF-1, hypogonadism, IR, and chronic inflammation appear to have important roles in the development of sarcopenia.

Altered protein, carbohydrate, and lipid metabolism

Alteration of protein turnover is an important contributor to sarcopenia in chronic illness. In general, body protein levels are maintained at the expense of carbohydrate and fat utilization as an energy source. Cirrhotic patients have a reduced ability to utilize carbohydrate as an energy source because of the diminished capacity of hepatocytes to synthesize, store, and break down glycogen.[46] In the early stages of LC, muscle depletion may coexist with normal or even increased body fat, particularly visceral fat. Advanced cirrhosis, however, has more pronounced fat depletion.[47,48] As a result, fat that may protect muscles in the early stages of cirrhosis is no longer available as the disease progresses, causing increased muscle protein breakdown. Increased mobilization of amino acids for gluconeogenesis and energy results in skeletal muscle loss.[47] Thus, dysregulated muscle protein turnover underpins the pathogenesis of sarcopenia in LC patients. However, studies on muscle protein turnover have yielded inconsistent results in cirrhosis, with significant decreases in protein synthesis and contradictory reports of protein breakdown.[49] These variations could be the result of differences in methodology and patient characteristics. Cirrhotic patients are thought to have anabolic resistance, which refers to reduced synthesis of muscle protein in response to dietary protein or exercise.[50,51] One of the primary drivers of muscle anabolic resistance in patients with LC is increased myostatin expression.[3] In patients with NAFLD, one of the key proinflammatory cytokines, TNF-alpha, inhibits muscle protein synthesis by interfering with mTORC and promotes muscle protein breakdown by increasing UPP activity.[52] In alcoholic liver disease, ethanol contributes to sarcopenia by increasing myostatin levels and inhibiting mTORC1 activation.[53]

Hyperammonemia

Every day, adult humans produce roughly 1,000 mmol of ammonia from amino acids and other nitrogen containing compounds. The intestines and kidneys are the primary ammonia producers, while the liver and muscle are the primary ammonia consumers. Some ammonia is used in the synthesis of proteins, amino acids, and nucleic acids, but the rest is waste, neurotoxic, and is largely eliminated in the urine as urea.[54] The liver is involved in ammonia detoxification via the urea cycle and glutamine synthesis, although that is hampered in patients with LC, resulting in hyperammonemia. During a state of hyperammonemia, muscle has an important role in detoxifying ammonia to nontoxic glutamine.[55]

In patients with LC, hepatocellular dysfunction, reduced ureagenesis, and portosystemic shunting, all contribute to hyperammonemia.[55] Gut dysbiosis, infection with urease-positive bacteria, gastrointestinal hemorrhage, and constipation also contribute to hyperammonemia. Increased ammonia absorption by skeletal muscle secondary to hyperammonemia contributes to the development of sarcopenia, which further reduces the muscle mass available to eliminate excess ammonia, setting up a vicious cycle.[56–58]

