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A North American Expert Opinion Statement on Sarcopenia in Liver Transplantation

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Loss of muscle mass and function, or sarcopenia, is a common feature of cirrhosis and contributes significantly to morbidity and mortality in this population. Sarcopenia is a main indicator of adverse outcomes in this population, including poor quality of life, hepatic decompensation, mortality in patients with cirrhosis evaluated for liver transplantation (LT), longer hospital and intensive care unit stay, higher incidence of infection following LT, and higher overall health care cost. Although it is clear that muscle mass is an important predictor of LT outcomes, many questions remain, including the best modality for assessing muscle mass, the optimal cut-off values for sarcopenia, the ideal timing and frequency of muscle mass assessment, and how to best incorporate the concept of sarcopenia into clinical decision making. For these reasons, we assembled a group of experts to form the North American Working Group on Sarcopenia in Liver Transplantation to use evidence from the medical literature to address these outstanding questions regarding sarcopenia in LT. We believe sarcopenia assessment should be considered in all patients with cirrhosis evaluated for liver transplantation. Skeletal muscle index (SMI) assessed by computed tomography constitutes the best-studied technique for assessing sarcopenia in patients with cirrhosis. Cut-off values for sarcopenia, defined as SMI < 50 cm^2/m^2 in male and < 39 cm^2/m^2 in female patients, constitute the validated definition for sarcopenia in patients with cirrhosis. *Conclusion:* The management of sarcopenia requires a multipronged approach including nutrition, exercise, and additional pharmacological therapy as deemed necessary. Future studies should evaluate whether recovery of sarcopenia with nutritional management in combination with an exercise program is sustainable as well as how improvement in muscle mass might be associated with improvement in clinical outcomes. (Hepatology 2019;70:1816-1829).

Sarcopenia, the disproportionate loss of muscle mass, is common in patients with cirrhosis awaiting liver transplantation (LT). Sarcopenia has been shown to be a significant risk factor for wait-list mortality, postoperative complications, and post-LT death.[1-5] The new international statistical classification of diseases and related health problems, 10th revision (M62.84) code for sarcopenia represents a significant recognition of sarcopenia as a disease.[6] Although it is clear that muscle mass is an important predictor of LT outcomes, many questions remain, including the best modality for measuring muscle

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; ESLD, end-stage liver disease; LT, liver transplantation; MRI, magnetic resonance imaging; PMI, psoas muscle index; SMI, skeletal muscle index.

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mass, the optimal cut-off values for sarcopenia, the ideal timing and frequency of muscle mass assessment, and how to best incorporate the concept of sarcopenia into clinical decision making.

Therefore, in 2018, we convened a group of experts to form the North American Working Group on Sarcopenia in Liver Transplantation to use evidence from the medical literature to address these outstanding questions regarding sarcopenia in LT. This document represents the product of our efforts to develop a statement by experts in the field on the current state of knowledge and key gaps for future high-impact research on sarcopenia in the LT setting.

The Importance of Sarcopenia as a Construct

Sarcopenia is a term derived from the Greek *sarco* (flesh) and *penia* (deficiency). Sarcopenia was initially defined as age-related loss of skeletal muscle[7] but has since been expanded to reflect low muscle mass leading to negative effects on physical performance and clinical outcomes across a broad range of disease states outside of geriatric populations.

Conceptually, sarcopenia is only one—but likely the dominant—component of the larger construct of global physical dysfunction that is prevalent in patients with cirrhosis that has most recently been described with the term "frailty." Whereas frailty is the manifesting symptom of impaired global physical functioning, loss of muscle mass is an obvious sign that frailty may be present. Sarcopenia is the metric of clinically relevant skeletal muscle depletion that can be objectively measured in clinical practice and is least likely to be affected by acute illness or alterations in cognitive function. For this reason, our working group chose to define sarcopenia using only muscle mass, although we acknowledge that muscle function (e.g., grip strength) is incorporated into definitions of sarcopenia by other groups including the European Working Group on Sarcopenia in Older People and Asian Working Group for Sarcopenia.[8,9]

Although multiple definitions of sarcopenia for patients with cirrhosis exist in the literature, low muscle mass, regardless of how it is measured, is a powerful predictor of clinically relevant adverse outcomes, including poor quality of life,[10] hepatic decompensation,[11] mortality in patients with cirrhosis on the LT wait list,[3,11-14] longer hospital and intensive care unit stay,[2,15] higher incidence of infection following LT,[2,16] higher overall health care cost,[17] and post-LT mortality.[3,18]

