TOPIC HIGHLIGHT

2015 Advances in Liver Transplantation

Sarcopenia and liver transplant: The relevance of too little muscle mass

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Author contributions: Kallwitz ER is entirely responsible for the drafting, editing and final version of this manuscript.

Conflict-of-interest statement: Kallwitz ER has no conflicts of interest to declare.

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Abstract

Loss of muscle mass and function is a common occurrence in both patients with decompensated cirrhosis and those undergoing liver transplantation. Sarcopenia is associated with morbidity and mortality before and after liver transplantation. The ability of skeletal muscle mass to recover after transplant is questionable, and long term adverse events associated with persistent sarcopenia have not been well studied. Limited data is available examining mechanisms by which decreased muscle mass might develop. It is not clear which interventions might reduce the prevalence of sarcopenia and associated health burdens. However, measures to either decrease portal hypertension or improve nutrition appear to have benefit. Research on sarcopenia in the liver transplant setting is hampered by differing methodology to quantify muscle mass and varied thresholds determining the presence of sarcopenia. One area highlighted in this review is the heterogeneity used when defining sarcopenia. The health consequences, clinical course and potential pathophysiologic mechanisms of sarcopenia in the setting of cirrhosis and liver transplantation are further discussed.

Key words: Sarcopenia; Liver transplantation; Cirrhosis; Body composition

Core tip: The loss of skeletal muscle mass, termed sarcopenia, is common in the setting of cirrhosis and liver transplant. Before liver transplant, it has been associated with increased morbidity and mortality. The long term effect of sarcopenia upon morbidity and mortality after transplant has been less rigorously studied. Data linking sarcopenia to adverse outcomes such as diabetes in the non-transplant setting are of interest especially with the high prevalence of post transplant metabolic syndrome. Current research on sarcopenia is limited by heterogeneity in the method to measure muscle mass and varied definitions of sarcopenia.

Kallwitz ER. Sarcopenia and liver transplant: The relevance

INTRODUCTION

Sarcopenia describes an involuntary loss of muscle mass and function that is observed with aging[1] and has been applied to persons with chronic diseases. In aging populations, loss of muscle mass was found to increase the risk of disability[2]. However, the consequences of sarcopenia are much greater than a decline in functional ability and include numerous adverse health manifestations. One such example is sarcopenic obesity, a condition when compared to obesity with normal muscle mass was associated with a higher risk of metabolic syndrome and coronary artery disease[3,4]. Sarcopenia is common in liver transplant candidates and recipients[5-9]. Sarcopenia in the setting of liver transplantation was associated with worse outcomes, including reduced survival[10-18]. The potential long term consequences of sarcopenia in the transplant setting, such as the development of sarcopenic obesity, are not well known. Many challenges exist in the study of sarcopenia in the setting of liver transplant and include defining sarcopenia, understanding mechanisms by which it develops and formulating preventive and therapeutic treatment options. The initial sections of this review describe the difficulty in defining sarcopenia and the heterogeneity in clinical studies relating to liver transplantation. Later sections in this review focus on the health consequences of sarcopenia in the transplant setting and potential mechanisms by which sarcopenia might develop.

HETEROGENEITY IN DEFINING SARCOPENIA IN THE SETTING OF CIRRHOSIS AND TRANSPLANT

The concept of sarcopenia is straightforward, representing a threshold of diminished lean body mass. Although the term sarcopenia is widely used, methods to assess sarcopenia and the thresholds to define it differ significantly. A common definition of sarcopenia is measured muscle mass two standard deviations below a reference range obtained from a young and healthy population[2]. However, measuring muscle mass alone does not account for the loss of muscle function that occurs with sarcopenia. Recognizing this limitation, the Society of Sarcopenia, Cachexia and Wasting Disorders in 2011 added a definition of "sarcopenia with limited mobility". Sarcopenia with limited mobility was defined as lean appendicular skeletal mass corrected for height greater

than 2 standard deviations below the mean of healthy persons aged 20 to 30 years of the same ethnic group and walking speed less than 1 meter per second or total distance walked during a six minute walk test less than 400 m[19]. Investigators examining muscle loss in the setting of cirrhosis and liver transplantation have used both quantitative and functional measures of muscle.