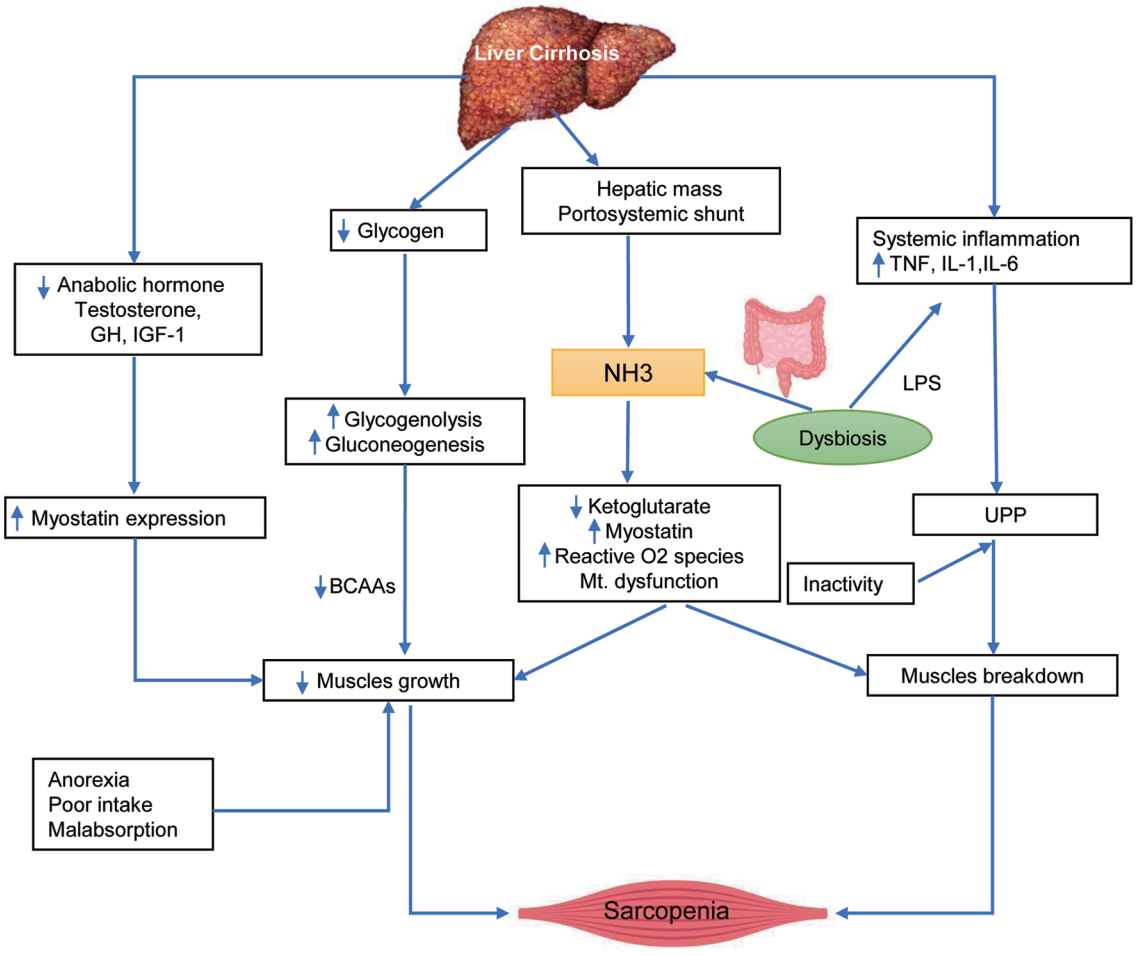

Fig. 1. Schematic explanation main drivers and mechanism contributing to sarcopenia in patients with liver cirrhosis. Sarcopenia in chronic liver disease is a multifactorial disorder with a complex pathophysiology associated with a dysregulated muscle protein turnover. Numerous factors such as hyperammonemia, hypogonadism, impaired insulin/IGF-1 signaling, pro-inflammatory cytokines, and depleted glycogen stores are involved in the pathophysiology of sarcopenia in cirrhosis. Hyperammonemia contributed by decreased hepatic mass, portosystemic shunt, and gut dysbiosis lead to an increased myostatin expression, cataplerosis of α-ketoglutarate, altered integrated stress response, and mitochondrial dysfunction, resulting in impaired muscles protein synthesis as well as increased muscles autophagy. Hypogonadism and impaired insulin/IGF-1 signaling in cirrhosis also result in increased myostatin expression. Depleted glycogen stores and an accelerated starvation in patients with liver cirrhosis lead to increased gluconeogenesis resulting in a low concentration of skeletal muscle amino acids (BCAA) contributing to sarcopenia. Physical inactivity, pro-inflammatory cytokines and poor insulin/IGF-1 transmission can all activate UPP, causing increased muscles protein breakdown. BCAA, branch chain amino acid; GH, growth hormone; IGF-1, insulin-like growth factor-1; IL-interleukin; LPS, lipopolysaccharide; Mt, mitochondrial; NH3, ammonia; O2, oxygen; TNF, tumor necrotic factor; UPP, ubiquitin-proteasome pathway.

