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Sarcopenia in chronic viral hepatitis: From concept to clinical relevance

Coelho MPP *et al*. Sarcopenia and chronic viral hepatitis

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Abstract

Although the frequency of metabolic risk factors for cirrhosis and hepatocellular carcinoma (HCC) is increasing, chronic hepatitis B (CHB) and chronic hepatitis C (CHC) remain the most relevant risk factors for advanced liver disease worldwide. In addition to liver damage, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are associated with myriad extrahepatic manifestations including mixed cryoglobulinaemia, lymphoproliferative disorders, renal disease, insulin resistance, type 2 diabetes, sicca syndrome, rheumatoid arthritis-like polyarthritis, and autoantibody production. Recently, the list has grown to include sarcopenia. Loss of muscle mass or muscle function is a critical feature of malnutrition in cirrhotic patients and has been found in approximately 23.0%-60.0% of patients with advanced liver disease. Nonetheless, among published studies, there is significant heterogeneity in the aetiologies of hepatic diseases and measurement methods used to determine sarcopenia. In particular, the interaction between sarcopenia, CHB, and CHC has not been completely clarified in a real-world setting. Sarcopenia can result from a complex and multifaceted virus-host-environment interplay in individuals chronically infected with HBV or HCV. Thus, in the present review, we provide an overview of the concept, prevalence, clinical relevance, and

potential mechanisms of sarcopenia in patients with chronic viral hepatitis, with an emphasis on clinical outcomes, which have been associated with skeletal muscle loss in these patients. A comprehensive overview of sarcopenia in individuals chronically infected with HBV or HCV, independent of the stage of the liver disease, will reinforce the necessity of an integrated medical/nutritional/physical education approach in the daily clinical care of patients with CHB and CHC.

Key Words: Chronic hepatitis B; Chronic hepatitis C; Sarcopenia; Skeletal muscle loss; Cirrhosis; Clinical outcomes

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Core Tip: Sarcopenia is a key feature of malnutrition in liver cirrhosis and has been found in approximately 23.0%-60.0% of patients with advanced hepatic disease. Skeletal muscle loss is associated with poor quality of life and increased mortality, which are significant cirrhosis-related complications. In individuals chronically infected with HBV or hepatitis C virus, the muscle-liver-immune crosstalk during the development of sarcopenia has not been completely clarified. Based on these findings, an overview of the concept, prevalence, clinical relevance, and potential mechanisms of sarcopenia in patients with chronic viral hepatitis is of utmost importance.

INTRODUCTION

Globally, chronic hepatitis B (CHB) and chronic hepatitis C (CHC) were responsible for almost 96.0% of the 1.3 million deaths related to hepatitis viruses in 2015[1,2]. Two-thirds of the global burden of cirrhosis could be attributed to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[2] and approximately 720000 deaths involving

chronically infected individuals have occurred, mostly from cirrhosis and hepatocellular carcinoma (HCC)[1,2].

HBV and HCV affect hepatocytes and can cause both acute and chronic diseases[3]. Individuals with long-term chronic infections have a considerable risk of developing cirrhosis and HCC during their lifetime[3]. Although the frequency of metabolic risk factors for cirrhosis and HCC, such as metabolic syndrome, obesity, type II diabetes, and non-alcoholic fatty liver disease (NAFLD) is increasing, HBV and HCV are currently the most relevant global risk factors for severe hepatic diseases[4,5].

In addition to potential liver diseases, HCV infection is associated with several extrahepatic manifestations, including mixed cryoglobulinaemia, lymphoproliferative disorders, renal disease, insulin resistance, type 2 diabetes, sicca syndrome, rheumatoid arthritis-like polyarthritis, and autoantibody production[6]. Similar to CHC, CHB can be associated with extrahepatic systemic and/or autoimmune manifestations such as systemic vasculitis, glomerulonephritis, and cutaneous manifestations[7].

