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Sarcopenia and Myosteatosis in Cirrhotic Patients: A Cross-Sectional Study

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Abstract

Background: Liver cirrhosis is an important cause of morbidity and mortality especially if associated with malnutrition and sarcopenia. The accumulation of intramuscular fat, known as myosteatosis, generates an early changes in muscle architecture, quality and function and has also been considered a concept of sarcopenia by some authors. Sarcopenia implies an increase in hospital admissions and worse outcomes after liver transplants. Identifying sarcopenia early helps prevent these outcomes. Myosteatosis has been increasingly studied and its clinical significance in liver cirrhosis is still unclear. **Objective:** To know the prevalence of sarcopenia and myosteatosis in cirrhotic patients. **Methods:** Observational, cross-sectional study performed in a tertiary gastroenterology hospital from October 2018 to October 2020 in outpatients with liver cirrhosis to identify the presence of sarcopenia and myosteatosis and correlate with variables capable of predicting these situations. The patients were submitted to a number of tests including muscle strength, computed tomography analysis with evaluation of skeletal muscle index (SMI) and muscle attenuation coefficient (HU) at the level of the third lumbar vertebra (L3) and a 6-minute walk test for sarcopenia evaluation. **Results:** A total of 62 patients were studied, half of them male. Most participants were classified as CHILD-PUGH A (70.9%) and mean SMI of 25.78 kg/m^2. The median MELD score was 11.5 points. The average force measured with a dynamometer was 27.59 kgf and for this exam, eight patients had demonstrated reduced muscle strength. The distance covered in six minutes in the patients walk test was on average 418.34 m ± 59.21. The average SMI assessed by CT at the level of L3 was 113.25 cm^2/m^2, therefore it was not being able to identify sarcopenia in the 62 patients studied. It was observed that 19 had myosteatosis (30.6%). The mean attenuation of skeletal muscle at L3 level, used for myosteatosis evaluation, was 46.19 ± 11.73

HU. In the comparison between patients with and without myosteatosis, we observed that the walk test was lower and BMI was higher in those patients with myosteatosis. **Conclusion:** There were no cases of sarcopenia in these patients but myosteatosis was present in 30.6% of the patients and correlated with impaired results in the walk test. More robust studies need to be carried out to determine the impact of myosteatosis on the muscle quality of cirrhotic patients and, consequently, if it would precede sarcopenia in these patients.

Keywords: Sarcopenia; Myosteatosis Skeletal Muscle Index; Liver Cirrhosis; Muscle Strength; Walk Test.

Introduction

Liver cirrhosis is a major public health problem and an important cause of morbidity and mortality when associated with malnutrition and sarcopenia [1,2,3]. Malnutrition and sarcopenia usually coexist in cirrhotic patients and are caused by multifactorial mechanisms such as reduced nutrient intake, anorexia, neuroendocrine dysregulation, and olfactory and gustatory deficits [4,5].

The definition of sarcopenia, according to the European Working Group on Sarcopenia in Older People, in the 2018 update, is the reduction in muscle quantity and strength [6]. Its estimated prevalence is between 30% and 70% in cirrhotic patients, more frequent in those with advanced cirrhosis [7,8-21]. Impaired muscle performance can be established with the walk test, Timed Up and Go, and Short Physical Performance Battery [6].

The accumulation of intramuscular fat, known as myosteatosis, causes an early change in muscle architecture, quality, and function [9,10]. In 2009, it was defined that skeletal muscle aging was characterized not only by a reduction in muscle size and strength, but also by an increase in intramuscular adipose tissue [11]. Since then, several studies have been conducted to better understand the pathophysiological mechanisms of myosteatosis and its impact on muscle strength. More recently, myosteatosis has also been considered a part of sarcopenia by other authors [9,10,11,12]. Sarcopenia and myosteatosis imply increased hospital admissions, worse outcomes after liver transplantation, and decreased quality of life in cirrhotic patients [13,14-31]. It is interesting to evaluate the presence of sarcopenia and myosteatosis in cirrhosis and to know factors associated with these clinical conditions.

Methods

The study was observational, descriptive and cross-sectional, conducted in a tertiary gastroenterology hospital, between October 2018 and October 2020, in outpatients with liver cirrhosis. The research project was approved by the Research Ethics Committee of FEPECS (Foundation for Teaching and Research in Health Sciences) under CAAE number: 67763417.8.0000.5553. Patients were recruited for evaluation of the presence of sarcopenia after signing the Informed Consent Form (ICF).