Skeletal muscle hyperammonemia leads to an increase in myostatin expression and reduced NF-B activation, resulting in impaired synthesis of muscle protein as well as increased muscle autophagy.[56–58] Myostatin also influences muscle satellite cell function. In an animal model study, myostatin expression was associated with a decrease in satellite cell function, which was mediated by a decrease in myogenic transcription factors myoD, myf5, and myogenin.[17] Hyperammonemia potentially contributes to a reduction in muscle protein synthesis by interfering with tricarboxylic acid (TCA) cycle intermediate metabolism. Normally glutamate and glutamine are converted to ammonia and alpha-ketoglutarate in the TCA cycle.[59] However, because of hyperammonemia in LC, removal of TCA intermediates may be favored, resulting in decreased availability of alpha-ketoglutarate and reduced adenosine triphosphate synthesis, which may limit muscle protein synthesis.[59,60] Hyperammonemia has also been linked to an increase in reactive oxygen species, which can cause tissue damage and muscle loss.[60]

Substrate availability and energy expenditure

Anorexia, malabsorption, and altered macronutrient metabolism contribute to malnutrition and substrate availability in patients with LC.[61] Moreover, LC is a state of accelerated starvation.[62] An overnight fast causes a greater increase in fat oxidation, gluconeogenesis, and ketogenesis in LC patients than in healthy people.[62,63] Increased gluconeogenesis often leads to increased amino acid use, resulting in a low concentration of skeletal muscle BCAA.[63,64] Decreased BCAA levels in cirrhosis also result from increased use of BCAA as a donor of amino groups to alpha-ketoglutarate for synthesis of glutamate, which in muscles is involved in ammonia detoxification.[65] Because of a limited supply of BCAA in cirrhosis patients, synthesis of other essential proteins such as albumin takes precedence over muscle protein synthesis, resulting in sarcopenia.[64] BCAAs are involved in the metabolism of carbohydrates, proteins, and fats, as well as IR and cell proliferation.[64] BCAAs have been demonstrated to increase glucose uptake in skeletal

muscle via activating PI3K and protein kinase C.[66]

Generally, amino acid deficiency causes activation of the integrated stress response (ISR) via an amino acid deficiency sensor, i.e. general control nondepressed 2.[67] That causes eukaryotic initiation factor 2 to be phosphorylated, resulting in a decrease in protein synthesis and an increase in activating transcription factor 4 (ATF4) mRNA. Activated ATF4 lowers the need for amino acids and inhibits mTORC1 signaling to promote autophagy in an attempt to preserve amino acid levels.[68] LC patients have increased general control nondepressed 2 activation and eukaryotic initiation factor 2 phosphorylation, as well as reduced mTORC1 signaling, similar to the ISR that results from amino acid deficiency.[17,69] Hyperammonemia, on the other hand, affects the ISR by preventing the expression of ATF4 mRNA, which results in an increase in autophagy and a reduction in muscle protein synthesis.[17] Moreover, in a second route, an amino acid exchanger is activated in LC patients in response to hyperammonemia, resulting in an increase in leucine uptake.[17,69] Leucine is used in the mitochondria to produce acetyl-CoA to generate energy.[66] Leucine transport relies on glutamine transfer via the glutamine exchanger, while glutamine is largely used for ammonia detoxification in hyperammonemia.[17,70] Overall, these metabolic alterations result in a negative protein balance that contributes to sarcopenia development.

Endocrine dysfunction

Changes in the hypothalamic-pituitary-gonadal axis in male patients with LC can result in a decrease in testosterone production and an increase in aromatase activity, an enzyme that converts testosterone to estrogen.[71] Testosterone inhibits myostatin expression and signaling, and low testosterone levels promote sarcopenia in male patients with LC.[72] The growth hormone (GH)/IGF-1 axis is disturbed in patients with CLD, and endogenous GH secretion is elevated.[73,74] Because the liver is the principal source of IGF-1, LC patients with lower levels of IGF-1 produce more GH because of a loss of feedback inhibition. As a result, patients with LC have a state of hepatic GH resistance. Derangement of the GH/IGF axis may contribute to sarcopenia because GH and IGF-I are potent regulators of anabolism. Because IGF-1 and testosterone repress myostatin, lower levels of these growth hormones in LC patients result in increased myostatin expression.[74,75] IGF-1 promotes muscle growth by stimulating the mTORC1 signaling pathway and prevents muscle atrophy by inhibiting ubiquitin ligase activity.[76]