Numerous studies have demonstrated that both CHB and CHC are associated with nutritional disorders, especially in hepatic cirrhosis, and patients with impaired metabolic function of the liver are at a high risk of malnutrition. This nutritional abnormality has been identified in 13.0%-70.0% of patients with liver disease[8,9] and it is associated with poor quality of life[10-12] and relevant cirrhosis-related complications such as sepsis[13], refractory ascites[14], hepatic encephalopathy[15,16], spontaneous bacterial peritonitis[17], reduced survival[18], and high mortality[19–21]. Taken together, malnourishment and liver cirrhosis contribute to skeletal muscle wasting, an important marker of malnutrition. Loss of muscle mass or muscle function is the key feature of malnutrition in cirrhotic patients and has been found in approximately 23.0%-60.0% of patients with advanced liver disease[9,22-25].

Sarcopenia has been considered a relevant topic in clinical hepatology settings, and a comprehensive overview of skeletal muscle loss in individuals chronically infected with HBV or HCV, independent of the stage of the liver disease, will strengthen an integrated

medical/nutritional/physical education approach in the daily clinical care of patients with CHB and CHC.

Thus, we first contextualised our review in relation to the connection between liver and nutrient metabolism. We then briefly reviewed the origin of the concept of sarcopenia along with the progress in understanding viral hepatitis biology and its related clinical manifestations. Finally, we performed a review to identify and summarise available data on the prevalence and clinical implications of sarcopenia in patients with chronic viral hepatitis.

Essential crosstalk between liver metabolic functions and nutrient metabolism in the body

It is well known that liver plays a central role in the metabolism of nutrients, including macronutrients/micronutrients, vitamin storage and processing, and oxidant/antioxidant balance[26-29]. Hepatic dysfunction can impair the entire spectrum of metabolic and nutritional processes in the body. Therefore, liver diseases are strongly associated with nutritional disorders[9,23,25]. In fat metabolism, hepatocytes break down fats to generate energy[30]. In carbohydrate metabolism, hepatic cells are capable of storing or releasing glucose and contribute to maintaining a constant blood glucose level in circulation[31].

Additionally, the liver is crucial for maintaining protein and nitrogen metabolism[32]. Hepatic cells perform important functions in the balance between protein synthesis and degradation. In healthy individuals, the blood ammonia level originating from amino acid metabolism is controlled by functional hepatic glutamine metabolism and urea cycle in the liver[33,34]. In the presence of cirrhosis, hepatocyte dysfunction is associated with a state of overall protein deficiency and hyperammonaemia. In this setting, glutamine synthesis from glutamate in skeletal muscle mass plays a significant compensatory role in ammonia disposal[33-35].

Although glutamine synthetase activity is low in skeletal muscle[36] because of its large mass, skeletal muscle is quantitatively the most important site of glutamine

synthesis. Ammonia uptake by appendicular muscle has been measured in patients with acute liver failure[37] and was estimated to be 100 nmoL/100 g/min. In chronic liver disease, skeletal muscle also functions as an important extrahepatic site for the removal of ammonia[34,38].

Skeletal muscle encompasses 30.0%–40.0% of the total body mass; thus, this organ is the primary protein store in the human body[39]. The protein turnover balance is responsible for maintaining normal skeletal muscle mass[40]. Increased plasma ammonia levels have been linked to sarcopenia, as a potential mediator of muscle depletion in cirrhosis. Several investigations, including those using animal models, have demonstrated that hyperammonaemia stimulates myostatin expression[41-43]. Myokine is a well known inhibitor of protein synthesis[12]. Furthermore, hyperammonaemia results in muscle mitochondrial dysfunction, increased formation of reactive oxygen species, and oxidative stress, which impair muscle function and repair[44].

This evidence sheds light on the potential pathophysiological mechanisms involved in the liver-muscle axis in hepatic fibrosis[12,35]. Various investigations have shown that skeletal muscle wasting is associated with the progression and poor prognosis of chronic hepatopathy[9,17-21,45-47].