Further complicating research on sarcopenia in the setting of cirrhosis and liver transplantation are different methods to quantify muscle mass and muscle function. Some measures of muscle mass only account for a single anatomic area, such as single slice imaging or limb anthropometry. Other measures, including dual X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) are based on total body measurements. Often, total body measures are limited by their ability to measure different body compartments. Understanding the composition of these compartments is important as methods often measure skeletal muscle as a component of one compartment. For instance, some tests are only able to distinguish two compartments, fat mass and fat free mass. In a two compartment model, fat free mass consists of lean tissue, body water and bone mineral content. Many measures of body composition make assumptions on the proportion of total body water within lean body mass. In cirrhosis, when volume overload is present, the proportion of total body water is altered resulting in these methods being less accurate[20]. A combination of methods measuring four compartments is the most accurate means to measure body composition in cirrhosis with altered hydration[8,20]. These four compartments include fat mass and three compartments of fat free mass consisting of total body water (which can be divided into intracellular and extracellular water), total body protein and bone mineral content.

IS THERE A "GOLD STANDARD" MEASURE OF BODY COMPOSITION IN CIRRHOSIS?

Overall, there is no data to support any singular measure of body composition as a "gold standard" in the setting of cirrhosis and liver transplantation. As noted above, a four compartment model is likely required to make precise individual measurements of body composition in the setting of cirrhosis. This typically entails using combinations of measures, including a direct measure of total body water. Total body water can be directly measured by techniques such as radiolabeled water[8,21]. Measuring total body water is important to account for changes in total body water that occur with worsening severity of liver disease[8]. Early in the course of liver disease, excess fluid is mainly extracellular water[22], which was found

Table 1 Methods used to define muscle mass or function in cirrhosis

Method	Measurements obtained	Limitations	Notations
Multiple (four) compartment model	Total body water Body fat Fat free dry matter (protein) Bone mineral content	Requires combinations of methods (such as water dilution, densitometry)	Best model for cirrhosis when fluid overload is present
Dual X-ray Absorptiometry	Body fat Fat free body mass Bone mineral content	Limited ability to differentiate between lean tissue and body water with excess body water resulting in overestimation of fat free mass[1] Ascites, especially more than 4 liters, can significantly impact truncal measures[26,27]	Peripheral measures of lean tissue are less impacted by ascites[24,26]
Cross sectional imaging	Estimate skeletal muscle volume	Can be used to determine differences in skeletal muscle between groups[31] Studies use different muscle groups, anatomic levels and cutoff values to diagnose sarcopenia	Measurements 5 cm above the level of the 4th-5th lumbar vertebra had the highest correlation with total body skeletal volume[31]
Biochemical methods	Skeletal muscle mass	Total body protein is a measure of functional muscle mass and can be done through techniques such as *in vivo* neutron activation analysis 24 h urine creatinine is one method, but is limited in cirrhosis where renal insufficiency is common[93]	Use calculations based on these methods to quantify muscle mass
Bioelectrical impedence analysis	Fat free mass Fat mass	Guidelines recommend against routine use of BIA under states of altered hydration[94] BIA estimates of total body water were found to be accurate in cirrhotic patients without ascites, but performed poorly when ascites was present[23]	Segmental BIA was found to have a better correlation and lower standard error in estimating body cell mass in the setting of cirrhosis without ascites but still performs poorly with ascites present[95] Phase angle can be used. In a study including participants with a wide range in severity of liver disease, phase angle was positively correlated with total body protein, muscle mass and muscle strength[96]
Anthropometry	Estimate muscle mass	Edema alters results of anthropometry overestimating muscle mass[8]	Mid arm circumference was found to be one of the most accurate anthropometric measures[29] and was most predictive of clinical outcomes[97]
Functional Measures	Measures ability to perform physical task, for which muscle function is one component	Common functional measures assess all systems involved in exercise including cardiovascular, pulmonary, hematologic, neurologic and musculoskeletal[33]	Include tests such as submaximal cardiopulmonary fitness tests, six minute walk test, hand grip strength and isokinetic strength of flexion and extension at different joints Often simple tests such as hand grip correlate with measures of skeletal muscle[29]

BIA: Bioelectrical impedance analysis.

to increase in patients with cirrhosis even without clinically apparent edema or ascites[23]. Any increase in total body water can lead to the overestimation of lean body mass.

