Implications of pre-transplant sarcopenia and frailty in patients with non-alcoholic steatohepatitis and alcoholic liver disease

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Contributions: (I) Conception and design: All authors; (II) Administrative support: P Puri; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
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Abstract: Frailty manifesting as sarcopenia is an independent risk factor for mortality in cirrhosis, and often presents in low model for end-stage liver disease (MELD) patients. Its etiology is multifactorial, but key physiologic changes culminate in altered energy utilization in the fasting state, preferentially utilizing muscle amino acids for gluconeogenesis thereby promoting sarcopenia. Hyperammonemia alters the circulating amino acid profile, diminishing pro-muscle branched-chain amino acids like leucine. The metabolic syndrome worsens sarcopenia through multi-tissue insulin resistance. Alcohol also exacerbates sarcopenia as a direct muscle toxin and inhibitor of growth signaling. Therapy is aimed at alcohol cessation, frequent high-protein meals, branched-chain amino acid supplementation, and diminished time spent fasting. Moderate exercise can improve muscle mass and muscle quality, though precise exercise regimens have not yet been explicitly determined. Studies are ongoing into the effects of myostatin antagonists and insulin sensitizers. The Liver Frailty Index can predict patients most at risk of poor outcome and should be considered in the management of all cirrhotic patients. Specialty testing like dual-energy X-ray absorptiometry (DEXA) scanning and cross-sectional estimates of muscle mass are areas of active research and may play a future role in clinical risk-stratification.

Keywords: Sarcopenia; frailty; non-alcoholic steatohepatitis (NASH); alcohol; transplant

Introduction

When the model for end-stage liver disease (MELD) was implemented for liver allocation in 2002 it was praised for its objectivity and capacity for reducing liver transplant wait-list mortality (1). Unfortunately, significant pre-transplant wait-list mortality persists, with growing interest to identify additional risk factors that might predict early mortality, particularly factors amenable to intervention. Already there are several known predictive characteristics not captured by the MELD-Na score, including age, metabolic co-morbidities, and frailty with its associated deficits in muscle mass and nutritional status. While age was originally included in the MELD calculation for predicting transjugular intrahepatic portosystemic shunt (TIPS)-related mortality, this factor was removed from the MELD when applied to transplant allocation to avoid age-related bias. Nevertheless, frailty, while typically age-associated, represents an age-independent functional risk factor in cirrhotic populations that may better represent patients' overall fitness for transplant and perioperative mortality risks.

The concept of frailty has been well established in the geriatric and cancer literature, and has been more recently applied to transplant populations including liver transplant

candidates. Ongoing efforts have been made to simplify and objectively quantify frailty in order to equitably apply its predictive capacity towards pre-transplant management. Although the underlying pathophysiology is multifactorial, it is believed to result from an aggregate decline of numerous systems, including neuromuscular, inflammatory, skeletal and endocrine systems. Features of frailty include sarcopenia, decreased cardiopulmonary reserve, diminished functional status deficits, and overt disability. These features are exacerbated by malnutrition and uncontrolled medical comorbidities (particularly heart disease and diabetes).

Evaluating for sarcopenia

Sarcopenia can be characterized by measures of total body muscle, muscle function/strength, and muscle quality as determined by fat content and lipid hormone metabolism. Simple but imprecise assessments include anthropomorphic measurements of body mass index (BMI), waist circumference, and mid-arm circumference to estimates fat composition and muscle mass. More robust and prognostic measures have since been described to better estimate overall body composition, including bioelectric impedance analysis (BIA) and dual-energy X-ray absorptiometry (DEXA). BIA involves holding a hand-held device that delivers a weak electric current throughout the body. Changes in body composition (lipid-rich fat *vs.* water-rich muscle) alters impedance, which is detected as a delay between the two hand-held contacts of the device. In general, BIA has been considered to be too variable for clinical use, though newer devices may be more reliable. Still, the "gold standard" for body composition assessment is considered to be the DEXA scan. More commonly used to measure bone density, the same instrument can be used to measure lean soft tissue (muscle) and by extension estimate the fat fraction by subtracting lean tissue from total body mass.