Definition of sarcopenia in different scenarios – from the aging process to hepatic diseases

Sarcopenia and chronic viral hepatitis timelines: Understanding the potential interactions between muscle, liver, and chronic viral hepatitis. The neurologist MacDonald Critchley wrote a manuscript 90 years ago titled "The neurology of old age"[48], which is recognised as the first publication demonstrating age-related skeletal muscle loss. Later, in 1970, Nathan Shock conducted the Baltimore Study of Aging, in which functional changes with age were observed in physiological systems such as sensory, cardiovascular, respiratory, and renal systems[49,50]. However, the term sarcopenia from the Greek words "sarx" (flesh or muscle) and "penia" (loss) was first coined by Rosenberg in the late 1980s. According to the author, no decline is more dramatic or potentially more functionally significant

than the loss of muscle mass with advancing age[50]. Thus, in the first stage of concept elaboration, sarcopenia was operationally described as a gradual loss of muscle mass based on methods estimating muscle mass[50]. A pioneering study by Baumgartner *et al*[51] (1998) described sarcopenia as when the appendicular skeletal muscle mass measured by the dual-energy X-ray absorptiometry (DXA) and adjusted for squared height, was less than two standard deviations below the sex-specific means of healthy young adult individuals. However, following studies have shown that the loss of muscle function, defined as muscle strength and power, is two to five times higher than muscle mass wasting and is significantly linked to adverse outcomes[52,53].

The European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as a syndrome characterised by gradual and generalised loss of skeletal muscle mass and strength[54,55]. Finally, in 2016, sarcopenia was recognised as a disease in the 10th Edition of the International Classification of Diseases with the ICD code 10 - M62.84: Muscle insufficiency[56,57].

Although sarcopenia was originally recognised as an age-related loss of skeletal muscle mass, this clinical condition has been expanded to include loss of muscle function; in addition, it is related to a broad range of chronic diseases[58,59]. Translating this definition into the hepatic disease panorama, several studies have demonstrated that sarcopenia is of utmost significance[9,17-21,58]. Nevertheless, in literature, the term sarcopenia is marked by multiple definitions, diverse methods used to measure skeletal muscle mass, and heterogeneous study designs enrolling patients with cirrhosis of different aetiologies[58,59]. In addition, the major part of the investigations targeting sarcopenia in patients with hepatic diseases evaluated only the skeletal muscle mass[58,59]. Despite these conundrums, we have to bear in mind that most of the cirrhotic patients with skeletal muscle loss included in previous investigations had chronic viral hepatitis.

Although many studies have shown a relationship between liver damage and sarcopenia, the mechanisms underlying skeletal muscle injury have not been completely clarified. Sarcopenia can result from a complex and multifaceted virus-host-environment interplay in individuals chronically infected with HBV or HCV.

Concerning the overlap between viral hepatitis[60-64] and sarcopenia timelines[48-51;65-67] (Figure 1), even before Rosenberg proposed the term sarcopenia[50], Storch (1984) reported a clinical case of 'lupoid' hepatitis with the detection of hepatitis B core antigen (HBcAg) in motor endplates and cross-striations of skeletal muscle in a 12-year-old female patient[67]. Although the diagnostic significance and causes of the described findings were unclear, extrahepatic deposition of this viral marker has been proposed as an indicator of HBV replication in skeletal muscle[67]. Subsequently, inclusion body myositis, a chronic progressive inflammatory myopathy in the elderly, was associated with HCV infection[68,69].

In particular, the prevalence of sarcopenia has been associated with the progression of liver fibrosis[24,70,71]. A study by Hiraoka *et al*[71] (2016) in Japan, using computed tomography and handgrip strength (based on the EWGSOP criteria), found sarcopenia in 7.1%, 11.8%, and 21.9% of the patients with chronic viral hepatitis B and/or C without cirrhosis, with compensated (Child-Turcotte–Pugh A), and decompensated (Child-Turcotte–Pugh B/C) cirrhosis, respectively. Bering *et al*[72] (2017), also using the reference values recommended by EWGSOP, identified the presence of sarcopenia in 7.1% and 11.8% of the non-cirrhotic and compensated cirrhotic (Child–Turcotte–Pugh A) Brazilian patients, respectively. In both studies, 7.0% of the CHC subjects had sarcopenia prior to the onset of cirrhosis[71,72]. In line with these findings, a cross-sectional study from the National Health Examination and Nutrition showed that low muscle mass, as evaluated by mid-upper arm circumference measurements, antedates the development of cirrhosis in American patients with CHC[73]. Taken together, these data shed light on putative risk factors for skeletal muscle loss other than advanced hepatopathy-related factors. Among the potential predictors, virus, host, and environmental factors, such as viral load/genotype, nutritional status, and immune response should be highlighted.