Often singular measures are chosen to estimate skeletal muscle. This is especially relevant when serial measures are being performed in a cohort. Limitations to using a singular test must be understood. Those limitations exist in both the methods of quantifying muscle and the definitions of sarcopenia. Table 1 highlights methods and limitations in techniques measuring muscle mass in cirrhosis. DXA and cross sectional imaging appear to have the most utility when using a single technique. In the non-transplant setting, a commonly accepted method to quantify sarcopenia is DXA[2]. Many investigators studying liver transplantation used cross sectional imaging, with the majority of data derived from this method. These two methods are discussed in further detail.

DXA is considered a gold standard examination of body composition in the non-transplant setting[2,24,25], however, it is recognized that fluid overload and ascites can impact the reliability of this technique. DXA can measure body fat, fat free mass and bone mineral content. Limitations in the ability to differentiate between lean tissue and body water are the main drawback to this technique[1] as excess body water may result in the overestimation of fat free mass. The greatest effect of volume overload and ascites upon measurements occurred in those made from the trunk[26-28]. This is particularly true when the ascites volume was greater than four liters[26]. Peripheral measures obtained by DXA, which is how sarcopenia is often quantified, were influenced less by ascites. Additionally, measurement of peripheral lean tissue mass was not altered after draining ascites[24,26]. In groups with cirrhosis, DXA was found to be more than 80% accurate in determining depleted body cell

mass[29]. When comparing DXA with anthropometry, single-frequency BIA, multiple frequency BIA and whole body gamma counting against gold standard multi-compartment measures of fat free mass in a cohort of patients with cirrhosis, DXA was found to have the smallest bias[30].

Cross sectional imaging has been frequently applied when studying sarcopenia in the setting of cirrhosis and liver transplantation. This method is appealing as imaging studies are often done for clinical indications during the care of patients with cirrhosis or around the time of liver transplantation. Single slice imaging was found to correlate highly with whole body skeletal muscle ($r = 0.924$)[31]. However, deviation in measurements obtained from single slice imaging compared to whole body imaging make this technique better for group comparison, as opposed to individual characterization, of muscle mass[31]. This method is additionally limited by the lack of a standardization in the technique of measuring muscle volume and the heterogeneity in defining sarcopenia (shown in Table 2). Muscle measurements 5 cm above the level of the 4th-5th lumbar vertebra were found to have the highest correlation with total body skeletal mass[31]. Imaging is often done based on clinical indications, and serial computed tomography measurements may be influenced by selection bias. A notable advantage of this method is the ability to measure quantity and quality of muscle simultaneously[14]. This can be done through measuring intramuscular adipose tissue content[32].

Functional measures of muscle are another common assessment undertaken in cohorts with cirrhosis. Measures of muscle function often measure strength of localized muscle groups or overall performance. One advantage is many of these measures such as six minute walk testing (SMWT) or hand grip dynamometry can be done quickly with little expense in large numbers of patients. The main disadvantage is many of these tests measure all systems involved in exercise or movement including cardiovascular, pulmonary, hematologic, neurologic and musculoskeletal[33]. For example, decreased performance on a submaximal exercise test could result from hepatopulmonary syndrome, cirrhotic cardiomyopathy, and sarcopenia simultaneously present in an individual transplant candidate.

CLINICAL CONSEQUENCES OF SARCOPENIA IN THE SETTING OF CIRRHOSIS AND TRANSPLANT

Measured decreases in both muscle mass and muscle function have been associated with multiple adverse clinical outcomes as shown in Table 2 and Table 3. Table 2 highlights the varied definitions of sarcopenia used in cirrhosis and transplant. Both tables highlight key outcomes and limitations in the