Patients were included who had liver cirrhosis with or without portal hypertension of any stage (Child-Pugh-Turcott A, B or C) and of any etiology, without previous liver transplantation, over 18 years of age and of both sexes. Patients were excluded who had any type of current or past malignant neoplasm, severe heart or lung diseases that precluded the walk test, those who were hospitalized or discharged less than 30 days ago, and patients who presented changes in pulmonary function tests (spirometry) or pulmonary imaging, or who refused to sign the ICF. The diagnosis of liver cirrhosis was made by demonstrating hepatic histopathological parameters characteristic of liver cirrhosis or morphological features typical of cirrhosis on imaging examinations, defined by a liver of reduced size and lobular outline, accompanied by parenchymal heterogeneity, splenomegaly, with or without signs of portal hypertension with or without ascites using ultrasonography (USG), computed tomography (CT), or magnetic resonance imaging (MRI).

Sarcopenia was defined by a simultaneous reduction in muscle quantity and strength according to the consensus of the European Working Group on Sarcopenia in Older People [6]. Muscle quantity was assessed by non-contrast abdominal CT. Psoas muscle diameter was measured by the skeletal muscle index (SMI). In a multislice equipment (with at least 16 rows of detectors) images were obtained for the evaluation of psoas muscle measurements at the level of the third lumbar vertebra (L3), using specific software (OsiriX®, Pixmeo, Switzerland). Cirrhotic patients with SMI below 50 cm^2/m^2 for men and below 39 cm^2/m^2 for women were considered as having deficient muscle quantity [14,15].

Muscle strength was assessed by a dynamometer. Muscle strength was considered decreased in those men who had an assessed strength value lower than ≤ 29 kgf if BMI ≤ 24 kg/m^2; ≤ 30 kgf if BMI from 24.1 to 28 kg/m^2; ≤ 32 kgf if BMI > 28 kg/m^2. In women, on the other hand, muscle strength was considered decreased in those who presented muscle strength ≤ 17 kgf if BMI ≤ 23 kg/m^2; ≤17.3 kgf if BMI from 23.1 to 26 kg/m^2; ≤18 kgf if BMI from 26.1 to 29 kg/m^2 and ≤ 21f kg if BMI > 29 kg/m^2 [16]. Handgrip strength was assessed with a Crown brand analog dynamometer of 50-Kgf capacity with numerical divisions of 500 gf. This dynamometer was used immediately before the six-minute walk test using the patient's dominant hand. The arithmetic mean

of two to three force tests was considered a valid measurement, after a previous demonstration of the correct execution of the movement, and the test result was expressed in units of kilogram-force (kgf).

Myosteatosis was assessed by muscle attenuation values in Hounsfield unit (HU) and for diagnosis, a cut-off point < 41 HU was adopted for patients with BMI < 25 kg/m² and < 33 HU for those with BMI ≥ 25 kg/m², regardless of gender, using cross-sectional cut at the height of the third lumbar vertebra by CT [17,18,19]. The measurement of muscle performance was evaluated by the walk test according to the Brazilian standardization published and proposed by Britto and Sousa [20]. In the walk test the distance walked in meters by each patient was measured for six minutes on a flat corridor, without obstacles or curves, using comfortable shoes.

Data were presented as mean and standard deviation for normally distributed data, median and interquartile range for non-parametric distribution data, and percentage for categorical data. Patients were identified as with or without sarcopenia, with or without myosteatosis, and the presence of sarcopenia and myosteatosis were correlated with the following variables: age, sex, BMI, Child-Pugh classification, MELD score, muscle strength, walking, SMI-L3, attenuation coefficient-L3. There was no statistical correlation between sarcopenia and the variables described, however, there was a correlation among myosteatosis, BMI and the walk test results.

The patients were divided into those with or without myosteatosis. Bivariate analyses and respective tests were performed between the presence and absence of myosteatosis and the other variables. Multivariate model analyses were performed, meeting the prerequisites of homoscedasticity, absence of outliers, absence of multicollinearity, independence, and normality of residuals. The most statistically significant variables were presented in the bivariate models and those clinically relevant were incorporated into the multivariate model. Variables with statistical significance were those with $p < 0.05$. The software R version 4.2.2 was used.

Results

A total of 106 patients were initially recruited and 44 patients were excluded due to the presence of hepatocellular carcinoma (HCC) in 19 patients, endometrial carcinoma in 1 patient, 8 patients died from complications of cirrhosis, and 16 patients dropped out. A total of 62 patients were studied. The epidemiological, clinical, and laboratorial characteristics of these patients are shown in (Table 1). It is observed that the frequency between genders was similar. Most participants were classified as Child-Turcotte-Pugh A and the median BMI was 25.78 kg/m². The median MELD score was 11.5.