Currently, advancements in direct-acting antiviral agents (DAAs) have resulted in outstanding improvements in the management of patients chronically infected with HCV, with sustained virological response rates that surpass 95.0% in real-life scenarios[74]. Treatment with DAAs is safe and effective and has been associated with

liver and non-liver benefits, such as the prevention of hepatic disease progression and improvements in quality of life scores[74,75]. However, a study showed that DAA-induced clearance does not completely restore the altered cytokine and chemokine milieu in CHC patients[76]. Hence, in these individuals, cytokine and chemokine signatures vary depending on the stage of the liver disease and the response to antiviral therapy[77-80]. This knowledge can be transferred to the muscle-liver axis in the context of HCV eradication, especially with the introduction of interferon-free (IFN-free) treatments in clinical practice. More recently, results from interventional studies have demonstrated that HCV eradication by DAAs suppresses skeletal muscle loss in patients with CHC[81-84], suggesting a direct role of the virus in muscle mass depletion. However, the role played by the host immune response, especially pro-inflammatory effects, on skeletal muscle cells in CHC should not be overlooked[6,77-79,85]. Future longitudinal and multicentre studies are required to reduce this gap in knowledge.

Concerning extrahepatic manifestations of HCV infection, several studies suggest that an imbalance between pro-inflammatory and anti-inflammatory cytokines might induce immune activation in sites outside the liver, and consequently, generate a wide range of systemic symptoms and signals, including myalgia, weakness, fatigue, nausea, abdominal pain, weight loss, arthralgia, purpura, Raynaud's phenomenon, xerostomia, dry eyes, depressive feelings, and anxious mood[6,86]. Therefore, CHC has been identified as a systemic disease, and 40%-74% of patients chronically infected with HCV may develop at least one non-liver manifestation throughout the clinical course of the infection[86].

It is generally acknowledged that the mechanisms involved in HCV-related extrahepatic manifestations are attributable to antibody- and cell-mediated immune responses[87-90]. Among these mechanisms, cryoglobulinaemia (type II cryoglobulin) is associated with chronic HCV[6,86]. Cryoglobulins are immunoglobulins that precipitate *in vitro* at temperatures < 37 °C and solubilise upon warming. HCV can trigger the expansion of B cell clones that secrete monoclonal IgM with rheumatoid factor activity. IgM then binds to polyclonal IgG molecules, which recognise HCV antigens. The

resulting immunocomplexes activate complement proteins, which bind cell receptors on endothelial cells, leading to the recruitment of mononuclear and polymorphonuclear cells resulting in vasculitis. Vasculitis may occur in the brain, skin, joints, kidneys, lungs, heart, and digestive tract[6,86]. Another site that may be affected by immune-mediated occurrence is the skeletal muscle. Although secondary sarcopenia is frequently identified in patients with cirrhosis, the mechanisms underlying the interaction between the loss of skeletal mass, inflammatory mediators, and chronic viral hepatitis are still unclear. Given the potential role of circulating pro-inflammatory cytokines in mediating age-related sarcopenia[91,92], the effects of these inflammatory mediators on the pathogenesis of skeletal muscle loss occurring in HBV and HCV should be evaluated.

Other potential predictors of sarcopenia in chronic viral hepatitis should be considered, such as environmental factors, which are strongly linked to nutritional disorders and muscle homeostasis. Several lifestyle aspects in individuals with CHB and CHC may contribute to muscle damage, such as dietary patterns, diet-related non-communicable diseases, sedentarism, cigarette smoking, alcohol, and non-alcohol substance use. Analysing data from the Korean National Health and Nutrition Examination Surveys 2008-2011, Han *et al*[93] observed that sarcopenia was independently associated with liver fibrosis in patients with CHB. The authors also observed that when the study population was stratified according to metabolic factors, sarcopenia was independently associated with fibrosis among subgroups with obesity, insulin resistance, metabolic syndrome, and liver steatosis.

