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EDITORIAL

Impact of muscle wasting on survival in patients with liver cirrhosis

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Abstract

Muscle wasting is defined as the progressive and generalized loss of muscle mass. Muscle depletion is a common feature of chronic liver disease found in approximately 40% of patients with cirrhosis. Its etiology is multifactorial subsequent to liver failure and its prevalence increases along with disease severity. Cross-sectional analytic morphometry using computed tomography (CT) scan or magnetic resonance imaging are considered by consensus the gold standards to assess muscle size in cirrhosis for research purposes because they are not biased by fluid accumulation. Several studies have assessed the impact of muscle wasting on overall survival of patients in the waiting list for liver transplantation and there is a general agreement that decreased muscle size assessed by CT scan is an independent predictor for mortality in cirrhosis. It has been proposed that the addition of cross-sectional muscle area into the Model for End-stage Liver Disease can increase its prognostic performance. Nevertheless, the use of CT scan in assessing muscle size is inappropriate for routine clinical practice and an alternative cost-effective, easy to use and accurate tool should be developed. In conclusion, muscle wasting has a detrimental impact on survival of patients with cirrhosis and, thus, it remains to be elucidated if nutritional interventions and exercise could improve muscle wasting and, subsequently, survival in this setting.

Key words: Cirrhosis; Sarcopenia; Malnutrition; Survival; Muscle wasting

Core tip: Malnutrition is a common feature of cirrhosis and its detrimental impact on the survival of these patients has been early recognized. Malnutrition is not synonymous to muscle wasting but there is a great overlap between them with malnutrition to be significantly associated with muscle depletion. Muscle wasting assessed by using the computed tomography cross-sectional area of skeletal muscles at the level of the third lumbar vertebra has been found to be independently associated with mortality. The hypothesis that nutritional interventions and exercise aiming to correct muscle depletion could possibly improve

the survival of patients with cirrhosis needs to be further investigated.

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MUSCLE WASTING AND CIRRHOSIS

Muscle wasting is defined as the progressive and generalized loss of muscle mass and is considered by a European consensus[1] the main criterion to diagnose sarcopenia together with a decline of muscle function (loss of strength or physical performance). The primary cause of muscle depletion is ageing but the etiology of sarcopenia is multifactorial with many chronic diseases to be accompanied with secondary sarcopenia[1].

Muscle wasting is considered one of the major complications of end-stage liver disease and its incidence increases along with disease progression. A variety of mechanisms contribute to muscle wasting in liver cirrhosis[2]. Reduced nutrient intake is frequent and it is mainly associated with dietary restrictions in sodium and water for the prevention of fluid accumulation or in protein intake for hepatic encephalopathy, with a decrease in taste sensation related to micronutrient deficiencies, or with a decrease in appetite caused by increased leptin and pro-inflammatory cytokine levels. Nausea and early satiety caused by tense ascites, gastroparesis or small bowel dismotility can contribute to the poor nutrient intake of these patients. Another important mechanism is the reduced intestinal absorption secondary to maldigestion caused by pancreatic insufficiency, to drug-related diarrhea or to intestinal bacterial overgrowth due to decreased small bowel motility. The disturbances in the metabolic rate consequent to liver cirrhosis include increased energy expenditure, high protein catabolism, insulin resistance and increased fat turnover resulting in a hypermetabolic state[2]. Molecular studies have shown that patients with cirrhosis have a higher skeletal muscle expression and increased plasma concentrations of myostatin, a member of the transforming growth factor-b family that inhibits protein synthesis through impaired mammalian target of rapamycin (mTOR) signaling, compared to controls[3]. Furthermore, skeletal muscle autophagy is enhanced in cirrhosis[4]. Hyperammonia seems to be the underlying mechanism that induces both autophagy and up-regulation of myostatin[3,4].

As described previously, muscle wasting is a component of sarcopenia and sarcopenia is not synonymous to malnutrition or frailty or cachexia; however, there is a great overlap among these conditions. Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by muscle mass loss with or without fat mass loss[5]. Malnutrition is defined as a continuum of inadequate intake and/or increased requirements and the diagnosis is documented based on 2 or more of the following 6 characteristics: weight loss, inadequate energy intake, loss of muscle mass, loss of subcutaneous fat, fluid accumulation and diminished functional status assessed by hand grip strength[6]. Sarcopenia is significantly associated with physical inactivity and low dietary intake in liver cirrhosis[7], reflecting the wide overlap among these conditions. Sarcopenic obesity is defined as muscle loss and dysfunction associated with pathological accumulation of adipose tissue and is highly prevalent in ageing, malignancy and rheumatoid arthritis. Approximately 20% of patients with cirrhosis awaiting liver transplantation have sarcopenic obesity. This condition is of highest importance because it is associated with increased morbidity and mortality as it combines the risks of sarcopenia with those of obesity[8].