Aside from being an important marker of pre and post-LT mortality, sarcopenia is associated with additional important clinical parameters independent of scoring systems for severity of liver dysfunction. Skeletal muscle plays an integral role in ammonia detoxification, and sarcopenia has been

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identified as an independent risk factor for hepatic encephalopathy in patients with cirrhosis.[19] Other complications such as ascites and infections are more common in patients with cirrhosis with sarcopenia compared with patients with cirrhosis without sarcopenia.[2]

Modalities to Evaluate Muscle Mass in the Liver Transplant Candidate

There currently exists significant heterogeneity in the metrics used to define sarcopenia in the published domain. The great challenge in identifying a single standard is that many modalities exist for muscle mass quantification, including anthropometry, bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DEXA), ultrasound, magnetic resonance imaging (MRI), and computed tomography (CT). The advantages and limitations of each modality as they relate to measurement of muscle mass in patients with end-stage liver disease (ESLD) are summarized in Table 1.

We advocate for the use of CT-based skeletal muscle area, measured at the third lumbar vertebra on an abdominal CT scan (either noncontrast or contrast-enhanced scans are acceptable), in patients with cirrhosis for the following reasons (please see example in Fig. 1). First, cross-sectional imaging is

TABLE 1. Quantitative Tools Evaluating Sarcopenia in Cirrhosis

Modalities	Experience	Advantages/Limitations
DEXA	• 36-month mortality in 144 men with cirrhosis[54] • Concordance between various muscle mass assessment techniques in 59 patients with cirrhosis listed for LT[55]	Advantages: • Safe, inexpensive, and readily available • Reproducible • Low radiation exposure Limitations: • Failure to differentiate water from muscle; therefore, affected by lower limb edema • Weak concordance between DEXA and CT in identification of sarcopenia in cirrhosis
Bioelectrical impedance analysis	• Prognosis of sarcopenia in 161 patients with cirrhosis[56]	Advantages: • Safe, rapid, easy, inexpensive Limitations: • Affected by fluid retention, diuretic use, liquid and food intake before the test, physical activity, and BMI
Ultrasound (thigh muscle thickness)	• Development of sarcopenia model in 159 patients evaluated for LT[57]	Advantages: • Safe, easy, inexpensive • No radiation exposure • High intraobserver and interobserver reliability Limitations: • Reproducibility is unknown
Mid-arm muscle circumference	• Concordance between various muscle mass assessment techniques in 59 patients with cirrhosis listed for LT[55] • Nutritional assessment by Royal Free Hospital Global Assessment in 232 patients with cirrhosis listed for LT[23]	Advantages: • Safe, inexpensive, and readily available Limitations: • Low intraobserver and interobserver reliability • Affected by subcutaneous adipose tissue loss • Weak correlation with CT-determined muscle mass
CT/MRI	• MRI-based muscle assessment in 166 patients with decompensated cirrhosis treated with transjugular intrahepatic portosystemic shunt[58] • Development of sarcopenia model in 159 patients evaluated for LT[57]	Advantages: • No radiation exposure (MRI) • Fast, accurate • Ability to differentiate three main body compartments, i.e., muscle, visceral, and subcutaneous adipose tissue • Ability to identify muscle radiodensity to determine ectopic fat accumulation in muscle • Appears not to be affected by the presence of ascites or edema • Reduction in price and radiation exposure to only 2.6 millisieverts by single slice CT[45] Limitations: • Cost • High ionizing radiation exposure makes whole-body CT scan unsuitable for longitudinal assessments

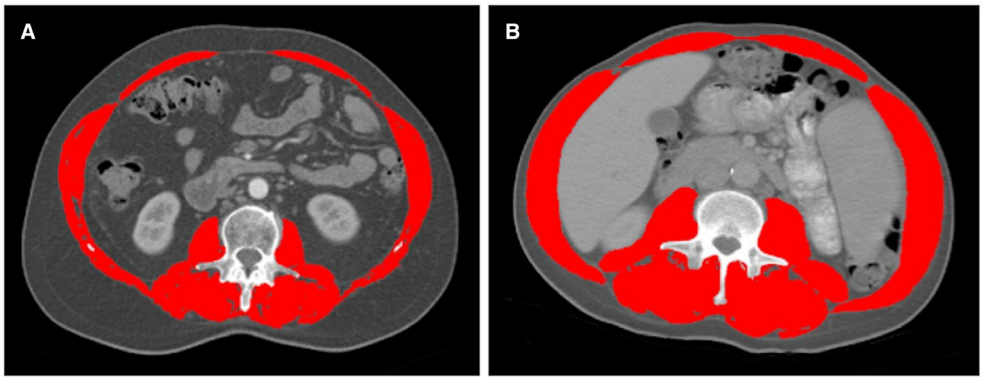

FIG. 1. Total muscle area quantification at the level of third lumbar vertebra using abdominal CT images from two male patients with cirrhosis. (A) and (B), respectively, present a patient who had low SMI (46 cm^2/m^2) and high SMI (60 cm^2/m^2) as indicated by the red shading.