Age, years	51.11 ± 12.14
Male	50% (31)
BMI kg/m²	25.78 ± 3.96
CHILD-TURCOTTE-PUGH	
A	71% (44)
B	21% (13)
C	8% (5)
MELD	11.5 (8 – 14.5)
Muscle strength, kgf	27.59 ± 10.81
Walk test, m	418.34 ± 59.21
SMI-L3 area cm²/m²	113.25 ± 31.97
Muscle attenuation coefficient -L3 HU	46.19 ± 11.73

Table 1: Epidemiological, clinical and laboratory characteristics of patients studied with liver cirrhosis. *BMI = body mass index; MELD score= Model for End-Stage Liver Disease score; kgf = kilogram-force; SMI L3= skeletal muscle index at the level of the L3 lumbar vertebra; L3 HU= muscle attenuation coefficient at the level of L3, in Hounsfield units.

The mean skeletal mass index assessed by CT at the L3 level was 113.25 cm²/m². The mean strength measured with a dynamometer was 27.59 kgf. According to the muscle strength criterion, evaluated by dynamometer, eight patients presented decreased muscle strength: four males aged 45 to 68 years and four females aged 60 to 75 years.

It was not possible to identify sarcopenia by the criterion of reduced muscle quantity and strength since in all the patients the muscle quantity by SMI was determined as normal and decreased muscle strength alone is not enough to determine sarcopenia by this criterion. Of the 62 patients analyzed, 19 (30.6%) presented myosteatosis. The mean attenuation of the skeletal muscle at the level of L3, used to evaluate myosteatosis, was 46.19 ± 11.73 HU. The distance walked in six minutes in the walk test of the patients was on average 418.34 ± 59.21 m.

(Table 2) shows the characteristics of the 62 patients with or without myosteatosis. The variables correlated with the presence of myosteatosis were lower performance in the 6-minute walk test ($p = 0.01$) and higher BMI ($p = 0.024$). The other parameters examined were not statistically different in their correlation with myosteatosis. The walking variable measured in meters within six minutes was statistically significant and independent for the correlation with the presence of myosteatosis (Table 3). Thus, individuals with better walking performance were less likely to have myosteatosis (Figure 1).

	Present (19)	**Absent (43)**	***p***
Male	6 (31.6%)	25 (58.1%)	*0.05*
Age, years	55.43 ± 19.97	50.1 ± 11.16	*0.3*
MELD	16 ± 5.3	12.8 ± 5.0	*0.6*
Walk test, m	357.14 ± 79	432.62 ± 43.86	*0.01*
Muscle strength, kgf	21.43 ± 5.8	29.03 ± 11.26	*0.40*
BMI	27.26 ± 4.51	25.44 ± 3.82	*0.024*
SMI L3	86.27 ± 14.56	119.52 ± 31.75	*0.78*
HU L3	29.84 ± 3.60	50.01 ± 8.51	*< 0.001*

Table 2: Clinical, laboratorial and radiological characteristics of patients with and without myosteatosis; MELD score= Model for End-stage Liver Disease score; BMI= body mass index in kg/m2; SMI L3= skeletal muscle index at the level of the L3 lumbar vertebra in cm2/m2; HU L3= muscle attenuation coefficient at L3 level in Hounsfield units.

Residuals Min	1st Quartile	Median	3rd Quartile	Max
- 0.33582	-0.22616	-0.07758	0.04699	0.93108
Coefficients	Estimated	Std. Error	T value	Pr(>|t|)
(Intercept)	1.367640	0.416472	3.284	0.00233
Walk Test (m)	-0.002996	0.000946	-3.167	0.00319
MELD	0.015855	0.010661	1.487	0.14595
Muscle strength (kgf)	-0.004870	0.005256	-0.926	0.36054

Table 3: Multivariate analysis; Residual standard error: 0.3326 on 35 degrees of freedom; Multiple R-squared: 0.3259; Adjusted R-squared: 0.2682; F-statistic: 5.641 on 3 and 35 DF; p-value: 0.002914.