The detrimental impact of malnutrition on survival of patients with cirrhosis has been early recognized with Pugh *et al*[9] to include nutritional status as a qualitative variable in the original Child-Pugh (CP) classification-a prognostic tool to assess disease severity, and subsequently prognosis, in cirrhotic patients. Gunsar *et al*[10] aimed to evaluate the survival prognostic value of nutritional status in 222 cirrhotic patients using the Royal Free Hospital-Global Assessment (RFH-GA) tool which includes both subjective and objective anthropometric variables, namely body mass index, mid-arm muscle circumference and dietary intake. In the final multivariate Cox regression model, moderate and severe malnourishment by RFH-GA, together with CP grade, urea, prothrombin time and age were independent predictors of survival.

A number of assessment techniques have been introduced to evaluate muscle mass. According to the European Working Group on Sarcopenia in Older People (EWGSOP) guidelines[1], computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standards to estimate muscle mass for research purposes. These techniques can accurately distinguish between fat and other soft tissues, can provide quantitative measurement of skeletal muscle size and, most importantly, they are not biased by the fluid retention, which is common in decompensated cirrhosis and which makes other techniques (*i.e.*, bioelectrical impendance or dual energy X-ray absorptiometry) inappropriate for muscle mass assessment in this setting[11,12]. However, they are not without their limitations; the high cost, the potential unavailability at some sites and, mainly, the exposure to radiation limit their use in routine clinical practice.

A number of recent clinical studies have used cross-sectional analytic morphometry to evaluate the prevalence and the clinical significance of muscle wasting in cirrhosis. In a study by Tandon *et al*[13], sarcopenia was assessed using the skeletal muscle

cross-sectional area at the third lumbar (L3) vertebra level and was defined using certain cut-offs based on a study comprised of cancer patients; 41% of 142 cirrhotic patients in the liver transplant waiting list were sarcopenic. Male sex, dry-weight body mass index and CP class C cirrhosis were independent predictors of sarcopenia. In the multivariate analysis, sarcopenia was a predictive factor for overall waiting-list mortality with a hazard ratio (HR) of 2.36 (95%CI: 1.23-4.53), together with increasing age (1.06; 95%CI: 1.01-1.1) and Model for End-stage Liver Disease (MELD) score (1.13; 95%CI: 1.09-1.19). In a study by Montano-Loza *et al*[14], 45 (40%) of 112 cirrhotic patients had sarcopenia defined using the L3-skeletal muscle index as in the study by Tandon *et al*[13]. However, in this study sarcopenia was not associated with the severity of liver disease measured by the MELD or the CP score. Sarcopenic patients had worse median survival than non-sarcopenic patients (19 ± 6 mo *vs* 34 ± 11 mo). By multivariate Cox regression, sarcopenia (HR = 2.21; 95%CI: 1.23-3.95), CP (HR 1.85; 95%CI: 1.02-3.36) and MELD score (HR = 1.08; 95%CI: 1.03-1.14) were independently associated with overall mortality. In a recent study, Durand *et al*[15] aimed to evaluate if CT muscle mass measurements add prognostic information to the MELD score. Thus, they evaluated transversal psoas muscle thickness (TMPT) assessed by CT as a predictor of waiting list mortality in a pre-MELD cohort (n = 186) and in a MELD-era cohort (n = 376) of patients with cirrhosis. In the pre-MELD cohort, a score combining both MELD and TMPT/height (MELD-psoas score) had a c-statistic of 0.84 (95%CI 0.62-0.95), moderately superior to that of MELD score (0.82; 95%CI: 0.59-0.93). In the MELD-era cohort, the c-statistic of MELD-psoas score (0.82; 95%CI: 0.64-0.93) was slightly superior to that of MELD score (0.80; 95%CI: 0.60-00.91) and similar to that of MELD-Na score (0.82; 95%CI: 0.63-0.93). The discrimination of MELD-psoas score was also superior in patients with MELD < 25 and in patients with refractory ascites. Lastly, in a retrospective study of 120 patients with cirrhosis, 86% of patients had sarcopenia using the skeletal muscle index. Sarcopenia was more prevalent in alcoholic liver cirrhosis compared to other etiologies. Independent predictors of mortality were sarcopenia, CP class B and C, and no supplementation with branched-chain amino acids (BCAA)[16]. Muscle wasting is characterized by both a decrease in muscle size and an increased fat accumulation; the latter can be assessed by measuring the density in CT Hounsfield Units with lower density to reflect more fat infiltration. In a recent study of 98 patients with cirrhosis, lower L4-L5 average total psoas density (HR = 0.965, 95%CI: 0.936-0.995) was independently associated with mortality together with higher CP score (HR = 1.2, 95%CI: 1.021-1.41)[17].

Muscle wasting has been shown to be a significant survival predictor also in patients with cirrhosis and hepatocellular carcinoma (HCC). A total of 116 patients with cirrhosis and HCC evaluated for liver transplantation had CT scans at the L3 level to define sarcopenia using the L3 skeletal muscle index. Sarcopenic patients were older, had higher INR values and showed a trend towards higher MELD and CP scores. The L3-skeletal muscle index was not correlated with tumor characteristics. Median survival for sarcopenic individuals was 16 ± 6 mo compared to 23 ± 8 mo for non-sarcopenic patients. By multivariate Cox regression analysis, only MELD score (HR = 1.08; 95%CI: 1.01-1.12), Child-Pugh (HR = 2.14; 95%CI: 1.43-4.01), sodium (HR = 0.89; 95%CI: 0.81-0.98), TNM stage (HR = 1.92; 95%CI: 1.45-2.84), and sarcopenia (HR = 2.04; 95%CI: 1.21-4.02) were independently associated with mortality[18]. The prevalence of muscle wasting according to the etiology of cirrhosis is shown in Table 1.