study of sarcopenia in cirrhosis and transplant. Studies of muscle mass[5-9] and function[34-37] were consistently found to be decreased in persons with cirrhosis and post liver transplant when compared to healthy control populations. When assessed by gender, decreases in lean body mass may be more pronounced in men[7]. Decreased measured skeletal muscle mass[10-18], muscle function[34,36,38] and performance during cardiopulmonary testing[39] all have been associated with pre- and post-transplant mortality. Decreased muscle quality, defined as increased intramuscular adipose tissue, was additionally associated with higher post transplant mortality[14]. The effect of diminished muscle mass and function on survival appears to be mostly independent of model for end stage liver disease (MELD) or Child-Pugh classification[12,40]. However, as the severity of liver disease increased, the effect of sarcopenia on survival might diminish. For example, one study found sarcopenia was associated with mortality only when MELD was less than 15[12]. Measures of muscle function also capture the risk of mortality in patients with debility, to which sarcopenia contributes. Distance ambulated on a six minute walk test less than 250 m was independently associated with increased mortality[34,36], and it was found that wait list survival improved for every incremental increase of 100 m walked (HR = 0.58, 95%CI: 0.37-0.93)[34]. Nutrition may be one means to improve these observed outcomes with sarcopenia. In patients with pretransplant sarcopenia, nutritional supplementation, including branched chain amino acids, provided before and after transplant was found to improve post transplant survival[11].

The loss of muscle mass and muscle function tends to occur as patients with cirrhosis develop complications typical of end stage liver disease. Although associations do not equate causality, many measures of decreased muscle mass or function were linked to complications of cirrhosis. Decreased hand grip strength alone was found to be associated with complications including ascites, hepatorenal syndrome and spontaneous bacterial peritonitis[41]. Another study found an association between anthropometric measures of malnutrition with psychomotor assessments of hepatic encephalopathy[42]. However, another series found no association between body composition characterized by anthropometry and BIA with hepatic encephalopathy[43]. One would predict as the severity of liver disease increases, the risk of sarcopenia would also increase, however, the relationship is not straightforward. Muscle function was found to be inversely correlated with Child-Pugh classification[36] or MELD score in some studies[34]. However, this observation is not universal. Other studies found a minimal or complete absence of an association between MELD or Child-Pugh classification and muscle mass or function[11,39]. In another series, sarcopenia increased with Child-Pugh classification, but was not correlated with MELD[12]. This difference may be

Table 2 Measures, definitions and outcomes relating to sarcopenia in the setting of cirrhosis and liver transplant