Insulin resistance

Hyperinsulinemia and IR are prevalent in LC patients.[77,78] Reduced hepatic insulin extraction and portosystemic shunting are thought to cause hyperinsulinemia, with hyperglucagonemia and pancreatic islet hypertrophy also having a role. As a result of persistent hyperinsulinemia, insulin receptors are downregulated on target cell membranes, leading to IR.[79] Clamp studies on whole-body glucose utilization revealed that IR in LC patients was associated with a decrease in non-oxidative glucose disposal, mainly in skeletal muscles.[80,81] Thus, sarcopenia also contributes to the development of IR as skeletal muscle is the predominant site of post-prandial glucose uptake.[82] On the other hand, IR promotes sarcopenia by causing an increase in muscle protein breakdown and a decrease in muscle protein synthesis. IR increases lipolysis and the release of free fatty acids in adipose tissue, which inhibits IGF-1 signaling.[83] IR leads to an increase in lipogenesis and suppression of beta-oxidation in muscles, resulting in myosteatosis.[83] Reduced circulation levels of adiponectin and vitamin D may cause IR, resulting in sarcopenia.[84] IR is a common link between sarcopenia and NAFLD.[13,14] However, there are different major pathways inducing NAFLD, and the one with a strong hepatic genetic component is only weakly associated with IR and dysregulated hepatokine release.[85] Thus, stratification of NAFLD by major metabolic pathways, may be done while investigating the relationship of fatty liver with metabolism and also skeletal muscle mass and function.

Gut dysbiosis

Changes in the composition and function of the gut microbiota are common in LC patients, influencing host immunity and many metabolic activities. The intestinal translocation of lipopolysaccharide, a gut-derived endotoxin, is associated with the pathogenesis of IR.[86] Obesity, metabolic disorders, and diabetes have all been linked to intestinal dysbiosis.[87] In LC patients, gut dysbiosis contributes to hyperammonemia, which has a role in the development of sarcopenia and peripheral IR.[88] Furthermore, the gut microbiota produces a number of compounds, including BCAA, whose levels in the blood have been associated to the risk of IR and DM.[89] A recent study demonstrated that the gut microbiome of CLD patients with sarcopenia was prodiabetogenic, with a high abundance of gram-negative bacteria and a low Firmicutes/Bacteroidetes ratio.[90] As a result, gut dysbiosis could play a role in sarcopenia and diabetes in LC patients.

Clinical and metabolic implications of sarcopenia

In patients with LC, sarcopenia is linked to a wide range of consequences, such as HE, worse quality of life, infection risk, and increased mortality (Table 2).[7–11,42,91–98] Notably, the impact of sarcopenia on survival has been found mainly in early stages of cirrhosis, with no such association found in patients with high MELD scores, Child-Pugh class C, and hepatic venous pressure gradient >20 mmHg, implying that sarcopenia has little additive impact on mortality prediction for patients who are severely ill.[91,99] Other clinical effects of sarcopenia include decreased functional independence, such as difficulty walking and doing daily basic activities, as well as an increased risk of falls and fractures.[100] From a metabolic standpoint, sarcopenia influences glucose tolerance, ammonia metabolism, amino acid metabolism, and bone production. Osteosarcopenia, defined as sarcopenia and osteoporosis occurring at the same time, is also common in CLD patients.[101] In cirrhosis patients, sarcopenia impairs creatinine production, affecting renal evaluation.