Radiographic studies are continually evolving to better quantify the anatomical distributions of muscle, subcutaneous and visceral fat [subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT)]. First described in 1985, the skeletal muscle index (SMI) approximates total body muscle from a single cross-sectional image at the level of the L3 vertebral body (SMI, or L3-SMI) (2). The SMI (and other radiographic variables) can be adjusted for the patient's sex, age and vertebral level, available under the Reference Analytic Morphomic Population (RAMP) tool at http://www.med.umich.edu/surgery/morphomics/ramp.

In general, cut-off values for sarcopenia in patients with cirrhosis are defined as SMI <50 cm^2/m^2 in males and <39 cm^2/m^2 in female patients (3). While alternative (simpler) radiographic measures have been more recently proposed, including the psoas muscle index (PMI), it should be noted that PMI has been found to correlate poorly with SMI, with overall less sensitivity for detecting sarcopenia (4,5).

Frailty assessment

Frailty (diminished physical function due in part to sarcopenia) is now a known predictor of wait-list mortality independent of the MELD-Na score in liver transplant candidates (and perhaps an even better predictor of mortality in sarcopenic patients with a MELD-Na score <18). In a comparative study (1), cirrhotic patients listed for liver transplantation with a MELD-Na >12 were assessed with four frailty indices including the Fried Frailty Instrument (FFI, assesses 5 domains of functionality, frail if score ≥3), Short Physical Performance Battery (SPPB, frail if <9), Activities of Daily Living (ADL), and Instrumental ADL scales. Both the FFI and SPPB were found to be predictive of wait-list mortality, independent of the MELD-Na score. For each 1-unit increase on the Fried Frailty assessment (increasing frailty) there was a MELD-adjusted 45% increased risk of wait-list mortality. Similarly, a 1-unit decrease in the SPPB (increasing frailty) was associated with a 19% MELD-adjusted increased risk in mortality.

It is notable that the FFI has both objective and subjective measures: hand-grip strength as quantified by a hand-held dynamometer, a 4-meter timed walk test, unintentional weight loss <10 pounds in the previous year, responses to a physical activity questionnaire over the last 4 weeks, and the patient's subjective assessment of personal exhaustion. Notwithstanding the valuable implications of patients' own subjective abilities to participate in their daily routines, the subcomponents of the test that most-predicted mortality were all objective: grip strength, unintentional weight loss, and physical inactivity. The SPPB, on the other hand, is entirely objective and requires no specific equipment, consisting of timed repeated chair stands, a sequence of balancing tests, and an 8 foot (2.44 meter) timed walk test. The advantages of either test are that they can be performed quickly, repeatedly, and in the clinical setting, negating the need for complex metabolic assessments (e.g., cardiopulmonary exercise testing, isokinetic muscle testing). Moreover, a hybrid test of the most objective and predictive components of both tests (age,

3 grip strengths, 5 chair stands, 3-second holding balance) can now be readily calculated as the Liver Frailty Index (LFI) from the authors' website: https://liverfrailtyindex.ucsf. edu. This assessment has since been subsequently validated as predictive for frailty in both cirrhotic and noncirrhotic populations (6).

Pre-transplant outcomes

Sarcopenia and frailty both predict morbidity and mortality in patients with cirrhosis. A prospective study demonstrated a significant increase in both overt and covert hepatic encephalopathy in hospitalized patients with sarcopenia (decreased mid-arm muscle circumference and hand-grip strength), but not BMI (7). Another study utilized anthropometric measurements to estimate malnutrition and determined that both severe muscle mass depletion (mid-arm circumference <5th percentile) and severe fat depletion (triceps skinfold thickness <5th percentile) were independent predictors of mortality in patients awaiting transplant (8). Similarly, estimates of total body muscle using L3-SMI found that radiographic sarcopenia was an independent predictor of pre-transplant mortality (9). Hamaguchi *et al.* further assessed muscle quality by measuring intramuscular adipose content (IMAC) by CT scan at L3. With this measurement, they found additive post-transplant mortality risks for both pre-transplant SMI muscle mass and muscle quality (myosteatosis) (10). For patients waiting on the liver transplant list, sarcopenia progresses with an average loss in SMI of 1.3% per 100 days along with worsening myosteatosis as detected by –2.5% Hounsfield units per 100 days, while visceral fat appears stable (11).

