# Ammonia and the Muscle on Hepatic Encephalopathy

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The link between the presence of muscular alterations and hepatic encephalopathy (HE), both minimal and overt, has been deeply studied. The pathophysiological background supporting the relationship between muscle depletion, and HE is characterized by an imbalance between the capacity of muscle in ammonia metabolism and trafficking and the inability of the liver in removing ammonia through urea synthesis due to liver failure and/or the presence of porto-systemic shunts.

Keywords: cirrhosis ; sarcopenia ; myosteatosis ; hepatic encephalopathy

## 1. Introduction

Hepatic encephalopathy (HE) is defined as a spectrum of neuro/psychiatric alterations caused by liver failure and/or porto-systemic shunts with different clinical conditions ranging from subclinical alterations to coma [1]. It's one of the most frequent complication of liver cirrhosis affecting up to 30–40% of cirrhotic patients. It can be divided into overt hepatic encephalopathy (OHE), that is clinically evident and minimal hepatic encephalopathy (MHE), a condition characterized by subclinical alterations detectable only with psychometric tests or electroencephalography. More recently the term "covert HE" has been coined to combining MHE and Grade I of overt HE. The aim is to unify the terminology, make the diagnosis clearer and allow the design of more inclusive and uniform clinical studies. The term "covert" refers to a condition that is not unapparent, but also not overt. Covert HE, if investigated, can reach up to 80% of cirrhotic patients [1]. It is well known that HE worsens the prognosis of patients with cirrhosis and it is one of the main causes of hospitalization [2]; in particular MHE has been associated with falls [3][4] and car accidents [5][6][7], a reduction in quality of life and the socio-economic status and has a major impact on economic health costs [8][9][10].

Another common complication of liver cirrhosis is malnutrition; it correlates with the severity of liver disease and disease complications, including hepatic encephalopathy [11]. Sarcopenia, the generalized loss of muscle mass and function, is the major component of malnutrition [12]. Skeletal muscle is the main protein reserve in the body, it is maintained thanks to a continuous balance between protein synthesis and catabolism (proteostasis), and represents up to half of the entire protein turnover of the body [13]. Although it is a pathophysiological mechanism that correlates with the advancement of age (primitive sarcopenia), some chronic pathologies can accelerate this process (secondary sarcopenia) [13].

Sarcopenia is present between 30% and 70% of cirrhotic patients, with an increasing trend depending on the degree of liver disease [14]. Sarcopenia is a part of the frailty complex in cirrhotic patients, with a decreased reserve and resistance to stressors. Furthermore, it has been demonstrated that sarcopenia increases mortality in cirrhotic patients. In recently published metanalysis by Tantai et al. [15], authors conclude that sarcopenia was highly and independently associated with higher risk of mortality in patients with cirrhosis.

It has been suggested that considering muscle alterations in addition to prognostic scores improves the prediction of death in patients with cirrhosis [16]. Despite this, nutrition is often overlooked as nutritional assessment could be complex in cirrhotic patients [17]. Moreover, muscular alterations not only affect muscle mass but also its quality and function, making the picture more complex.

The methods for the diagnosis of sarcopenia are not uniform. This makes the overall evaluation of the studies difficult. They can be based on the different aspects of sarcopenia, that are the assessment of muscle mass, muscle performance and muscle strength. The gold standard for assessing sarcopenia is CT-scan, which allows to evaluate the muscle mass at the level of the L3 section [17].

The link between muscle alterations and liver disease is not well defined; it is multifactorial and includes hormonal alterations [18], hyperammonemia [19][20] and endotoxinemia [21]. Portal hypertension could play a role regardless of liver function in sarcopenia genesis [22], although this link needs to be better investigated. Therapies that act by reducing portal hypertension, such as transjugular intrahepatic portosystemic shunt, seem to improve muscle structure [23][24].

## 2. Muscle Alterations and Hepatic Encephalopathy in Liver Cirrhosis

During the natural history of chronic liver disease, muscle alterations may appear and these include muscle wasting, sarcopenia and myosteatosis. Sarcopenia is the most prevalent muscle abnormality, with a generalized reduction in muscle mass and function. It is defined as a muscle mass two standard deviations below the healthy young adult mean [25]. Myosteatosis is a fat infiltration of the skeletal muscle mass with an increased proportion of intramuscular and intermuscular fat that could impact muscle function and lead to a systemic inflammation [26].