Sarcopenia and HE

Hyperammonemia is a common in LC and has been linked to the development of sarcopenia. Sarcopenia, in turn, tends to exacerbate hyperammonemia by limiting muscle ammonia consumption. Ammonia is a neurotoxic chemical that has been linked to the development of HE and minimal hepatic encephalopathy (MHE). Furthermore, skeletal muscle proteolysis compensates for high amino acid consumption in patients with advanced LC, allowing for enhanced gluconeogenesis. Both BCAAs and aromatic amino acids (AAAs) are produced in this process. In skeletal muscle, however, the localized branched-chain keto dehydrogenase preferentially catabolizes BCAAs.[48,102] As a result, BCAA levels drop while AAA levels rise, lowering the Fischer ratio. A decreased Fischer ratio has been linked to HE via increasing AAA uptake in the brain and altering neurotransmission.[103]

Several studies have found an independent link between

Table 2. Studies on clinical implications of sarcopenia in CLD

Author, year	Design	Aims/objectives	Population	Main outcomes
Koo *et al*., 2017[42]	Cross-sectional	Association between sarcopenia and histological severity of NAFLD	309 patients (240 with NAFLD)	Sarcopenia was significantly associated with NASH, OR 2.28 (1.12–4.30), and significant fibrosis, OR 2.05 (1.01–4.16)
Tandon *et al*., 2012[11]	Retrospective	Prevalence and clinical impact of sarcopenia in LC patients	142 LC patients listed for LT	Sarcopenia was independent predictor of mortality, HR 2.36 (1.23–4.53), after adjustments for age and MELD scores
Montano-Loza *et al*., 2012[7]	Cross-sectional	Incidence and association of sarcopenia with prognosis of LC	112 patients with LC	The incidence of sarcopenia was 40%. Sarcopenia was associated with mortality in patients with LC, HR 2.21, p=0.008
Montano-Loza *et al*., 2015[91]	Retrospective	Impact of sarcopenia on mortality prediction in LC	669 patients with LC	Sarcopenia was independently associated with mortality, HR 0.97 (0.96–0.99). Inclusion of sarcopenia in MELD further improved the prediction
Merli *et al*., 2013[92]	Prospective	Relationship between sarcopenia and HE	300 LC patients	HE were significantly higher in LC patients with muscle depletion or decreased muscle strength. (30% vs. 15%, and 29% vs. 16%, respectively)
Kim *et al*., 2014[94]	Retrospective	Association between sarcopenia and mortality in LC patients with ascites	65 patients with LC	Sarcopenia is an independent predictor for long-term mortality in LC patients with ascites, HR 0.812 (0.684–0.965)
Durand *et al*., 2014[8]	Retrospective	Prognostic value of muscle atrophy in cirrhosis	562 patients with LC	Transversal psoas muscle thickness /height on computed tomography independently predicted mortality in LC patients, HR 0.86 (0.78–0.94)
Masuda *et al*., 2014[95]	Retrospective	Impact of sarcopenia on mortality and sepsis after LDLT	204 LC patients	Sarcopenia was an independent predictor of mortality (HR 2.06) and sepsis (HR 5.31) after LDLT
Fujiwara *et al*., 2015[96]	Retrospective	Impact of sarcopenia and adiposity on HCC	1,257 patients with HCC	Sarcopenia (HR 1.52) and myosteatosis (HR 1.34) independently predicted mortality in patients with HCC
Nardelli *et al*., 2017[93]	Prospective	Association between sarcopenia and post-TIPS HE	46 LC patients	Sarcopenia independently predicted the development of HE after TIPS (HR, 31.3 (4.5–218.07)
Kaido *et al*., 2013[97]	Retrospective	Impact of sarcopenia on pot-LT survival	124 LC patients	Sarcopenia was an independent risk factor for mortality after LT (OR 4.846 (2.092–11.790))
Montano-Loza *et al*., 2014[98]	Retrospective	Impact of sarcopenia on outcomes after LT	248 LC patients	Sarcopenia was associated with longer hospital stays (40 vs. 25 days) and a higher risk of bacterial infection (26% vs. 15%) after LT

HR, hazard ratio; HCC, hepatocelluar carcinoma; HE, hepatic encephalopathy; LC, liver cirrhosis; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OR, odds ratio; TIPS, transjugular intrahepatic portosystemic shunt.