commonly used in transplant centers to monitor for hepatocellular carcinoma and to evaluate the vascular and biliary anatomy for surgical planning. Although preliminary reports suggest that MRI-based imaging yields equivalent results to CT scans,[20] CT scans tend to be more widely available, of lower cost, and more rapidly performed in clinical practice. Second, the majority of published reports on sarcopenia in LT have used standard-of-care CT imaging, summarized in Table 2. Several key questions remain regarding the use of CT-based estimation of skeletal muscle mass, including the use of values below specific percentiles (i.e., 5th percentile) of age- and sex-matched population or optimal cut-points for mortality discrimination, sensitivity of changes over time, and the validity of measurement of psoas alone versus the total muscle area.[21]

Defining Sarcopenia

A large, multicenter study of 396 patients with cirrhosis from five North American liver transplant centers established standardized cut-off values of skeletal muscle index (SMI) at < 50 cm^2/m^2 and < 39 cm^2/m^2 to define sarcopenia in men and women with cirrhosis, respectively.[22] These sex-specific SMI cut-points were strongly associated with pre-LT mortality independent of age and Model for End-Stage Liver Disease (MELD) score.[15]

Although muscle mass has been shown in multiple studies to be associated with post-LT mortality,[3,18,23] data reporting pre-LT muscle indexes associated with post-LT adverse outcome are limited. Recently, SMI < 48 cm^2/m^2 in acutely ill men undergoing urgent evaluation and LT was associated with higher post-LT mortality.[24]

When assessing sarcopenia by SMI on an abdominal CT scan, there does not appear to be a large difference between measurements at L3 versus L4 vertebrae.[25] There is also excellent agreement between the various software programs (i.e., SliceOmatic, ImageJ, and so on) with respect to measurements of abdominal skeletal muscle area.[26]

SMI seems to be a more complete and robust measurement than individual measurement of the psoas muscle or the psoas muscle index (PMI), especially in men with cirrhosis. In addition, low PMI identifies an incomplete subset of patients at increased risk of mortality indicated by low SMI.[21]

Although sarcopenia has classically been associated with increased mortality in both men and women with cirrhosis, emerging evidence suggests that sarcopenia is associated with disproportionately higher rates of mortality in men as compared with women.[27] This emphasizes the importance of survival analysis stratification by sex rather than simply adjusting multivariable models for sex. Furthermore, the role of ethnicity in baseline muscle mass and muscle loss has not yet been determined in patients with cirrhosis.[28] Although more data are needed, the prevalence of sarcopenia within each body mass index (BMI) category is another consideration when building a definition to incorporate into clinical practice. Lastly, divergent

TABLE 2. Summary of Studies Investigating the CT-Determined Low Muscle Mass in Patients With ESLD