Of particular interest, both Lai *et al.* and Tandon *et al.* observed that the greatest sarcopenia-related mortality risk was in patients with MELD-Na scores less than 15, suggesting that sarcopenia conveys a significant early-onset mortality risk not effectively captured by the MELD-Na score (1,9). These findings echo earlier observations that sarcopenia correlates with mortality in patients with Child-Pugh A and Child-Pugh B, but not Child-Pugh C cirrhosis (12). Alameri *et al.* also reported the same non-linear relationship between Child-Pugh status in chronic viral hepatitis patients with diminishing global function as measured by their six-minute walk distance (6MWD); specifically they noted a significant drop in functional status as patients progressed from chronic liver disease to Child-Pugh A cirrhosis, with a smaller decrease towards Child-Pugh B cirrhosis, but then found no further significant difference in the functional status of Child-Pugh B and C patients (13). The 6MWD was later shown to be predictive of mortality in patients listed for liver transplant (14).

Post-transplant outcomes

Several recent studies have looked at post-transplant outcomes of frail and sarcopenic patients. Pravisani *et al.* found that in a population with 35.1% sarcopenia in pre-living donor transplant patients, 28.9% still had sarcopenia by L3-SMI at 1-year post-transplant (15). Similarly, Bhanji *et al.* found sarcopenia in 50% of 293 pre-transplant patients by L3-SMI, 90% of which maintained sarcopenia at 1 year, with an additional 16% new onset sarcopenia (11). Follow-up CT scans within the first year demonstrated further decrease in muscle mass (median loss 2.4 cm^2/m^2), worsening myosteatosis (–5.0 Hounsfield units), and an increase in abdominal visceral fat (4.9 cm^2/m^2). From a functional perspective, Lai *et al.* recently determined that frailty worsens in the 3 months following liver transplant and improves modestly by 12 months, but with fewer than 40% achieving robustness (16). In a study of 69 post-transplant patients followed for a median of 2.8 years, there was ongoing evidence of sarcopenia in 45% by arm muscle area, with an even higher incidence of poor muscle function as measured by handgrip strength (71% with <30 kg) (17).

In the immediate post-operative period, a retrospective analysis demonstrated an increased risk of infections, longer ICU length of stay, and increased duration of hospitalization, but no apparently increased perioperative mortality risk (18). Longer-term outcomes, however, have been indeterminate. While one study suggests no additional risk of long-term mortality with sarcopenia (18), another notes a significant correlation between sarcopenia and long-term mortality after liver transplant (19). Among patients who underwent urgent inpatient evaluation and liver transplantation, sarcopenia predicted post-transplant mortality with higher rates of death at 1 year (86% *vs.* 95%) and 3 years (73% *vs.* 95%) compared to their non-sarcopenic peers (20).

Using CT estimates of muscle mass, DiMartini *et al.* found that 62% of pre-transplant patients with a BMI >25 (including both overweight and obese patients) were simultaneously sarcopenic, while 80% of cirrhotic patients with a "normal" BMI of 18.5–25 were also sarcopenic (21). In a retrospective analysis of 48,226 patients who had undergone liver transplant between 2002 and 2013 (Organ Procurement and Transplantation Network database),

Chang *et al.* reported best survival outcomes for patients with a BMI of 28–37, even after stratifying for MELD score, suggesting that patients listed for transplant may do better if they are able to maintain some of their BMI weight in the pre-transplant period (22). Moreover, they found that the relationship between BMI and mortality after transplant was "U"-shaped, with highest mortality risk at the extremes of BMI (<19 and >40), with a nadir (least mortality) at a BMI of 34. For patients with MELD scores below 19, a low BMI (<19) conferred additional mortality and graft loss risks compared to normal BMI transplant recipients (23). Post-transplant mortality outcomes for class-II obese patients (BMI 35–40) are comparable to those with normal BMI (24), however centers currently vary on the workup and listing of patients with morbid class-III obesity (BMI >40), including ongoing determinations about the role and timing of bariatric interventions (25).