More recently, Santos *et al*[94] (2022), used DXA, handgrip strength, and Timed Up and Go test to show that in patients with CHB, the presence of metabolic-associated fatty liver disease and central obesity was associated with low muscle mass and strength. Although secondary sarcopenia is a well-known predictor of liver fibrosis in patients with NAFLD[95], the interaction between sarcopenia and CHB is poorly understood. These findings encourage the evaluation of metabolic and skeletal muscle loss among individuals chronically infected with HBV and reinforce the need for further large-scale case-control studies.

Few studies have examined the effects of antiviral treatment on muscle mass in CHB patients. In an investigation centred on the measurement of psoas major muscle using computed tomography before and after long-term entecavir therapy, no significant change in the muscular area was identified in any of the patients, but a significant increase was detected in the group of patients with serum albumin < 4 g/dL before treatment[96]. In contrast, Kim *et al*[97] (2020) investigated the dynamic association between changes in fibrosis and muscle mass during antiviral therapy and reported that appendicular skeletal muscle mass (ASM) significantly decreased during treatment of HBV infection.

Approximately 462 million adults worldwide are underweight, whereas 1.9 billion are either overweight or obese[98,99]. According to the World Health Organization definition, the double burden of malnutrition is characterised by the coexistence of undernutrition along with overweight, obesity, or diet-related non-communicable diseases within individuals, households, and populations across the course of life[98,99]. Furthermore, a growing body of evidence has shown that excessive food intake and lack of physical exercise, considered serious characteristics of the modern lifestyle, have also been verified in patients with liver disease[100,101]. Health professionals face a great challenge particularly in the management of CHB and/or CHC patients, because malnutrition and overweight can simultaneously be present in a patient[47,102]. Sarcopenic obesity, which is characterised by a decrease in ASM and excess body fat, is associated with increased mortality and influences the metabolic profile and physical performance compared with clinical manifestations alone[47,100]. Consequently, an improvement in the comprehension of body composition and nutritional status of chronically infected HBV and HCV individuals, regardless of the severity of the liver disease, is highly relevant for clinicians, dieticians, and specialists in hepatic diseases[101,102].

PREVALENCE AND CLINICAL IMPLICATIONS ASSOCIATED WITH SARCOPENIA IN PATIENTS WITH CHRONIC VIRAL HEPATITIS

Sarcopenia is a relevant risk factor for adverse outcomes in cirrhotic patients[12,18]. As mentioned earlier, among the objectives of this review, we aimed to identify and summarise the available data on the prevalence and adverse clinical outcomes of sarcopenia in patients with chronic viral hepatitis. The steps involved in the review process are as follows:

Literature search

We first performed a sequential electronic search using PubMed, Embase, Biblioteca Virtual em Saúde, Cochrane Library, Scopus, Web of Science, and Cumulative Index to Nursing and Allied Health on September 1, 2022 to identify published scientific reports on sarcopenia in patients with chronic viral hepatitis. The search included studies that were published between January 1995 and September 2022. To do the research, a combination of the following descriptors was used: "hepatitis C", "chronic hepatitis C", "hepatitis B", "chronic hepatitis B", "sarcopenia", "low muscle mass", "sarcopenic obesity", "skeletal muscle mass", and "skeletal muscle" (Supplementary material).

The eligibility of the articles was evaluated by two independent reviewers (MPPC and TPV). Duplicate articles were excluded from the analysis. The articles were selected by title, abstract, and full text in separate and sequential steps, following the predefined inclusion and exclusion criteria. To evaluate whether the articles met all previously established criteria, each article was analysed individually. A third reviewer resolved the disagreements between the two reviewers.