Author/Year	Study Population/Center (Single, Multi)	Sarcopenia Definition	Muscle Included	Frequency of Sarcopenia
Englesbe et al., 2010[1]	163 LT recipients/Single	Lowest TPA quartile: TPA < 1,420 mm^2 at the level of the fourth lumbar vertebra (L4)	Total psoas areas	25%
Montano-Loza et al., 2012[59]	112 patients with cirrhosis evaluated for LT/Single	Mortality-associated SMI cutoffs in cancer*[60]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	50% males 18% females
Tandon et al., 2012[61]	142 patients listed for LT/Single	Mortality-associated SMI cutoffs in cancer*[60]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	54% males 21% females
Meza-Junco et al., 2013[62]	116 patients with hepatocellular carcinoma evaluate for LT/Single	Mortality-associated SMI cutoffs in 1,475 patients with solid tumors†[63]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	31% males 28% females
Krell et al., 2013[16]	207 LT recipients/Single	Lowest TPA Tertile: TPA < 1,499 mm^2 for men and < 954 mm^2 for women	Total psoas areas	33%
DiMartini et al., 2013[14]	338 LT recipients/Single	Mortality-associated SMI cutoffs in cancer*[60]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	76% males 51% females
Masuda et al., 2014[15]	204 patients undergoing LT/Single	PMA below the fifth percentile for each sex: PMA < 800 cm^2 for men and < 380 cm^2 for women	Sum of the areas of the two psoas	58% males 36% females
Durand et al., 2014[12]	562 patients listed for LT/Single	Optimal cutoffs of TPMT/height to discriminate waiting-list mortality TPMT/height (mm/m) at the level of umbilicus ≤ 16.8 mm/m	Right psoas muscle	NA
Yadav et al., 2015[4]	213 patients listed for LT/Single	Mortality-associated SMI cutoffs in cancer*[60]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	28% males 13% females
Carey et al., 2017[22]	396 patients listed for LT/Multi	Optimal cutoffs of SMI to discriminate waiting-list mortality: SMI < 39 cm^2/m^2 for women and < 50 cm^2/m^2 for men	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	50% males 33% females
Tandon et al., 2016[57]	159 patients evaluated for LT/Single	Mortality-associated SMI cutoffs in cancer*[60]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	57% males 25% females
Van Vugt et al., 2017[64]	585 patients listed for LT/Multi	Mortality-associated SMI cutoffs in 1,475 patients with solid tumors†[63]	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	42% males 47% females
Van Vugt et al., 2018[17]	224 patients listed for LT/Single	Lowest sex-specific quartile of SMI: L3 SMI < 44.1 for men and < 37.9 for women	Total cross-sectional areas of psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis (normalized to height)	25% males 24% females

*L3 SMI ≤ 38.5 cm^2/m^2 for women and ≤ 52.4 cm^2/m^2 for men.
†Defined as L3 SMI ≤ 41 cm^2/m^2 for women and ≤ 53 cm^2/m^2 for men with BMI ≥ 25 and ≤ 43 cm^2/m^2 in patients with BMI < 25.
Abbreviations: NA, not available; PMA, psoas muscle area; TPA, total psoas area; TPMT, transversal psoas muscle thickness.

study outcomes such as overall mortality in evaluated patients, wait-list mortality in listed patients, post-LT mortality in patients undergoing LT, and short-term versus long-term outcomes confound the comparison between published studies and development of generalized definitions.

KEY POINTS

1. Standardized tools and validation between techniques are important considerations for the evaluation of sarcopenia in patients with ESLD awaiting LT.
2. CT constitutes the best-studied technique for measuring sarcopenia in patients with cirrhosis.
3. FLEXIT (Fitness, Life Enhancement, and Exercise in Liver Transplantation Consortium) cut-off values (SMI < 50 cm^2/m^2 in men and < 39 cm^2/m^2 in women) constitute the most robust definition for sarcopenia in patients with ESLD awaiting LT.

RECOMMENDATIONS

1. We recommend the use of SMI as a marker of sarcopenia for outcome prediction.
2. We recommend the use of FLEXIT cut-off values to define sarcopenia in cirrhosis in order to characterize cohorts of patients for prospective clinical trials.
3. Future studies to define sarcopenia should be established for use in clinical practice with consideration of sex, age, and ethnicity.

Incorporating Sarcopenia into Clinical Practice

Although severe sarcopenia may be easy to identify visually (i.e., the "eyeball test"), objective and validated measures are needed to detect early stages of muscle loss, when interventions to slow the progression may be more effective. Ascites, obesity, and body fat distribution may render sarcopenia less apparent, and early stages of muscle loss are often not visually obvious. Furthermore, quantification of muscle mass provides objective data, which are especially critical in the setting of LT.

One of the advantages of determination of muscle mass is that it can be done on cross-sectional imaging (e.g., abdominal CT or MRI), which is often performed in patients undergoing LT as standard of care. Radiologists can provide total abdominal skeletal muscle area at the L3 vertebral level from these routine scans, from which SMI can easily be calculated. We anticipate that this will enable more widespread incorporation of the information provided from muscle mass measurement into clinical practice.

Objective assessment of sarcopenia in the LT candidate is important in two major areas: (1) clinical decision making and (2) intervention. We expand on both of these areas here.