Pathophysiology of sarcopenia in cirrhosis

The pathophysiology of muscle wasting in end-stage liver disease is multifactorial with significantly redundant cross-talk, but several key pathways predispose cirrhotic patients to a hyperactive catabolic state resulting in sarcopenia and subsequent frailty. Knowledge of the pathophysiology is important when identifying potential therapeutic targets for intervention.

First, the decompensated features of cirrhosis foment early satiety with subsequent reduced oral intake, nausea, and reduced physical activity. Patients later develop problems of malabsorption, reduced glycogen storage, increased systemic inflammation, and hypogonadism with decreased circulating testosterone (26). Hepatocellular dysfunction and portocaval shunting lead to hyperammonemia and a subsequent circulating amino acid imbalance. In particular, branched-chain amino acids (BCAA) are reduced, including the essential amino acid leucine, which are critical to maintaining and promoting skeletal muscle. Normally leucine, insulin, testosterone, and exercise-induced insulin-like growth factor (IGF-1) all converge to upregulate protein kinase B (Akt), which acts to inhibit FOXO-mediated protein degradation while simultaneously activating potent mTOR signaling for downstream muscle-protein synthesis. Growth hormone (GH) further contributes to IGF-1 signaling, however basal IGF-1 levels are significantly decreased in cirrhosis and demonstrate blunted response to exogenous GH

administration (27). The collective result is diminished protein synthesis, increased proteolysis, and impaired satellite cell function. Satellite cells act as precursors to new muscle fibers as myogenically-committed multipotent stem cells located in the periphery of terminally differentiated muscle fibers. When activated by Akt, satellite cells proliferate and promote the growth and repair of muscle tissue.

With overall diminished Akt activity, skeletal muscle loss proceeds through two primary catabolic pathways, the ubiquitin-proteasome pathway (UPP) and the lysosomal/autophagy system. Proteolysis via UPP involves conjugation of damaged substrates with ubiquitin followed by degradation in the 26S proteasome. Autophagy is a normal programmed cell death pathway that is activated in response to cell stress for the destruction and recycling of unnecessary, damaged, and/or dysfunctional cellular components. It involves the creation of a phagophore, followed by the capture of random and/or selected targets forming the autophagosome, fusion with the lysosome, and subsequent proteolysis of engulfed debris by lysosomal proteases (28).

As liver disease advances, skeletal muscle becomes increasingly important for ammonia detoxification, ultimately metabolizing up to 50% of circulating ammonia (29). Elevated ammonia depletes branched chain amino acids and potently activates skeletal muscle autophagy, exacerbating skeletal muscle wasting. Hyperammonemia further mediates expression of myostatin, a negative-regulator myokine which has been shown to circulate at high serum concentrations in cirrhotic patients (3). Myostatin activity is normally suppressed by IGF-1 signaling, but with blunted IGF-1 activity and ammonia-mediated NF-κB transcription, myostatin expression increases markedly. Myostatin becomes a potent inhibitor of skeletal muscle growth, diminishing protein synthesis through Akt/mTOR signaling and preventing satellite cell differentiation by promoting Smad3 interference of PCNA and Myo-D (30,31).

The fasting state is of particular concern in cirrhosis. Patients with liver cirrhosis have diminished glycogen stores, accelerated glycogenolysis (with accompanying hyperglycemia and glucotoxicity), and exhibit early-onset gluconeogenesis after short-term fasting, which predisposes to increased protein catabolic requirements and muscle depletion (32). Studies of the respiratory quotient (ratio of oxygen consumed to carbon dioxide produced) indicate an

increased reliance on gluconeogenesis rather than fatty acids during the fasting state in cirrhosis, driving consumption of muscle-derived amino acids (33).

