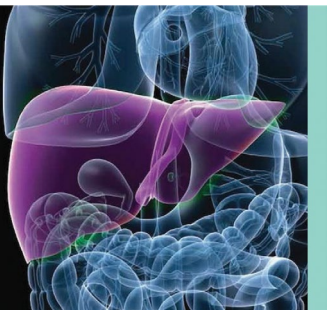

Causes of Sarcopenia in Liver Cirrhosis

Monica Bojko, M.S., R.D.

Sarcopenia is one of the most common complications in advanced liver disease, affecting 30% to 70% of patients with cirrhosis.[1] This condition is of significant concern in this population because sarcopenia has been associated with higher mortality, increased hospital admissions, worse post–liver transplant outcomes, decreased quality of life, and increased risk for other complications associated with cirrhosis (Table 1).[1] Sarcopenia in cirrhosis is multifactorial and is not completely explained by simple malnutrition (Table 2). It is difficult to treat, and there are currently no proven effective therapies to prevent or reverse sarcopenia.[2] Although it is inarguable that barriers to adequate calorie and protein intake exist, such as anorexia and nausea, sarcopenia is also associated with complex metabolic and hormonal changes that are not adequately treated by nutrition and physical activity (PA) alone. A better understanding of the etiology of sarcopenia in cirrhosis may produce additional targeted therapies which may improve patient outcomes when used in combination with PA and nutrition optimization techniques (Table 3).

MECHANISMS OF SARCOPENIA IN CIRRHOSIS

Sarcopenia in patients with cirrhosis is defined by loss of muscle mass and decreased functional capacity, as well as greater risk for morbidity and mortality.[3] Although the pathogenesis of sarcopenia in cirrhosis is poorly understood, a number of proposed mechanisms have been described previously which represent an imbalance between muscle breakdown and formation.[1,4] Sarcopenia in cirrhosis appears to be affected by alterations in protein turnover, energy disposal, and hormonal and metabolic changes which lead to muscle depletion[1,4] (Fig. 1).

Altered Carbohydrate and Lipid Metabolism

Metabolic changes and alterations in protein turnover are major factors in muscle depletion in sarcopenia of chronic disease. Carbohydrates are used less for energy because of the decreased ability of hepatocytes to synthesize, store, and break down glycogen, resulting in increased ketogenesis and amino acid consumption.[5] Increased mobilization

Abbreviations: BCAA, branched-chain amino acid; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; mTOR, mammalian target of rapamycin; PA, physical activity; REE, resting energy expenditure; TCA, tricarboxylic acid; UPP, ubiquitin-proteasome pathway.

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TABLE 1. NEGATIVE COMPLICATIONS ASSOCIATED WITH SARCOPENIA[1]

- Higher mortality
- Increased hospital admissions
- Worse post–liver transplant outcomes
- Decreased quality of life
- Increased risk for other complications associated with cirrhosis

TABLE 2. MECHANISMS THAT CONTRIBUTE TO SARCOPENIA IN CIRRHOSIS[1,4]

- Malnutrition and malabsorption
  - o Anorexia, nausea, dysgeusia
  - o Hypermetabolism
  - o Decreased intake
  - o Decreased bile production and pancreatic insufficiency
- Altered lipid and amino acid metabolism
  - o Decreased gluconeogenesis
  - o Increased ketogenesis
  - o Increased whole-body protein turnover
- Decreased hepatic ammonia clearance → hyperammonemia
- Increased inflammatory markers (TNF-α, IL-6)
- Increased myostatin
- Decreased anabolic hormones (IGF-1 and testosterone)
- Inactivity

TABLE 3. PROPOSED TREATMENTS FOR SARCOPENIA IN CIRRHOSIS[1,4]

Current nutrition and PA recommendations
- High-calorie/protein diet
- Late-evening or overnight snacks (high protein)
- PA (strength training)
- BCAA supplementation