INCORPORATING SARCOPENIA INTO CLINICAL DECISION MAKING

It is important to note that the North American Working Group on Sarcopenia in Liver Transplantation recommends that sarcopenia should not be the sole criterion for declining or delisting candidates for LT. A significant limitation of using sarcopenia for risk stratification is the lack of a threshold value of muscle loss that predicts health outcomes prohibitive for a particular intervention such as LT. Furthermore, the threshold of "futility" is not universally defined but instead varies by center, clinician, and patient values. Rather, we advocate that an objective metric of sarcopenia be taken into consideration within the full context of the other medical, physical, functional, and psychosocial factors of each individual patient with respect to their transplant candidacy as well as their own values of what a successful transplant looks like.

That being said, sarcopenia has important implications for a patient awaiting LT. At the minimum, in the outpatient setting, a patient with sarcopenia should be counseled that his or her higher risk of wait-list mortality exceeds that predicted by the MELD-Na score and that they have a higher risk of complication after LT. This information may help to motivate the patient to seek a faster path to transplant, including living donor LT or accepting higher-risk donor livers. In addition, this information may motivate patients and providers to engage in interventions that might mitigate muscle loss (see next section).

With respect to clinical decision making, sarcopenia may hold a unique place within the inpatient

setting where performance-based assessments of frailty may be misleading because of acute changes in functional performance that may not accurately reflect their underlying "steady state" physiologic reserve. An objective assessment of muscle mass may indicate that the patient has good underlying physiologic reserve that will support a full perioperative recovery. For a patient without multiple risk factors for poor post-LT outcomes, sarcopenia alone is not sufficient to deny LT but may guide the decision about the quality of liver to accept in an attempt to minimize liver-related complications and optimize overall patient recovery.[29] For a patient with multiple comorbidities that may also negatively impact post-LT outcomes, identification of sarcopenia—in combination with these other medical risk factors—may be added objective evidence to not proceed with LT.

INCORPORATING SARCOPENIA INTO MANAGEMENT AND TREATMENT OF THE LT CANDIDATE

We recommend that measurement of muscle mass best be integrated into clinical practice to identify patients for "prehabilitation" programs focused on optimizing nutrition and physical activity.[30] The management of sarcopenia requires a multipronged approach including nutrition, exercise, and additional pharmacological therapy as deemed necessary. The incorporation of behavioral change strategies while delivering nutrition[31] and exercise prescriptions[32] encourages exploration of the patient's individual personal and social factors to motivate and increase the likelihood of patient engagement.[33] We recommend the following strategies based on the current available evidence:

A Nutrition Prescription

At minimum, this consists of three major components:

1. A target caloric intake recommendation. For nonobese individuals (BMI < 30 kg/m^2), the latest European Association for the Study of the Liver Clinical Practice Guidelines on nutrition in chronic liver disease recommend an optimal daily energy intake of at least 35 kcal/kg of actual body weight corrected for fluid retention. In obese patients, a tailored moderately hypocaloric diet (with a reduction of 500 to 800 kcal/day) has been suggested.[34] The International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus[35] provides additional BMI-stratified target caloric recommendations based on an ideal body weight (also corrected for fluid retention), including BMI ranges of 20-30, 30-40, and > 40 kg/m^2. Supplemental enteral nutrition should be considered in hospitalized patients who are unable to meet calorie intake targets with oral intake alone.[34,36]
2. A target protein intake recommendation. Protein restriction is not necessary in patients with hepatic encephalopathy.[37] Guidelines recommend a daily protein intake of 1.2-1.5 g/kg body weight,[34,35] with further study required as to whether dairy/vegetable protein may have a benefit over meat protein in the setting of hepatic encephalopathy[34] and the variable impact of protein across the spectrum of liver disease severity.
3. A late-evening snack recommendation. In an attempt to shorten the overnight fasting period, patients are advised to eat a snack shortly before bedtime or during nighttime hours and to eat breakfast.[34,38] We would support the recommendation of a late-night snack across Child-Turcotte-Pugh classes. The optimal composition of the late-evening snack is not clearly defined, with recommendations varying from branched-chain amino acid–containing supplements[39] to snacks containing ~50 grams of carbohydrates and 10-20 grams of protein.[31]

Exercise

Although an evidence-based exercise prescription is still not available for patients with cirrhosis, extrapolating current knowledge from the 11 published studies on exercise in patients with cirrhosis (please refer to Table 3) into practice, it is recommended for patients to perform moderate-intensity exercise for no less than 30 minutes per day, starting with a brief warm-up (5-10 minutes) and ending with a stretching/cool-down phase (5-10 minutes), 3-5 times per week, aiming for a total of 150-200 minutes of exercise per week.[32] Exercise bouts should have a duration of no less than 5-10 minutes, depending on disease status and tolerance, with patients commonly