Pathophysiology of sarcopenia in non-alcoholic fatty liver disease (NAFLD)

In NAFLD and non-alcoholic steatohepatitis (NASH), metabolic dysregulation manifests as insulin resistance (IR), enhanced lipolysis and hypoalbuminemia resulting in an increase in free fatty acids (FFA), low adiponectin, and high myostatin levels. Excessive growth of adipose tissue recruits tissue macrophages that promote local inflammation, culminating in adipose tissue IR (34). There is a subsequent reduction in adiponectin and PPAR-γ, resulting in increased circulating FFA (inadequately sequestered due to diminished albumin levels). Excess FFAs are taken up by liver and muscle cells, promoting steatosis in both organs and exacerbating IR in those tissues. Skeletal muscle IR diminishes normal lipid metabolism by PPAR-δ and AMP-activated protein-kinase. Similarly, liver IR reduces PPAR-α and Nrf-2 while promoting SREBP-1c, DGAT-2, and the release of pro-inflammatory cytokines (35). This culminates in increased circulating insulin and glucagon, increased lipolysis, and further elevation of free circulating toxic FFA. Despite excessive triglyceride stores, diminished liver PPAR-α function reduces fatty acid beta-oxidation. Excessive caloric intake further promotes de-novo lipogenesis with simultaneous reduction in very low-density lipoprotein (VLDL) secretion, resulting in retained triglyceride and hepatic steatosis.

Obesity and sarcopenia are interrelated features of the metabolic syndrome. Indeed, muscle loss has been linked to visceral adiposity, which in turn has been shown to be a better predictor of metabolic complications, poor cardiovascular outcomes, and pre-transplant mortality than simple BMI (36). SAT and VAT are metabolically distinct, with the latter associated with more severe clinical morbidity and increased cardiovascular mortality (37). The anomaly of abundant fat stores with simultaneous sarcopenia complicates assumptions of malnutrition and limits the utility of simple anthropomorphic measurements like BMI in assessing frailty. As a result, research increasingly focuses on skeletal muscle mass as a surrogate for whole-body protein adequacy, giving rise to the concept of sarcopenic obesity (38). Cirrhotic patients with sarcopenic obesity have worse clinical outcomes and survival (39).

While there are no readily available assessments of insulin sensitivity, IR can be estimated by calculating Homeostasis Model Assessment index for insulin resistance (HOMA-IR), which is the normalized product of both circulating insulin and glucose levels. However, a response to glucose challenge (e.g., by a euglycemic hyperinsulinemic clamp) is thought to be more diagnostic of IR and elucidate a more time-dependent metabolic profile. A particular benefit of this technique is that the insulin dose can be adjusted to determine IR in the liver (low-insulin state) as compared to IR in the peripheral skeletal muscle (high-insulin state) (40).

Pathophysiology of sarcopenia in alcoholic liver disease

Alcohol use disorder has been steadily rising to become the third leading cause of preventable death in the United States (41). Interestingly, a direct comparison of cirrhotic patients with varying etiologies of liver disease suggests that alcohol-related liver disease produces a higher prevalence and greater severity of sarcopenia (33). While much of alcohol-related sarcopenia is due to the pathophysiology of cirrhosis as described above, alcohol also produces direct toxic effects in muscle. Exposing animal models to ethanol has been shown to directly impair protein synthesis (42). Alcohol inhibits mTOR signaling and protein synthesis, likely through upstream Akt inhibition and AMPK inactivation by dephosphorylation (43-45). Chronic alcohol exposure also produces a pro-inflammatory state, impaired muscle mitochondrial function, and subsequent oxidative stress (46,47). While the liver metabolizes the majority of alcohol, there is evidence that skeletal muscle contributes significantly. However, excessive levels of ethanol and its toxic metabolite acetaldehyde can induce muscle loss through autophagy and, in extreme circumstances, induce rhabdomyolysis (48).

Patients presenting with alcoholic hepatitis are severely malnourished, and aggressive nutritional supplementation is required to improve survival outcomes (49). Alcoholic hepatitis often affects relatively younger patients (47.6± 10.4 years), yet despite their younger age many already show radiographic evidence of sarcopenia that independently predicts longer hospital stay, sepsis, multiorgan dysfunction, hepatic encephalopathy, and higher MELD scores despite a diminished creatinine (50,51). Patients with alcohol-related cirrhosis are also less likely to recover their muscle mass (L3-SMI) following liver transplantation. While obesity and diabetes were both associated with less sarcopenia at 1 year

Table 1 Therapeutic strategies for sarcopenia in cirrhosis, with disease-specific interventions