Study	Method	Definitions used/proposed	Outcomes	Notes/Limitations
Selberg et al[96]	BIA, phase angle	> 5.4° normal 4.4°-5.4 borderline < 4.4° abnormal	Phase angle < 5.4° associated with significantly lower survival	Phase angle may remain normal in cases of severe tissue loss when proportional losses of extracellular mass and body cell mass may occur
Kaido et al[11]	BIA, multiphase device (InBody 720; BioSpace, Tokyo, Japan) Percent skeletal muscle mass against a standard and calculated body cell mass	< 90% skeletal muscle mass compared to standard or body cell mass below 23.0 kg	Survival was significantly decreased in recipients with low skeletal muscle mass or low body cell mass	No data is provided on volume status, although Child-Pugh classification is given Nutritional supplementation with branched chain amino acids improved survival in those with low skeletal muscle mass
Englesbe et al[15]	CT, combined area of right and left psoas muscle area at the highest level of the 4th lumbar vertebra Control population was 248 trauma patients	Percentile cutoffs for total psoas area in transplant population 1910 mm² 50th percentile 1420 mm² 25th percentile 950 mm² 5th percentile	Decreased psoas muscle area associated with higher risk of mortality 25th percentile HR = 1.88 5th percentile HR = 3.46	Retrospective definitions of sarcopenia were not derived from the control trauma patients, but were based on percentiles from the transplant population Included CT scans either 90 d before or after transplant; majority of scans were after transplant
Tandon et al[12]	CT or MRI, cross sectional area of muscle at 3rd lumbar vertebra (psoas, paraspinals, transversus abdominis, rectus abdominis and internal and external obliques)	Total L3 skeletal muscle area ≤ 52.4 cm²/m² in males ≤ 38.5 cm²/m² in females	Sarcopenia present in 41% of wait listed candidates Higher wait-list mortality with sarcopenia (HR = 2.36, 95%CI: 1.23-4.53) Greatest effect was in those with low MELD score	Retrospective Only study to report use of both MRI and CT
Montano-Loza et al[18]	CT cross sectional area of muscle at 3rd lumbar vertebra (psoas, paraspinals, transversus abdominis, rectus abdominis and internal and external obliques) Muscle identified by Housfield unit between -29 and + 150	Total L3 skeletal muscle area ≤ 52.4 cm²/m² in males ≤ 38.5 cm²/m² in females	Sarcopenia present in 40% of cirrhotics Sarcopenia was independent risk factor for mortality (HR = 2.28, P = 0.008) One year survival for cirrhosis with sarcopenia was 53% compared to 83% in cirrhosis without sarcopenia	Prospective data
Hamaguchi et al[14]	CT, cross sectional psoas muscle area at level of umbilicus Intramuscular fat accumulation of multifidus muscle (multifidus muscle Housfield units/ subcutaneous fat Housfield units)	ROC curves selected from study data for best accuracy in predicting death Intramuscular adipose tissue content -0.375 in males and -0.216 in females Psoas muscle mass normalized for height ≤ 6.868 cm²/m² in males ≤ 4.117 cm²/m² in females	Pretransplant increased intramuscular adipose tissue content (OR = 3.898, 95%CI: 2.025-7.757) and decreased psoas muscle mass (OR = 3.635, 95%CI: 1.896-7.174) were associated with mortality	Used umbilical level which can vary based on body habitus Constructed cutoffs based on diseased population Included intramuscular fat content as a measure of muscle quality
Tsien et al[13]	CT cross sectional at mid 4th vertebra level Total cross sectional area of psoas, paraspinals and abdominal wall muscles (rectus abdominis, oblique and transversus abdominis) normalized to height	Psoas muscle area normalized 5th percentile cutoffs ≤ 12.27 cm²/m² in males less than 50 yr of age ≤ 10.12 cm²/m² in males more than 50 yr of age ≤ 10.47 cm²/m² in females less than 50 yr of age ≤ 10.33 cm²/m² in females more than 50 yr of age	Sarcopenia was seen in 62.3% prior to transplant and increased to 86.8% after transplant Only 6.1% had reversal of sarcopenia after transplant and 75% without pretransplant sarcopenia developed it after transplant	Includes serial measures in the same patients Mean time from transplant to post-transplant CT was about one year (13.1 ± 8.0 mo)

	Reference ranges derived from 109 healthy control subjects undergoing CT for unspecified abdominal pain	Total abdominal muscle area normalized 5th percentile cutoffs $\leqslant$ 60.09 cm^2/m^2 in males less than 50 yr of age $\leqslant$ 48.97 cm^2/m^2 in males more than 50 yr of age $\leqslant$ 53.43 cm^2/m^2 in females less than 50 yr of age $\leqslant$ 41.28 cm^2/m^2 in females more than 50 yr of age	Reduction in muscle after transplant was associated with new onset diabetes mellitus	Since follow up scan was done for indications (ie HCC surveillance, infection, pain, increased aminotransferases) the potential for significant selection bias exists
Masuda et al[9]	Cross sectional CT of psoas muscle at L3 Calculated area by multiplying major and minor axis of psoas (a × b × ∏) Compared to a reference group of healthy donors	< 800 cm in men < 380 cm in women	3 and 5 yr survival with sarcopenia was 74.5% and 69.7% respectively, without sarcopenia was 88.9% and 85.4% respectively (P = 0.02) Sepsis was seen in 17.7% with sarcopena, 7.4% without sarcopenia (P = 0.03)	Enteral nutrition given in immediate post operative period appeared to decrease risk of sepsis when sarcopenia was present

MELD: Model for end stage liver disease; CT: Computed tomography.

explained by the inclusion of the degree of ascites in the Child-Pugh classification, a factor which has a large effect on nutrition.