TABLE 3. Exercise Clinical Trials Investigating the Effect on Muscle Mass or Function

Author/Year	Design	Main Exercise Intervention	Dietary Intervention	Skeletal Muscle Assessment	No. of Subjects		Primary Aim(s)	Skeletal Muscle Mass Outcomes
					Active	Control		
Konishi et al., 2011[67]	ONCT	Walking (6 months)	Optimal kcal	BIA lean mass (muscle weight)	3	NA	HOMA-IR change	22.5 kg (before) vs. 22.8 kg (after)
Patullo et al., 2013[68]	ONCT	Walking (24 weeks)	Optimal kcal/ protein	Handgrip strength	7	NA	HOMA-IR change	45 lbs. (before) vs. 44 lbs. (after)
Roman et al., 2014[69]	Open RCT	Cycle ergometry (12 weeks)	Leucine	Arm and thigh circumferences	10	10	6MWT, 2MST, muscle mass, and HRQoL	MAMC ↓ 0.5 cm in active and ↑ 0.6 cm in control; TC ↑ 5 cm in active* and ↓ 1 cm in control
Zenith et al., 2014[70]	Open RCT	Cycle ergometry (8 weeks)	Optimal kcal/ protein	Thigh US and circumference	9	10	Peak VO_2, muscle mass, and HRQoL	Thigh US† ↑ 0.05 cm/m^2 in active* and no change in control; TC ↑ 1.2 cm in active* and 0.2 cm in control
Debette-Gratien et al., 2015[71]	ONCT	Cycle ergometry (12 weeks)	NA	Quadriceps Strength	13	NA	Acceptability of exercise program	30 kg (before) to 37 kg (after)*
Macias-Rodriguez et al., 2016[72]	Open RCT	Cycle ergometry (14 weeks)	Optimal kcal/ protein	BIA phase angle	14	15	HRQoL and HVPG	Phase angle ↑ 0.3 in active* and no change in control
Roman et al., 2016[73]	Open RCT	Cycle ergometry (12 weeks)	NA	DEXA, thigh circumference	15	10	Peak VO_2, fat/lean body mass, and risk of falls	Lean mass ↑ 1.05 kg in active and ↓ 0.05 kg in control
Berzigotti et al., 2017[74]	ONCT	Aerobic and resistance (16 weeks)	kcal reduction	BIA lean mass	60	NA	HVPG and body weight	56.7 kg (before) vs. 55.6 kg (after)
Nishida et al., 2017[75]	ONCT	Bench step-ups (12 months)	BCAA	Intramuscular adipose content	9	NA	Anaerobic threshold, fat in liver and muscle, and glycemic control	–0.47 (before) vs. –0.42 (after)
Hiraoka et al., 2017[76]	ONCT	Walking (3 months)	BCAA (as late-night snack)	BIA-SMI, handgrip and leg strength	33	NA	Muscle volume and function	↑ 13% in muscle volume*, ↑ 5% in leg strength*, and ↑ 10% in handgrip*
Kruger et al., 2018[77]	Open RCT	Cycle ergometry (8 weeks)	Optimal kcal/ protein	Thigh US and circumference	20	20	Peak VO_2	Thigh US‡ ↑ 0.06 cm/m^2 in active* and 0.06 in control; TC ↑ 1.8 cm in active* and 0.6 cm in control

*Denotes comparison was statistically significant.
†Average feather index shown was significant in active group, whereas average compression index was not.
‡Average feather index showed a $P = 0.05$ in active group, whereas average compression index was not significant.
Abbreviations: 2MST, 2-minute step test; 6MWT, six-minute walk test; BCAA, branched-chain amino acids; BIA, bioelectrical impedance analysis; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HRQoL, health-related quality of life; HVPG, hepatic vein pressure gradient; kcal, kilocalories (nutritional requirement); MAMC, mid-arm muscle circumference; NA, not available; ONCT, open noncontrolled clinical trial; RCT, randomized clinical trial; SMI, skeletal muscle index; TC, lower thigh circumference; US, ultrasound.

having to undergo multiple exercise bouts per day in order to accomplish these goals. In general, it is recommended that aerobic and resistance training be combined in a 3:2 ratio, although for the purpose of improving sarcopenia, this ratio should favor resistance training.[40]

Pharmacotherapy (Table 4)