Consequently, muscle wasting is a common complication of cirrhosis, its prevalence increases as the disease progresses, and it is associated with diminished survival in the pre-transplant setting. Current dietary recommendations aim to provide cirrhotic patients with sufficient caloric intake considering the increased energy requirements consequent to liver disease, to prevent further protein breakdown, to meet nutritional daily requirements, to avoid prolonged fasting periods and to correct micro-nutrient deficiencies[19]. Apart from the basic energy and dietary recommendations, there is evidence that nutritional supplements can increase protein stores and, subsequently, improve muscle protein synthesis in patients with cirrhosis. According to a randomized controlled trial, nocturnal nutritional supplementation over a 12-mo period improved total body protein in cirrhotics[20]. Furthermore, a prospective study showed that a single oral BCAA mixture enriched with leucine reversed impaired mTOR1 signaling and increased autophagy in the skeletal muscles of patients with cirrhosis seven hours after administration[21]. The current nutritional guidelines seem to improve nutritional indices and quality of life[22] and combined with appropriate exercise could potentially improve long-term muscle mass and performance. However, there is no prospective or randomized controlled trial to provide evidence regarding the impact of nutritional interventions and/or exercise on muscle wasting of patients with cirrhosis. Lack of patients' compliance, difficulty in accessing dietary guidance, absence of both accurate and easy-to-use tools for longitudinal assessments of muscle size and the rather slow improvement in anthropometry indices following nutritional treatment are certain limitations in the management of muscle wasting. However, considering not only the effect of sarcopenia on survival but also to post-transplantation outcomes[23], further research is needed in this setting. Of note, muscle size is just one component of global health performance and novel studies should also take into consideration muscle strength, muscle performance, muscle fat accumulation, functional performance, anthropometry measurements

Table 1 Prevalence of muscle wasting in patients with cirrhosis according to etiology of liver disease

Ref.	Number of patients	Definition of muscle wasting	Method of assessment	Prevalence of muscle wasting according to etiology
Montano-Loza *et al*[14], 2014	112	L3-SMI ($\leq$ 52.4 cm^2/m^2 in men, $\leq$ 38.5 cm^2/m^2 in women)	CT scan	Alcohol: 44%, HCV: 46.9%, Alcohol + HCV: 38.9%, HBV: 0, AILD: 42.9%, Other: 21.4%
Hanai *et al*[16], 2015	130	L3-SMI ($\leq$ 52.4 cm^2/m^2 in men, $\leq$ 38.5 cm^2/m^2 in women)	CT scan	HBV: 73.3%, HCV: 67.2%, Alcohol: 82.8%, Other: 50%
Meza-Junco *et al*[18], 2013	116	L3-SMI ($\leq$ 41 cm^2/m^2 in women, and $\leq$ 53 cm^2/m^2 in men with body mass index $\geq$ 25 and $\leq$ 43 cm^2/m^2 in patients with BMI < 25)	CT scan	Alcohol: 53.8%, HCV: 20.8%, HCV+Alcohol: 40.3%, HBV: 25%, NASH: 62.5%, Other: 33.3%
Hayashi *et al*[7], 2013	50	SMI (< 6.87 kg/m^2 in men, < 5.46 kg/m^2 in women) and/or Muscle strength (< 24 kg in men, < 14 kg in women)	BIA Hand Grip Strength	Viral: 40%
Montano-Loza *et al*[24], 2014	248	L3-SMI ($\leq$ 41 cm^2/m^2 in women, and $\leq$ 53 cm^2/m^2 in men with body mass index $\geq$ 25 and $\leq$ 43 cm^2/m^2 in patients with BMI < 25)	CT scan	Alcohol: 52.2%, HCV: 40.9%, AILS: 40.5%, HBV: 47.6%, NASH: 71.4%, Other: 33.3%
Krell *et al*[25], 2013	207	L4-TPA (lowest sex-stratified tertile)	CT scan	HCV: 40.7%, HBV: 22.2%, HCC: 19.2%, Acohol: 36.7%, PSC: 28.6%, PBC: 40%, AIH: 36.4%, NASH: 25%, Other: 39.3%

SMI: Skeletal muscle index; L3: Third lumbar vertebra; CT: Computed tomography; BIA: Bioelectrical impedance analysis; NASH: Non-alcoholic steatohepatitis; AILS: Autoimmune liver diseases; TPA: Total psoas area; HCC: Hepatocellular carcinoma; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis; AIH: Autoimmune hepatitis.

and nutritional status. The way that all these overlap and correlate with each other is an area that needs to be elucidated and an appropriate assessment tool which would overcome the difficulties of CT/MRI scan should be developed.

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