The presence of sarcopenia predicts more complicated hospital stays during the transplant period. Diminished performance observed during cardio-pulmonary testing was associated with longer intensive care unit stays[39]. Decreased hand grip strength and diminished lean body mass noted on a DXA study were also associated with longer intensive care unit stays[44]. Multiple factors related to sarcopenia may account for prolonged intensive unit care stays, and includes respiratory muscle weakness which was observed in patients with cirrhosis and high MELD scores[45]. A higher rate of sepsis was observed in the setting of sarcopenia in one series[9], a complication that could account for both morbidity and mortality. Nutritional interventions represent a potential means to mitigate the effects of sarcopenia upon sepsis. Early after receiving a live donor liver transplant supplemental enteral feeding reduced the risk of sepsis in the group with sarcopenia from 28.2% to 10.5% (P = 0.03) in one study[9].

The consequences of sarcopenia extend beyond survival and the hospital stay. Skeletal muscle plays a critical role in insulin sensitivity. In the non-transplant setting, population based data showed sarcopenia was associated with insulin resistance and metabolic syndrome[4,46]. The prevalence of the post-transplant metabolic syndrome ranges from 44%-58%[47-51], and it is possible that sarcopenia may be a significant contributing factor. As an example, reduced psoas muscle area after transplant was associated with a 3 fold higher risk of developing diabetes mellitus[13]. The effect of sarcopenia on the health of long term survivors after liver transplant has not been well studied.

CLINICAL COURSE OF SARCOPENIA AFTER TRANSPLANT

Increased weight and body mass index are commonly observed after liver transplantation[35] with one series finding the median weight gain at 1 and 3 years was 5.1 kg and 9.5 kg, respectively[52]. Most weight gain occurs within the first year after liver transplant[53-55], and it appears that much of this weight gain is an increase in fat mass. Longitudinal data differs on changes in lean body mass after liver transplant with some series showing continued decreases in lean body mass[13,56-58], some studies finding increased lean body mass[59,60] and one without significant change[61]. Decreased lean mass does not always reach the threshold of sarcopenia, and one study examined the rate of sarcopenia before and after transplant. In that study, the prevalence of sarcopenia, defined by cross sectional imaging, increased from 62.3% pretransplant to 86.8% post-transplant roughly one year after transplant[13]. Most longitudinal studies have examined outcomes within the first one to two years after transplant. Less information is known about changes long term in body composition. In a group of long term survivors after liver transplantation, measurements of body composition in many transplant recipients were similar to those seen with sarcopenic obesity[62]. In another study of long term survivors (> 10 years) after transplant, body mass index identified 7.3% as malnourished whereas bioimpedance identified 31.7% as malnourished, highlighting how a gain in fat mass may result in the under recognition of persistent sarcopenia[63].

Muscle function improves after transplant with increases in maximal oxygen uptake[35,59,60], distance walked during six minute walk testing[35] and isokinetic joint strength being observed[35,59]. Most of these

Table 3 Methods and outcomes when measuring muscle function in the setting of cirrhosis and liver transplant