sarcopenia and HE.[92,93,104] Merli *et al*.[92] reported that sarcopenia was independently linked with overt HE during hospitalization in a multivariate logistic regression analysis of 300 cirrhotic patients.[92] A Japanese group of researchers revealed that handgrip strength stratifies LC patients at high risk of developing overt HE.[104] In a study of 46 LC patients undergoing transjugular intrahepatic portosystemic shunt (TIPS), Nardelli *et al*.[93] found that all patients who developed post-TIPS-HE (46%) had sarcopenia, and only MELD score and sarcopenia were independently linked with the development of HE.[93] In a prospective study, 84% of LC patients with MHE had sarcopenia, compared with only 31% in those without MHE. Sarcopenia also independently predicted the occurrence of MHE in the multivariate analysis.[105]

Sarcopenia and HD

LC has long been known to have diabetogenic potential, and the term hepatogenous diabetes was coined to describe the condition.[106] Although the pathophysiology of HD is complex and poorly understood, sarcopenia, sarcopenic obesity, gut dysbiosis, and hyperammonemia have been linked to the abnormal glucose metabolism in LC.[10,107] The majority of postprandial glucose consumption occurs in skeletal muscle, making it an important insulin target organ for glucose uptake and utilization.[14] As a result, skeletal muscle loss can lead to significant IR.[14,107] Patients with HD often have abnormal oral glucose tolerance tests despite having normal fasting blood glucose levels, prompting us to believe that

Table 3. Studies on BCAA treatment for sarcopenia in patients with liver cirrhosis

Author, year, country	Study type	Study subjects	Intervention	Main results
Tsien, 2015, Canada[69]	Prospective study	06 compensated, alcoholic cirrhosis patients and 08 controls	Single dose of BCAAs mixture enriched with leucine	Acute reversal of Impaired mTOR1 signaling and skeletal muscle autophagy by BCAA/leucine
Hiraoka, 2017, Japan[114]	Prospective study	33 patients with LC	BCAA supplementation (protein 13.5 g) as a late evening snack and walking exercise for average of 2.7±0.7 months	Average daily steps, muscle volume, leg strength, and handgrip strength were increased at 3 months
Uojima, 2017, Japan[115]	Prospective study	82 patients with LC	24-week, twice a day, treatment with oral BCAAs supplement powder	BCAAs improved low muscle strength without any positive effect on muscle mass
Kitajima, 2018, Japan[116]	Prospective study	21 patients with LC	48 weeks of supplementation with BCAAs	Amelioration of hypoalbuminemia associated with BCAAs was correlated with decreased myosteatosis with better survival rates, maintained skeletal muscle mass, and improved glucose sensitivity
Ruiz-Margáin, 2018, Mexico[117]	Randomized trial, open label	37 LC patients in the intervention group and 35 in the controls	BCAAs (110 g daily) plus HPHF (1.2 g/kg protein and 30 g fibers). Controls were given only HPHF; For 6 months	BCAA group had an increased muscle mass and a decreased fat mass, compared with the control group
Marchesini, 2003, Italy[118]	Randomized study, double-blind	174 patients with advanced cirrhosis.	1-year BCAAs against lactoalbumin or maltodextrins	BCAAs prevented progressive hepatic failure and improved or maintained nutritional parameters and liver function tests
Les, 2011, Spain[119]	Randomized study, double-blind,	116 patients with cirrhosis	30 g of BCAA or maltodextrin during 56 weeks	BCAA supplementation improved muscle mass and minimal hepatic encephalopathy

BCAA, branched-chain amino acid; HPHF, high-protein, high-fiber diet; LC, liver cirrhosis.

cirrhosis-related sarcopenia may play a role in HD pathophysiology. Sarcopenia is commonly accompanied by myosteatosis, macrophage infiltration, inflammatory cytokine production, and mitochondrial dysfunction, all of which contribute to IR and reduced glucose uptake and utilization.[15] Moreover, skeletal muscles release a number of cytokines, including irisin and IL6, that control insulin sensitivity.[108,109] As a result, sarcopenia-related reduction of muscle secretary function may contribute to the glucose intolerance in LC patients. Sarcopenic obesity has even greater impact on metabolic profile than sarcopenia alone.[45]