Alcohol cessation	Indicated in cirrhosis of all etiologies; alcohol exacerbates sarcopenia
Nutrition	
Daily requirements	Recommend 35–40 kcal/kg/day, including protein intake 1.2–1.5 g/kg/day (approximately 20–25 g of high-quality protein with each meal)
6 oz. chicken	36 g protein, 6.6 g BCAA
6 oz. salmon	34 g of protein, 5.9 g BCAA
6 oz. peanuts	12 g of protein, 6.8 g of BCAA
1 egg	6.3 g of protein, 1.3 g of BCAA
Late night snacks	Ample evidence for late-night snacks, reducing time spent fasting
Leucine-rich supplementation	12–14 g/day (e.g., 5–6 servings of commercially available supplements)
Exercise	Walking 30–40 min 3 to 4 times per week, lifting light weights 2 to 3 times per week
Metformin	Actively being studied in NAFLD patients
Myostatin antagonists	Investigational agents in cirrhosis, demonstrated benefit in geriatric trials
TIPS	May be considered in low MELD patients who already have indications
Gut microbiome	Investigational status at present, ongoing research underway
Diminished roles	
Ammonia-directed therapies	Hyperammonemia exacerbates sarcopenia, but anti-ammonia therapies beyond standard of care do not improve sarcopenia
Statins	Statin therapies have pleotropic benefits in cirrhosis and NASH, but do not appear to have a role in modifying sarcopenia
Testosterone	Studies have shown limited benefit
Growth hormone	Studies have shown limited benefit, however, the development of growth hormone agonists may provide new opportunities for study

BCAA, branched-chain amino acids; TIPS, transjugular intrahepatic portosystemic shunt; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

post-transplant [odds ratio (OR) of 0.847 and 0.408, respectively], patients transplanted for alcohol were more likely to have persistent sarcopenia (OR of 1.174) (15).

Treatment—nutrition

Treatment for frailty and sarcopenia begins with nutrition and exercise (*Table 1*). Nutrition efforts focus on high-energy high-protein diet (HEHP) and/or BCAA-rich protein supplementation, with increased meal frequency and late-evening snacks. European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on enteral nutrition in liver disease recommend overall energy intake of 35–40 kcal/kg/day, and protein intake 1.2–1.5 g/kg/day (approximately 20–25 g of high-quality protein with each meal) (52). This represents a 25–50% increase in

recommended daily protein for normal adults (0.8 g/kg/d). Examples of high-quality protein (containing essential amino acids in a proportion needed by the human body) include 6 oz. of chicken (36 g protein, 6.6 g BCAA), 6 oz. of salmon (34 g of protein, 5.9 g BCAA), 6 oz. of peanuts (12 g of protein, 6.8 g of BCAA), or 1 egg (6.3 g of protein, 1.3 g of BCAA). Adding two cans of Ensure Plus or Diabetic Resource to regular meals adds 710 kcal per day. For hospitalized patients, nutritional needs and malnourishment risks can be assessed using the Royal Free Hospital Nutrition Prioritizing Tool (53), which accounts for tube feeding, fluid status, unintentional weight loss, and admission circumstances (i.e., alcoholic hepatitis) to determine how aggressive inpatient nutrition measures should be applied.

Multiple studies have also shown that late-night snacks

(taken between 2,100 and 700 h) offers better protection against muscle loss compared to calorie-equivalent day-time snacks, decreases lipid oxidation and improves nitrogen balance (32,54). A HEHP diet of 1.56 g/kg/d in decompensated cirrhotic populations [Child-Turcotte-Pugh (CTP)-B/C] yields significant improvement in nitrogen balance over fasting individuals (55). Supplementation with leucine-rich protein (12–14 g/day) has also been of particular interest as a direct activator of mTOR-mediated protein synthesis. Cirrhotic patients placed on oral BCAA/leucine supplementation show reversal of impaired mTOR signaling and autophagy measures (56).