Eligibility criteria

We used the Patients, Intervention, Comparison, Outcome model to develop literature search strategies[103]. Eligible manuscripts included adults aged ≥ 18 years who were chronically infected with HBV or HCV. We also considered the following conditions: presence of inpatients and outpatients, sample size of at least 30 subjects, and loss of skeletal muscle mass and/or function as the variable of interest. In addition, the clinical outcomes included infectious and noninfectious complications (clinical outcomes),

increased length of hospital stay, mortality, survival, and health-related quality of life scores. Moreover, data on the prevalence of low skeletal muscle mass and/or function, including pre-sarcopenia, sarcopenia, and sarcopenic obesity, independent of the grade of liver fibrosis, were also assessed.

Quality assessment

The methodological quality of the studies was assessed by two independent reviewers using the Joanna Briggs Institute Critical Appraisal tools applicable to each specific study design[104]. Each criterion was assessed as ''yes'' (fulfilled), ''no'' (not fulfilled), or ''unclear''. Any differences in opinion between the reviewers regarding the methodological quality were resolved by consensus through direct discussion. Disagreements were resolved through discussion with a third research member.

A total of 1427 articles were identified in the aforementioned databases. After discarding duplicates, non-English language papers, and non-relevant articles, 17 full-length published articles were selected for appraisal and were retained in the current mini-review (Supplementary material).

Prevalence, definitions, and clinical outcomes associated with sarcopenia

One of the most remarkable consequences of aging is the involuntary loss of muscle mass, strength, and function, termed sarcopenia[54-56]. Various attempts have been made to apply this operational definition to hepatic disease settings, as summarised in Table 1 [47,71-73,93,94,105-109,110-114,115]. The designs of the 17 included studies were retrospective cohort (n = 8), cross-sectional (n = 8), and prospective cohort (n = 1). Most of the studies were performed in Asia (7/17, six in Japan and one in Korea[71,93,108,109,111,112,114]) and America (four in the United States[73,106,107,115], two in Canada[47,105], and two in South America[72,94]), while one each was performed in Europe[113], and in Australia/Oceania[110]. The overall sarcopenia prevalence varied from 3.8%-53.7% in the 17 studies.

The median age of the participants ranged from 49.2 to 70.5 years[112,113]. One study included only men[110] while all the others were mixed-sex investigations, with the

number of women varying between 26[72] and 9287[73]. Different aetiologies of liver diseases were observed in these studies [47,71-73,93,94,105-109,110-114,115]; with respect to chronic viral hepatitis, two studies included only patients chronically infected with HBV[93,94] and HCV[72]. In 53.0% of the investigations, sarcopenia was diagnosed according to one of the four consensus diagnostic criteria for age-related sarcopenia proposed by the Asian Working Group for Sarcopenia, EWGSOP, the Foundation for the National Institutes of Health Sarcopenia Project, and the Japan Society of Hepatology[71,72,93,108,111,112,114,115]. Muscle mass was measured using computed tomography in the majority of studies (8/17 studies[47,71,105-107,109,111,113]), followed by bioelectrical impedance analysis (4/17[108,112,114,115]), DXA (4/17 studies[72,93,94,110]), and anthropometric measurements (1/17 studies[73]). Muscle strength was measured using handgrip strength in 5/17 studies[71,72,94,112,114]. Physical performance was evaluated in two studies[94,112].

The studies reported results for approximately six different types of outcomes: mortality (five studies[47,105,106,110,113]), decreased survival (four studies[108,109,113,114]), severity of liver fibrosis (two studies[71,93]), osteopenia/osteoporosis and vertebral fractures (two studies[72,112]), while one each identified poor quality of life[111], and malnutrition[72]. In HBV scenario, sarcopenia was associated with metabolic derangements, central obesity, and metabolic syndrome[93,94].

DISCUSSION

Globally, sarcopenia is a research hotspot [116] and its clinical significance in patients with chronic liver disease is of utmost importance. In cirrhosis, sarcopenia intensely affects the health status and health-related quality of life [10,13-17,18-21]. Muscle wasting that affects cirrhotic patients is accelerated, and losses greater than 3.0% annually have been related to adverse outcomes[59].