Sarcopenia and serum creatinine

Creatinine is a low-molecular-weight endogenous molecule generated from creatine and creatine phosphate, both of which are present mainly (95%) in muscle. Because serum creatinine levels correlate with muscle mass, it has been used as marker to measure muscle mass.[110] Creatinine is a useful agent for estimating glomerular filtration rate (GFR) because it is uncharged, unbound to serum proteins, and filtered freely by the glomerulus without tubal reabsorption. However, creatinine production is reduced in cirrhosis patients with sarcopenia, which may lead to an overestimation of GFR and consequently an underestimation of renal impairment.[111]

Therapeutic perspective of metabolic correction

Sarcopenia is treated with a multifaceted strategy that includes lifestyle, nutrition, exercise, and adjunct medicine to treat metabolic imbalance. Several therapeutic options have been explored for sarcopenia, but only a handful have focused on CLD patients, with the majority of them being nutritional. A caloric energy intake of 3.0–35 kcal/kg/day should be advised, with a target protein consumption of 1.2–1.5 g/kg/day.[112] Eating 3–5 meals each day and a late evening snack is also recommended to keep the starvation period short and improve protein turnover.[112] Alcohol and smoking cessation should also be recommended. Recent studies have looked into ways to minimize ammonia, replenish BCAA, address hormonal imbalances, and use myostatin antagonists.

In a preliminary study, ammonia-lowering treatment using L-ornithine L-aspartate improved skeletal muscle mass and strength, along with lowered circulation and skeletal muscle ammonia levels.[113] Ammonia-lowering strategies for the treatment of sarcopenia in CLD need to be proven in large, well-controlled clinical trials. The use of BCAAs to promote muscle protein synthesis appears to be supported by research.[69,114–119] Long-term BCAA supplementation has been reported to improve protein metabolism in LC patients, resulting in increased muscle mass and MHE (Table 3).[69,114–119] However, despite the positive results, a formal

recommendation on the use of BCAA for sarcopenia in CLD is still in the works. Testosterone treatment has been found to help LC patients gain muscle and bone mass.[120] Testosterone increases IGF-1 and decreases myostatin, both of which are beneficial to muscle growth. However, in patients with CLD, adverse events such as cardiovascular disease, fluid retention, gynecomastia, and prostatic disease progression have been reported, and long-term safety has yet to be proven. Similarly, while GH replacement therapy can increase muscle mass, it is associated with a high rate of adverse effects, such as increasing ascites and edema, as well as expensive cost.[121] Because of the deleterious effects of myostatin on muscle protein turnover, many myostatin inhibitors (e.g. stamulumab, landogrozumab, and trevogrumab) are now being investigated for their safety and efficacy.[122] Furthermore, glucose-lowering medications such as metformin and thiazolidinedione have been shown to improve skeletal muscle mass, strength, and performance in diabetes patients, indicating the need for their evaluation in a long-term, well-designed study in CLD patients.

Conclusions

In conclusion, sarcopenia is common in patients with CLD and is associated with a number of metabolic dysregulations. The decreased endocrine activity of both the liver and the skeletal muscles in such patients has reciprocal implications that necessitate special attention. Hyperammonemia, amino acid depletion, hormonal imbalance, and IR are among the key pathophysiological changes seen in LC patients that contribute to sarcopenia development. Given the clinical implications, a thorough metabolic evaluation in LC patients with sarcopenia should be performed for improved risk stratification and therapeutic guidance. However, therapy for sarcopenia that targets potential risk factors is still evolving, and more study in this field is needed.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (RK, SSP), data acquisition (RK, SSP, RNP, UA), and drafting of manuscript (RK, SSP, RNP), Critical revision and technical support (UA, RNP). All authors have made a significant contribution and have approved the final manuscript.

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