Study	Method	Outcomes	Notes/limitations
Andersen et al[37]	Isokinetic strength of flexion and extension of six joints	Upper and lower extremity strength was decreased in cirrhotics vs controls	Only included patients with alcohol related cirrhosis
		Lower extremity strength was associated with lean body mass and mid arm circumference, an effect independent of severity of liver disease, neuropathy, biochemical data and recent alcohol use	The majority of patients had Child-Pugh A or B classification
			Included 24 cirrhotics and 24 controls
Tarter et al[98]	Isokinetic strength measured by upper and lower extremity peak force, peak torque, total work and power	Most measures of strength were decreased in cirrhotic patients vs controls	Study included 49 with alcoholic cirrhosis, 42 with non-acoholic cirrhosis and 50 controls
		There was no difference in any measure between those with alcohol vs non-alcohol related cirrhosis	No patient had consumed alcohol in greater than one year prior to testing
Beyer et al[35]	Maximal oxygen uptake measured on a cycle ergometer SMWT Isokinetic knee flexion and extension	Maximal oxgen uptake, SMWT and isokinetic knee strength increased over the first six months after transplant compared to pretransplant values	Small study with only 17 patients having post transplant data and 13 patients completing both pretransplant and posttransplant assessment of maximal oxygen uptake
		No changes were noted between six and 12 mo after transplant	Used a supervised exercise program after transplant
Epstein et al[38]	Symptom limited cardiopulmonary testing on a cycle ergometer	When examining patients that went on to transplant, a significantly higher proportion of patients that died within the first 100 post-operative days had a peak oxygen consumption < 60% predicted and had oxygen consumption at the anaerobic threshold < 50% predicted peak oxygen consumption	Median MELD at the time of exercise testing was low (7-12)
			The median time from exercise testing to transplant was long (471 ± 300 d)
Prentis et al[39]	Symptom or exertional limited cardiopulmonary testing on a cycle ergometer	Sixty tested patients went on to liver transplant with a 10% 90 d mortality	Mean MELD at transplant was low (< 20)
		Mean aerobic threshold was higher in survivors and was only variable in multivariate analysis that was associated with mortality	Compared to above study (Epstein 2004[38]), the authors did not make comparisons to population based reference values, but used ROC curve analysis to define thresholds associated with outcomes
		Optimal anaerobic threshold associated with survival was > 9 mL/min per kg	
		Anaerboic threshold > 11 mL/min per kg was associated with shorter stay in critical care setting	
Carey et al[34]	Six minute walk test	Candidates awaiting liver transplant had decreased SMWT distance (369 ± 122 m), significantly lower than reference values	Included patients too ill to walk, and designated zero m for this group
		When controlling for other factors including age and MELD, SMWT distance was significantly associated with wait list mortality (HR = 0.58, 95%CI: 0.37-0.93)	
		ROC analysis found cut off value of 250 m having the highest sensitivity and specificity for mortality	Designated patients removed from the list as a waitlist death
Alameri et al[36]	Six minute walk test	Patients with cirrhosis had significantly diminished SMWT distance (306 ± 111 vs 421 ± 47 m, P < 0.0001)	Used Child-Pugh to assess severity of liver disease, no data on MELD
		SMWT was an independent predictor of survival and was inversely correlated with Child-Pugh classification	
		The lowest quartile walked < 250 m	

SMWT: Six minute walk test; MELD: Model for end stage liver disease.

improvements occur early, within the first six months after liver transplant[35]. In one series comparing SMWT at 7 and 14 d after transplant, mean SMWT increased nearly 100 m[64]. Such rapid improvement in functional testing would suggest much of this early recovery is independent of increases in muscle mass. In studies measuring skeletal muscle mass and hand grip strength, hand grip values rapidly improved within the first 3 mo after transplant whereas skeletal muscle remained below pretransplant values[58].

POTENTIAL MECHANISMS BY WHICH SARCOPENIA MIGHT DEVELOP AND PERSIST IN THE SETTING OF LIVER CIRRHOSIS AND TRANSPLANTATION

There are numerous mechanisms by which sarcopenia might develop in patients with cirrhosis. Findings of both increased muscle protein catabolism[65,66] and decreased muscle protein synthesis[67] were observed in cohorts with cirrhosis. Malnutrition is commonly observed in patients with cirrhosis. Dietary total caloric intake is often decreased with consumption of protein, carbohydrate and fat observed to be less than healthy controls[68]. Coupled with decreased intake, increased protein requirements and increased amino acid catabolism often observed with cirrhosis suggest inadequate stores of hepatic glycogen which result in gluconeogenesis from amino acids[6,69]. Further evidence of reduced glycogen stores comes from observing the rapid development of a catabolic state after short periods of fasting in cirrhotic patients[70,71]. Poor absorption of nutrients could contribute to malnutrition. For example, malabsorption of fat was found to occur in patients with cirrhosis even with normal intestinal mucosal function[72]. Benefits of nutritional supplementation in patients with cirrhosis highlight the role of malnutrition in the development of sarcopenia. Night time snacking was found to decrease skeletal muscle proteolysis, but study results differed when improvements in skeletal muscle mass were examined[73].

Branched chain amino acids are another means of supplementation. Activation of the mammalian target of rapamycin (mTOR)/Akt pathway was found to result in muscle hypertrophy and regeneration[74,75]. Increased availability of branched chain amino acids, particularly leucine, were found to stimulate Akt/mTOR[76,77]. In a randomized trial, supplementation of branched chain amino acids in patients with cirrhosis was associated with increased triceps skin fold thickness and decreased mean Child-Pugh scores, an effect not seen with carbohydrate or other protein supplementation[78]. It is not clear if a particular deficiency in branched chain amino acids exists in patients with cirrhosis outside of the overall state of malnourishment observed.