1. Vitamin D3: Vitamin D deficiency is highly prevalent in cirrhosis and is a well-defined contributor to sarcopenia. Detection and repletion with cholecalciferol is standard practice in transplant hepatology.[41]
2. Ammonia-lowering treatments: Excess ammonia delivered to muscle is the pre-eminent metabolic driver of sarcopenia.[42] It is reasonable to expect that current and potentially future ammonia-lowering treatments[43,44] to prevent encephalopathy will also be helpful in minimizing sarcopenia.
3. Hormonal therapy: Standard hormonal therapy to sustain a euthyroid and euglycemic state defends muscle mass and function. In addition, the majority of men with advanced cirrhosis have hypogonadism as measured by decreased total and free testosterone levels. A randomized trial showed that intramuscular androgen therapy of hypogonadal men with cirrhosis improved muscle mass, bone mass, and hemoglobin A1C[45]; transdermal therapy also appears effective with fewer potential adverse events.
4. L-Carnitine: L-carnitine is a quaternary amine (3-hydroxy-4-N-trimethylaminobutyrate) needed for fatty acid oxidation. Binding of L-carnitine to acetyl groups enables movement of acetylated fatty acids into mitochondria and their oxidation to generate energy in the form of adenosine triphosphate. Carnitine supplementation was recently reported to suppress muscle loss in an initial study of patients with cirrhosis.[46]

KEY POINTS

1. We believe sarcopenia should not be a sole criterion on which to determine candidacy for LT.
2. Attaining nutritional goals appropriate for patients with cirrhosis is currently the predominant treatment for sarcopenia.

RECOMMENDATIONS

1. We recommend that the presence or absence of sarcopenia be considered part of the multidisciplinary assessment in cirrhosis.
2. Until more evidence is available, we recommend for patients with cirrhosis and sarcopenia to exercise 150-200 minutes per week, including both aerobic and resistance training (ratio favoring the latter), along with a nutritional intervention with an adiposity-tailored caloric intake that favors protein with key amino acids and aims to prevent starvation.
3. Male patients with cirrhosis and sarcopenia are potentially eligible for pharmacologic treatment with testosterone replacement.

TABLE 4. Pharmacotherapy for Cirrhotic Sarcopenia

Author/Year	Intervention	Typical Dosing	Comment
Corey et al., 2014[41]	Cholecalciferol	2000 IU/day	Deficiency common in cirrhosis
Davuluri et al., 2016[43] Tsien et al., 2015[44]	Leucine	7.5 g/day typically in divided doses with additional amino acids	Included in many nutritional supplements
Holecek et al., 2017[65]	2-hydroxymethyl butyrate	1 g tid	Metabolite of leucine Nutritional supplement with anticatabolic action
Sinclair et al., 2016[45]	Testosterone in androgen-deficient men	Testosterone undecanoate 1,000 mg IM, schedule per RCT; or transdermal gel 50 mg/day[66]	Gel preferred for sustained physiologic levels, concerns for thrombosis and prostate cancer
Ohara et al., 2018[46]	L-carnitine	1,000 mg/day or bid	Essential nutrient for fatty acid metabolism One fourth is synthesized in the kidney and liver

Abbreviations: bid, twice daily; IM, intramuscularly; RCT, randomized clinical trial; tid, three times a day.

Sarcopenia in Children

Children with irreversible liver disease offer a complex challenge to clinical care teams that is distinct from adults because they have a time-limited opportunity for growth and development and may suffer lifelong consequences if not expeditiously transplanted.

The Pediatric End-Stage Liver Disease (PELD) score does not adequately capture wait-list and perioperative risk or the extent to which ESLD impairs functional development. Clinical (weight, height, anthropometrics) and biochemical (serum total protein and albumin) data fail to fully characterize malnutrition in chronically ill children/those with end-stage organ/liver failure and are often confounded. Objective nutritional biomarkers are lacking for children with ESLD.

Children with ESLD suffer from malnutrition, muscle wasting, and deconditioning that result from the insidious effects of underlying hepatic synthetic dysfunction and systemic inflammation. Broader nonlaboratory assessment metrics are needed to more fully capture the extent of ill health status associated with chronic or end-stage liver disease in children. Pilot studies have demonstrated that children with ESLD have smaller psoas muscle areas than healthy controls and that the psoas muscle area does not correlate with weight z scores or PELD score.[48,79]

Significant gaps exist, including the (Table 5) absence of unifying definition of sarcopenia in growing children; the paucity of evidence to date of how to measure sarcopenia in children, with different modalities used; the evolving validated reference data for total psoas muscle area (tPMA; through CT abdominal images) in children; the near-term impact of interventions such as nutritional support, exercise programs, and so on limited by challenges of longitudinal/serial evaluation of sarcopenia due to cumbersome (DEXA) or radiation-heavy (CT) assessment methods; the lack of full understanding of how the presence of sarcopenia before LT affects outcomes after LT; and whether sarcopenia should be considered in clinical decision making.