Treatment—exercise

In geriatric patients and healthy controls, exercise increases skeletal muscle mass and functional capacity through an increase in insulin signaling, protein synthesis, AMPK activity, and satellite cell activation. However, the role of physical exercise regimens (either aerobic or resistance activity) in preventing or reversing sarcopenia in cirrhotic patients is unclear. Patients with cirrhosis experience reduced exercise capacity secondary to fatigue and complications secondary to portal hypertension, including ascites and hepatic encephalopathy. There is also increased muscle ammoniagenesis and hepatic ureagenesis in cirrhotics during exercise, potentially limiting traditional exercise benefits (57). While concerns have been published about how resistance activity, even at a moderate level, could predispose decompensated patients to transiently increased portal pressures and risk complications like variceal bleeding, a review of thirteen exercise regimens in cirrhotic patients found exercise training to be well-tolerated, and results in improvement in exercise capacity and muscle mass (58). Accordingly, low-resistance aerobic exercise can be recommended to cirrhotic patients, e.g., walking 30–40 min 3 to 4 times per week, and lifting light weights such as hand weights 2 to 3 times per week.

Myostatin antagonists

Myostatin antagonists have shown promise in reversing sarcopenia in murine models of cirrhosis, with efforts underway to describe their use in human clinical trials. In non-cirrhotic elderly patients, myostatin inhibitors significantly increased lean body mass and functional capacity (faster stair climbing, chair rising, and gait speed) (59). Monoclonal antibodies against the myostatin receptor activin IIb (e.g., bimagrumab) have also demonstrated efficacy in mice, with upcoming randomized controlled trials (60).

Insulin sensitizers

Insulin sensitizing therapy (e.g., metformin) has been proposed as a mechanism for reducing complications of NASH cirrhosis (61). Furthermore, post-transplant patients are prone to developing metabolic complications that reduce muscle mass and quality, including post-transplant diabetes mellitus (PTDM) and IR. Often referred to as "new-onset diabetes after transplant" (NODAT), this specific term may not be accurate since PTDM patients likely harbor early metabolic derangements making them predisposed to developing diabetes in the perioperative period. Indeed, pre-transplant SAT on imaging has been found to accurately predict the risk of developing PTDM (62). Insulin sensitizers may reduce this complication.

Gut microbiome

The gut microbiome is known to contribute to energy balance and metabolism, and in some cases promote obesity (63). There is evidence now that the microbiome may also predispose to sarcopenia (64). Alcohol is known to change the microbiome and alter epithelial tight junctions, resulting in dysbiosis, pro-inflammatory cytokines and elevated lipopolysaccharides, which can predispose to sarcopenia (33,65,66). Whether the microbiome can be altered to effect benefits in muscle maintenance is a focus of ongoing research.

TIPS *vs.* liver transplant

There are several reports that TIPS for refractory ascites may also reduce visceral fat and halt or reverse sarcopenia in patients with advanced liver disease (67,68). Failure to improve sarcopenia after undergoing TIPS is associated with a significant increase in post-TIPS mortality (9.8% *vs.* 43.5% at 40 months). In contrast, there is conflicting data regarding whether liver transplantation alters the course or prevalence of sarcopenia and frailty, as mentioned previously. Limited data are available regarding muscle function and quality post-transplant, however one retrospective study of 213 post-transplant patients demonstrated worsening LFI at 3 months, with only modest improvement at 12 months, suggesting that liver

transplantation has limited impact on muscle function (16). It is unclear why TIPS might confer a significant benefit on the reversal of sarcopenia while liver transplantation may not. Mechanistically both therapies decrease portosystemic pressures, with transplant also improving hepatic synthetic function. Moreover, hyperammonemia following TIPS could be expected to worsen sarcopenia rather than improve it. Still, the explanation may be related to the use of post-transplant calcineurin inhibitors, which have been directly implicated as mediators of persistent post-transplant sarcopenia (69,70).

Other therapies

Many other studied therapies have unclear, limited, or definitively no value. A careful evaluation of statin therapy in NAFLD has demonstrated no benefit in improving IR or liver fat percentage (40). Hyperammonemia, while known to contribute to sarcopenia, remains an unclear target for therapies; ammonia-reducing medicines have not yet been shown capable of reducing sarcopenia. Testosterone therapy has been considered but has also been demonstrated to have minimal benefit in cirrhotic patients, thought in part to be limited by high aromatase activity (71). Overall, the field of sarcopenia in cirrhosis is developing rapidly, with great interest in workup, evaluation, and the implementation of evidence-based interventions.

Acknowledgments

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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