Potential future hormonal and metabolic targeted therapies
- L-Leucine and/or L-citrulline supplementation
- Testosterone supplementation (men)
- Myostatin antagonists
- mTOR signaling upregulators
- Mitochondrial antioxidants

of amino acids for gluconeogenesis and energy favors a more rapid transition from carbohydrate metabolism to ketogenesis, such as during the span of an overnight fast, resulting in risk for skeletal muscle loss and reduced fat stores.[5,6] One proposed intervention for sarcopenia is a high-protein late-night or overnight snack to prevent this shift in metabolism. Decreased hepatic glycogen stores in cirrhosis promote the use of fat and protein for gluconeogenesis and also result in lower circulating branched-chain amino acids (BCAAs). BCAA supplementation has been proposed to address increased protein catabolism by providing additional energy substrate, as well as stimulation of muscle protein synthesis via activation of the mammalian target of rapamycin (mTOR) pathway; however, more randomized control trials are needed to determine efficacy.[3,4,6,7]

Inhibition of Muscle Growth

Imbalance in muscle formation and degradation is mediated by multiple factors including hyperammonemia, increased myostatin, and decreased growth hormones. Of these, hyperammonemia, due to decreased hepatocellular clearance of ammonia from amino acid metabolism, appears to be the most well-documented factor in cirrhosis to contribute to sarcopenia.[1,4,8] Hyperammonemia upregulates myostatin production, which inhibits muscle growth by decreasing satellite cell proliferation and differentiation. Myostatin is typically suppressed by testosterone and insulin-like growth factor 1 (IGF-1); therefore, decreased levels of these growth hormones observed in cirrhosis also likely contributes to elevated myostatin expression in these patients.[4,9] Low levels of IGF-1 may also reduce mTOR activation of muscle protein synthesis, further contributing to sarcopenia.[9] Physical activity, specifically resistance training, has been proposed as an intervention in patients with sarcopenia of cirrhosis to prevent muscle breakdown and maintain physical function through its role in upregulating IGF-1. This upregulation of IGF-1 could result in downregulation of myostatin and subsequent increase in circulating growth hormones; however, more evidence is needed to support this recommendation for this condition. Another mechanism by which hyperammonemia contributes to sarcopenia is through the liver-muscle axis; ammonia accumulates in skeletal muscle and prevents production of α-ketoglutarate, a major substrate for the tricarboxylic acid (TCA) cycle. Due to reduced flux of the TCA cycle, mitochondrial function may be impaired, resulting in lower concentrations of adenosine triphosphate, which may translate to reduced protein synthesis.[1,10]

Inflammation

Inflammation of chronic disease and circulating cytokines lead to inappropriate muscle autophagy. Research in sarcopenia of aging indicates increased muscle autophagy through the ubiquitin-proteasome pathway (UPP), which is upregulated by increased levels of inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6).[4,5] Cirrhosis, a known proinflammatory condition, may also contribute to sarcopenia because of increased resting energy expenditure (REE) partially driven by inflammatory mediators leading