KEY POINTS

1. The majority of children are too young to undergo functional or performance-based (frailty) testing[47] before the time of LT, underscoring the special role and importance of muscle mass assessment in this vulnerable patient population.
2. Pilot studies demonstrate that tPMA increases over time until late adolescence and is smaller in pediatric ESLD than healthy controls.

RECOMMENDATIONS

1. Sarcopenia assessment should be considered in children with ESLD. Among those pediatric patients requiring clinically indicated CT imaging, the availability of recent pediatric-specific tools[80] providing age- and sex-specific reference growth curves will facilitate targeted interventions and their near-term impacts.
2. Targeting noninvasive assessment strategies for children is a high-needs research area.

Sarcopenia in Special Patient Populations

SARCOPENIC OBESITY

Sarcopenic obesity can be present in 20%-40% of LT candidates with cirrhosis.[49,50] Patients with sarcopenia are more likely to be obese, and those with sarcopenic obesity are more likely to have nonalcoholic fatty liver disease as the etiology of liver disease.[50] Of particular concern is the fact that sarcopenia can be difficult to recognize in the presence of obesity. Future research should include measures of obesity beyond BMI such as CT measures of adipose tissue.

CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) alone can affect muscle mass. Sarcopenia occurs in roughly 10% of patients with CKD alone and is associated with increased mortality.[51] In renal transplant recipients, sarcopenia may persist for years after transplantation, with age and duration of dialysis being important predictors.[52] Little is known about the relationship between sarcopenia and CKD in LT candidates. Normal renal function in patients with cirrhosis has been correlated with higher measures of muscle mass.[53] Data on measures such as duration of renal

TABLE 5. Summary of Published Literature on Sarcopenia in Pediatric Liver Disease

Article	Design	Study Population	Definition of Sarcopenia	Key Findings/Clinical Outcomes
Mager et al., 2018[78]	Retrospective	n = 41 children after LT (age 0.5-17 years)	DEXA—to measure appendicular SMM *z* score < –2	• SMM *z* score < –2 in 41% of cohort, persisting up to 8 years after LT • Sarcopenia associated with increased hospital duration and ventilator dependency (total PICU stay), higher readmission rates/LOS readmission, and younger age, female sex, and impaired catch-up growth at 1 year after LT
Lurz et al., 2018[79]	Retrospective	n = 23 children with ESLD with clinically indicated CT Control: 2:1 age- and sex-matched healthy controls (trauma victims with CT)	CT - PMSA at L3/4 and L4/5	• Children with ESLD have a smaller PMSA than healthy controls • The PMSA is independent of anthropometric markers in children with ESLD
Mangus et al., 2017[48]	Retrospective	n = 81 subjects with organ failure—ESLD[35], ESRD[20], IF[26], Control[39]	CT - PMSA at L2/3	• Reduction in muscle mass (ESLD 23%, ESRD 19%, IF 24%) vs. healthy controls • Serum total protein and albumin, and BMI, fail to fully characterize malnutrition in chronically ill children

Abbreviations: ESRD, end-stage renal disease; IF, intestine failure; LOS, length of stay; PICU, pediatric intensive care unit; PMSA, psoas muscle surface area; SMM, skeletal muscle mass.

insufficiency and renal replacement therapy in LT candidates with sarcopenia are not available.

Future Directions for Research

Sarcopenia has become a topic of prolific exploration in patients with ESLD over the last few years. Currently, the evaluation of sarcopenia in patients with cirrhosis appears in more than 1,500 publications. Important research questions that merit exploration for sarcopenia assessment in patients with ESLD include (1) the availability of reliable, accessible, and practical tools to be used in clinical practice; (2) the optimal frequency of measurement over time; (3) how to assess the clinical meaning of changes over time and whether they have prognostic value independent of other measurements; and (4) how they can best be used to engage patients in self-motivation.

One of the most important knowledge gaps in cirrhosis care is our limited understanding of the time frame associated with the efficacy of interventions. We lack information on whether recovery of sarcopenia with nutritional management in combination with an exercise program is sustainable as well as how an improvement in muscle mass might be associated with improvement in clinical outcomes.

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