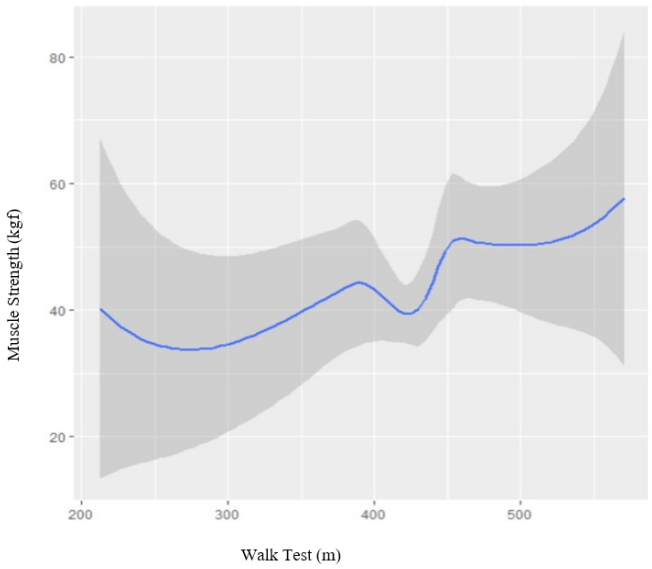

Figure 1: Correlation between functional walk test and muscle strength.

Discussion

In this study we observed that no cirrhotic patients with sarcopenia were identified. We did find that 30.6% of the cirrhotic patients had myosteatosis. In the last two decades, the study of sarcopenia in cirrhotic patients has advanced greatly and today there is robust evidence that reduced muscle mass and strength substantially worsens the quality of life of patients with chronic liver disease, in addition to increasing the complications of the disease before and after liver transplantation [22,23]. It is necessary to use a more elaborate and complementary set of tools.

The mean SMI assessed by CT at the level of L3 was 113.25 cm^2/m^2 and, even considering the lower standard deviation, it was not possible to establish a diagnosis of sarcopenia in any patient in the study since sarcopenia is still traditionally defined by the simultaneous reduction of muscle area and muscle strength [6,21]. This was perhaps due to the small number of participants or the fact that most of them belonged to the early and most compensated stage of cirrhosis, the Child-Pugh A stage with MELD score < 15. CT has a relatively high economic cost, restricting the universal access of patients to the exam and, in particular, for users of the public health system. In the present study we had the opportunity for cirrhotic patients to undergo. CT for evaluation of disease complications and we took the opportunity to extend the evaluation of sarcopenia using the SMI and of myosteatosis using the muscle attenuation coefficient, both at the L3 level.

The study of the prevalence of myosteatosis in the mainly decompensated cirrhotic population has increased in recent years. A prospective Japanese study of cirrhotic patients conducted in a cohort of 362 patients with a mean age of 68 years (186 men and 176 women) from 2013 to 2017 revealed the presence of myosteatosis in 93% of the population [30]. Another prospective study conducted in China from 2017 to 2021 with 473 patients with decompensated, hospitalized cirrhotic patients demonstrated prevalence of myosteatosis in 83 participants (17.55%) with a mean age of 69 years and slight predominance of men (55%) [31]. This reveals a varied prevalence of the condition among cirrhotic patients, highlighting the importance of its investigation.

In relation to the walk test and myosteatosis in cirrhotic patients in the present study, there was a correlation with statistical significance. Patients without myosteatosis performed better by walking longer distances in the 6-minute walk test than those with myosteatosis. Perhaps the myosteatosis present in the psoas muscle justifies this lower performance in the walk test but this observation will be better delineated in the future. In our study we verified by the logistic regression model that walking was the best predictor of myosteatosis. Thus, we call attention to the possibility that the walk test may be considered a useful, low-cost tool in the initial screening for myosteatosis. Some authors already consider muscle fat infiltration one of the initial manifestations of sarcopenia [9-12]. However, further studies are needed to establish myosteatosis as a diagnostic criterion for sarcopenia since this theory is not accepted universally.

When we compared the clinical, laboratorial, and radiological characteristics between the groups of patients with and without myosteatosis we found that the walk test was lower and the BMI was higher in those with myosteatosis. Since BMI can infer overweight/obesity, perhaps in these patients greater muscle fat infiltration is identified. We observed no significant correlation between the walk test with strength and MELD.

Patients with myosteatosis had higher BMI values when compared to the group without myosteatosis. It is important to point out that BMI alone does not reflect the real nutritional status of the patient. The mean BMI of patients with myosteatosis was higher than that of patients without myosteatosis with statistical significance ($p < 0.024$). However, caution should be exercised when interpreting these data, as it is known that individuals with the same BMI can have different SMI values and individuals with the same SMI can have different BMI values [18]. Thus, in this study, the fact that patients with myosteatosis have higher BMI values does not necessarily mean that they have higher SMI values. Perhaps future studies are needed to establish whether body composition interferes with the diagnosis of myosteatosis. In this study no body composition survey was performed. Sarcopenic obesity is a situation that has been increasingly addressed as a disease in recent publications [24, 25].