Portal hypertension was shown to have a significant role in malnutrition seen with cirrhosis. In animal models, portal hypertension was found to decrease intestinal absorption of carbohydrates[79]. Ascites is another manifestation of portal hypertension that contributes to malnutrition and muscle loss. Measures causing resolution of ascites, such as the placement of a transjugular intrahepatic portosystemic shunt, were found to improve body nitrogen measures of malnutrition, but interestingly did not result in increased muscle strength[80]. Nutritional supplementation can be another means to combat the effect of ascites upon muscle mass. Patients with cirrhosis and refractory ascites were found to have preserved anthropometric measures of lean body mass along with improved survival when provided with parenteral nutrition for 24 h after large volume paracentesis, an effect not seen with enteral nutritional support[81].

The etiology of liver disease may also play a role. Alcohol abuse can induce both a neuropathy[5] and a myopathy[5,82]. However, the pathophysiology of these changes in patients with alcohol induced liver disease is complex. This is illustrated by a study of men with alcoholism where muscle strength was related to total lean body mass, but not to the presence of neuropathy or the degree of liver disease[37]. Viral hepatitis may also impact muscle function as non-cirrhotic patients with either chronic hepatitis B or chronic hepatitis C found to have decreased SMWT distance compared to healthy controls[36]. Reasons for this decreased performance on the SMWT in those with chronic viral hepatitis were not examined.

After liver transplantation, immunosuppression contributes to both ongoing muscle loss and delayed regeneration. Calcinuerin inhibitors (CNIs), the mainstay of liver transplant immunosuppression regimens, have multiple effects on muscle. Intracellular calcineurin activation regulates genes involved in skeletal muscle maintenance, growth and remodeling[83]. Administration of calcinuerin inhibitors was found to inhibit skeletal muscle hypertrophy in animal models after the administration of growth factors or during periods of increased muscle work[84,85]. CNIs additionally were found to prevent a switch in the type of muscle fiber from slow to fast fibers[86]. Myostatin appears to be one important mediator between CNI use and sarcopenia. Myostatin inhibits muscle growth and regeneration[87], an effect mediated through reduced satellite cell activation[88]. CNI use, in animal studies, was found to increase myostatin expression, a growth differentiation factor which inhibits muscle growth[89]. Small pilot data in transplant recipients found increased skeletal muscle myostatin expression compared with controls[13].

Although CNIs are the most commonly used immunosuppressive agents after transplant, other agents affect muscle. Inhibitors of mTOR, such as rapamycin, were found to block muscle hypertrophy[75].

Steroids have long been described to result in myopathy which is histologically characterized by type Ⅱ muscle fiber atrophy[90]. Although not commonly reported, the anti-metabolite mycophenolate mofetil was implicated in a case report of a medication induced myopathy that reversed with the withdrawal of this agent[91].

Lifestyle may also play a significant role in the persistence of sarcopenia after transplantation. Many transplant recipients remain sedentary[51]. Even when enrolled in a study to assess the benefit of exercise after transplant, less than half adhered[60]. However, among those that did adhere with exercise recommendations, there was a trend toward improved body composition[60]. The best type of exercise has not been defined after transplant. Much focus has centered on aerobic fitness. In the non-transplant setting, resistance exercise has been noted to increase muscle protein synthesis[92]. Exercise before and after transplant could offer a means of both prevention and treatment.

CONCLUSION

The development of sarcopenia is common in patients with cirrhosis. It is associated with numerous adverse events including wait list and post-transplant mortality. A key area in the study of sarcopenia and cirrhosis is standardization of methods and definitions of sarcopenia in this setting. Further investigations should focus on the pathophysiologic basis in which sarcopenia develops and persists in the setting of liver disease and liver transplant. Special focus should be maintained on modifiable risk factors which could include diet and physical activity interventions. Finally, more data is needed on the long term effects of sarcopenia after transplant, especially in light of the high rate of metabolic syndrome and cardiovascular events observed in this population.

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