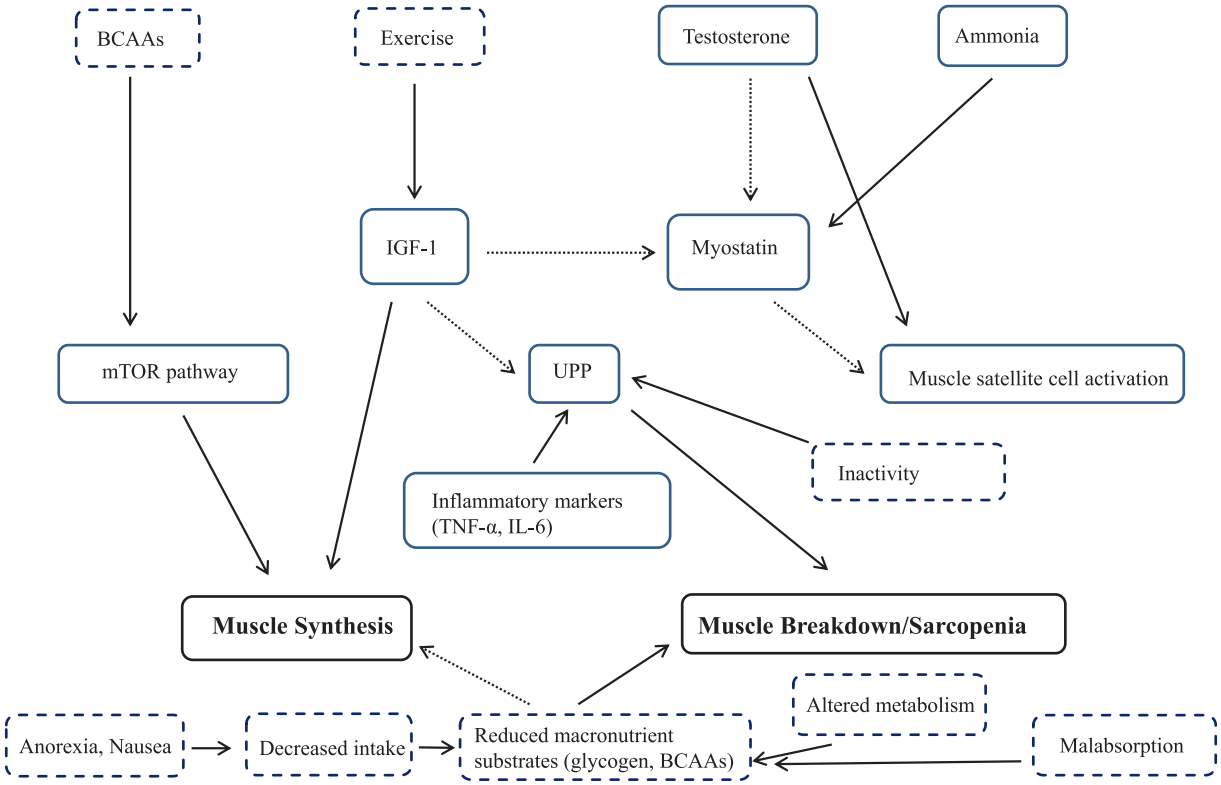

FIG 1 Overview of the mechanisms of muscle synthesis and breakdown in liver cirrhosis. Solid arrows indicate upregulators/promoters, dashed arrows indicate downregulators/inhibitors, solid boxes represent hormonal/chemical/inflammatory factors, and dashed boxes represent nutritional/metabolic/PA factors.

to increased whole-body protein turnover.[1,4] Inactivity also stimulates the UPP pathway, providing further rationale for PA interventions.[4]

Malnutrition

Changes in nutrient ingestion, absorption, and utilization contribute to malnutrition in this population. Abdominal ascites, a major complication of cirrhosis, often causes abdominal pain and pressure, reduced appetite, and increased nausea. Elevated inflammatory markers such as TNF-α may also exacerbate nausea and anorexia.[4] Pancreatic insufficiency and decreased bile flow in a subset of this population may lead to increased fat malabsorption and decreased absorption of fat-soluble vitamins.[6] Malnutrition may also contribute to higher REE, increasing total energy and protein needs and further exacerbating the altered macronutrient metabolism and increased whole-body protein turnover observed in cirrhosis. High-calorie/high-protein diets, oral nutrition supplements, and enteral or parenteral nutrition support (when appropriate) are often recommended to mediate sarcopenia in cirrhosis through increased nutrient intake; however, nutrition interventions alone cannot fully address the many other factors that contribute to sarcopenia in this population.[6,11]

CONCLUSION

Sarcopenia may be considered one of the most common and significant complications of liver cirrhosis, and has been associated with adverse outcomes and increased morbidity and mortality. Current interventions are focused mainly on nutrition and PA, and have been inadequate on their own to prevent or reverse sarcopenia. A comprehensive understanding of many interconnected mechanisms is needed to develop a therapeutic approach that addresses increased energy and protein requirements, hormonal abnormalities, altered metabolic pathways, and nutritional deficiencies contributing to sarcopenia in cirrhosis.

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