Despite the awareness and clinical recognition of sarcopenia in cirrhotic patients, large heterogeneity permeates studies focused on sarcopenia in these individuals. It should be highlighted that in literature, the term sarcopenia is marked by multiple definitions, diverse measurement methods, and heterogeneous study designs enrolling

patients with cirrhosis of diverse aetiologies and different stages of liver fibrosis[59]. In addition, most investigations targeting sarcopenia in patients with hepatic diseases have evaluated only skeletal muscle mass[59].

In the current review, the overall prevalence of sarcopenia varied from 3.8%-53.7%. This difference can be attributed to the different criteria used to detect sarcopenia. In patients with chronic liver disease, there is neither a gold-standard definition nor a universal operational criterion for identifying sarcopenic cases. Additionally, the aetiology of the liver disease and severity of hepatic fibrosis varied among the investigations included in this minireview. Using computed tomography and hand grip strength, Hiraoka *et al*[71] (2016) (based on EWGSOP1 criteria) found that sarcopenia was present in 7.1%, 11.8%, and 21.9% of Japanese patients with chronic B and/or C viral hepatitis with non-cirrhosis, compensated cirrhosis (Child-Turcotte-Pugh A), and decompensated cirrhosis (Child-Turcotte-Pugh B/C), respectively. The authors observed that the prevalence of sarcopenia increased with the progression of hepatic fibrosis. Of particular concern was the finding that patients with CHC had sarcopenia prior to the onset of cirrhosis[71]. These findings reinforce the need for further research focusing on the biological mechanisms underlying the concurrent occurrence of sarcopenia in patients with chronic viral hepatitis.

Concerning the clinical outcomes associated with sarcopenia in patients chronically infected with HBV or HCV, skeletal muscle loss has been considered an independent prognostic marker of mortality in cirrhotic patients and is associated with an increased risk of complications, such as sepsis[13], refractory ascites[14], hepatic encephalopathy[15,16], and spontaneous bacterial peritonitis[17].

Considering other clinical implications of sarcopenia in patients with CHC, an association between skeletal muscle loss and bone loss was verified, independent of the severity of liver fibrosis[72]. In cirrhosis settings, bone disorders have been linked to hypogonadism[117], vitamin D deficiency[118], and low levels of insulin-like growth factor[119]. Nevertheless, little is known about the bone status of patients with CHC, especially before the onset of cirrhosis. Among the potential factors, chronic

inflammation, inadequate diet and nutrition, and weight and muscle loss may contribute to low bone mineral density in subjects chronically infected with HCV. Taken together, muscle mass and muscle strength stimulate osteogenesis through connections between the bone and skeletal muscle[120]. In addition, skeletal muscle mass is recognised as an independent predictor of bone mineral density in healthy[121] and diseased individuals[122,123].

In the current review, metabolic derangements, central obesity, and metabolic syndrome were associated with sarcopenia in patients with CHB[93,94]. However, there are few studies exploring skeletal muscle loss in CHB patients. To date, among the various aetiologies implicated in liver diseases, liver-muscle interaction has been the most studied in patients with NAFLD/NASH[66,70]. Of particular concern in fatty liver disease is the fact that various evidence point to the complexity of the mechanisms implicated in skeletal muscle damage. In a previous investigation, Lee *et al*. observed that up to 12.0% of patients diagnosed with NAFLD had sarcopenia independent of obesity and insulin resistance, and approximately 30.0% of sarcopenic individuals without metabolic syndrome and obesity had NAFLD[124,125].

CONCLUSION

There is no universal consensus regarding the diagnosis of sarcopenia in patients with chronic viral hepatitis. Although the prevalence of sarcopenia increased in parallel with the progression of hepatic fibrosis, interestingly, sarcopenia was observed in patients chronically infected with HCV before the onset of cirrhosis. Even in studies not focused on evaluating only patients with chronic viral hepatitis, relevant adverse health-related outcomes were associated with sarcopenia in CHB or CHC patients. These findings highlight the importance of addressing skeletal muscle mass and strength loss in patients with chronic viral hepatitis. Effective strategies should be implemented to screen for sarcopenia in these patients, independent of the stage of the liver disease. An integrated medical/nutritional/physical education approach will enable greater understanding of

the significance of musculoskeletal changes in patients chronically infected with HBV or HCV.

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