Despite altering muscle composition and quality, myosteatosis has not yet been globally recognized as a diagnostic criterion for sarcopenia. This situation raises discussions and the need for large multicenter studies with a greater number and variability of cirrhotic patients to better study the impact of myosteatosis on sarcopenia. Perhaps the reduction in muscle area appears later in sarcopenia and even in patients with normal SMI-L3 it is possible to estimate sarcopenia by a new criterion based on the presence of myosteatosis.

The measurement of muscle attenuation in Hounsfield units by CT has been considered a highly accurate complementary test in the investigation of sarcopenia and, consequently, to corroborate the nutritional status [12,13]. In the present study the presence of myosteatosis was observed in 19 patients (30.6%). However, prognostic aspects and cut-off points capable of predicting the impact of myosteatosis on the reduction of muscle area or strength are unknown.

Muscle strength measured with a dynamometer was lower in patients with myosteatosis (mean of 21.4 kgf) when compared to those without myosteatosis (mean of 29 kgf), although without statistical significance. Studies with larger numbers of patients are needed to clarify whether muscle strength does indeed correlate with myosteatosis and to define cut-off points adjusted for cirrhotic populations.

Decreased muscle strength, diagnosed by the dynamometer, was present in eight patients with equal frequency between genders. Of the 19 patients with myosteatosis, eight showed low muscle strength (42.10%): 4 women with BMI ranging from 22 to 35 kg/m^2 and SMI of 67.9 to 94.3 cm^2/m^2 and 4 men with BMI of 26 to 31 kg/m^2 and SMI of 101.5 to 180.5 cm^2/m^2. The finding of low muscle strength in some participants without sarcopenia corroborates the possible importance of the handgrip test as a screening for altered muscle quality. However, it is possible that studies with larger sample sizes of cirrhotic patients with and without myosteatosis and with stratification of muscle strength according to sex and BMI may obtain statistical significance.

It is worth highlighting that simpler and less expensive assessments also have great importance in the evaluation of muscle performance. The 6-minute walk test and handgrip strength (HGS) are safe and easily applicable in clinical practice as long as established protocols and safety criteria are followed [26,27]. However, in the current study we observed that HGS was normal in the majority of patients with myosteatosis. It is possible that with a larger sample size this could be found.

In the present study it was not possible to establish a significant correlation between MELD score, SMI-L3 and absence/presence of myosteatosis. Importantly, the MELD-psoas criterion has already been proposed to try to establish a more appropriate way to assess the severity of cirrhotic patients, including prioritizing them in the waiting list for liver transplants [28,29].

In the present study, sarcopenia was not diagnosed using the universally accepted criterion of concomitant reduction in skeletal mass index and muscle strength. In the present study the presence of myosteatosis is related to worse performance in the 6-minute walk test. This result may suggest that fat infiltration into the muscle may precede the actual reduction in skeletal muscle mass and perhaps contribute to warn about the need for further and larger studies evaluating the inclusion of the concept of myosteatosis in the diagnosis of sarcopenia.

Conclusion

Sarcopenia was not identified by the traditional criteria in the study population, but myosteatosis was identified in 30.6% of patients. The walk test correlated with myosteatosis, but more robust studies need to be conducted to determine the impact of myosteatosis on muscle quality in cirrhotic patients and consequently on their sarcopenia. The concept of sarcopenia may be expanded and reformulated depending on future studies that investigate the effect of myosteatosis on reducing muscle quantity and strength.

Authorship contributions

Bruno Barbosa Bandeira: Conceptualization, data acquisition, analysis and interpretation of data, writing-original draft, and approval of the final version; email:brunobbandeira@hotmail.com.

Liliana Sampaio Costa Mendes: Data acquisition, writing review, conceptualization, investigation, methodology, project administration, formal analysis editing, and approval of the final version.

Mayra Veloso Ayrimoraes Soares: Data acquisition, writing review, conceptualization, investigation, methodology, project administration, formal analysis editing, and approval of the final version.

Luiz Augusto Casulari: Data acquisition, writing review, conceptualization, investigation, methodology, project administration, formal analysis editing, and approval of the final version.

Wladimir Magalhães de Freitas: investigation, methodology, project administration, formal analysis editing.

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Institutional Review Board Statement

The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Institute Hospital de Base do Distrito Federal, Brasília, Brazil.All subjects gave written informed consent.

Declaration availability statement

All data was included in the manuscript. Raw data are available upon request.

Declaration

We declare that we have no conflicts of interest. All the authors contributed equally to this review.

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