The presence of myosteatosis and sarcopenia has been associated with a poor prognosis in patients with liver cirrhosis [27]. Moreover, these conditions are associated to several complications of liver cirrhosis, such as ascites [28], Spontaneous bacterial peritonitis (SBP) [29], variceal bleeding [30], hepatocellular carcinoma [31] and infections [32][33].

One of the closest and well-known relationship between muscle alterations and complications of liver disease is between sarcopenia and hepatic encephalopathy [34] (**Table 1**).

### 2.1. Sarcopenia and Cognitive Impairment

From as far back as 1964 it has been known that malnutrition could impact the prognosis of patients with liver cirrhosis in specific settings [35]. This link was confirmed by a large Italian multicentric prospective study conducted in 1996 [36]. Since that moment, several studies were conducted to investigate the link between malnutrition and liver complications. Among these, it was immediately clear that patients with malnutrition were at higher risk to develop cognitive impairment.

Soros et al. in 2008 analyzed 223 cirrhotic patients' muscle mass (assessed by bioelectrical impedance analysis): parameters of fat and fat-free mass were found to be similar in patients with and without HE [37].

Despite this, more recent studies demonstrated different results. Using handgrip strength (HGS) in 84 cirrhotic patients in 2011, Huisman et al. [28] found that muscle strength was an independent predictor of complications (including HE) after correcting for comorbidities, age and Child Pugh score. In a large cohort of patients (675 cirrhotic patients enrolled from 2000 to 2014) [38], sarcopenia was found to be associated with a higher risk of overt hepatic encephalopathy (OHE). In this study, sarcopenia was evaluated with CT scan, in particular cross-sectional areas were obtained from transverse CT images at the level of L3 of each patient and adjusted for height to calculate the Skeletal Muscle Index (SMI). In this study there was a strong correlation between sarcopenia and mortality, after adjusting for multiple confounding factors.

More recently, a Japanese group retrospectively analyzed nearly 300 patients that have a HGS measurement [39]. They found that HGS was able to stratify patients at high risk to develop OHE. Despite the retrospective nature of this study, it demonstrated that a simple and economical measurement bedside of the patient can reliably discriminate patients at risk for this complication.

In 2013 Merli et al. [40] enrolled 300 cirrhotic patients and at multivariate logistic regression analysis, muscle depletion, evaluated with BMI, mid-arm-muscle-circumference (MAMC), triceps skinfold-thickness (TSF) and HGS, was found as an independent risk factor for OHE during hospitalization. Moreover, this study was one of the first study that investigated the relationship between muscle depletion and minimal hepatic encephalopathy (MHE). MHE is a subclinical condition in which cognitive impairment isn't detectable with physical examination, but only with psychometric tests [41][42], electrophysiological and other functional brain measures [43][44]. In this study [41] MHE was evaluated with psychometric tests and the reduction in muscle mass and muscle function were significantly associated not only with overt HE but also with MHE. Although the relationship between muscular alterations and MHE was directly researched for the first time in this study, in 2007 it has been demonstrated that patients with malnutrition (assessed by anthropometry and estimation of recent weight change) and patients with diabetes mellitus were at higher risk of cognitive impairment [45].

In a retrospective study conducted by Hanai et al. in 2017 [46], appendicular skeletal muscle mass (ASM) using bio-impedance analysis and HGS were performed to investigate the presence of sarcopenia. In this cohort of patients (120) sarcopenia was strongly associated with the presence of MHE. In addition to the retrospective and single-center nature of this study, another limit is that MHE was investigated with number connection test-A (NCT-A), number connection test-B (NCT-B), digit symbol test (DST) and block design test (BDT), a combination easier and quicker than the gold-standard PHES (psychometric hepatic encephalopathy score) [11].

However, all these results have been recently confirmed in a prospective study of 64 patients with liver cirrhosis [34]. The muscle assessment was investigated with CT-scan using Carey's cut-off of the SMI for determination of sarcopenia [47]. Thirty-two patients (50%) had MHE at the time of enrollment, of whom 84% had sarcopenia; only 31% of patients without

MHE had sarcopenia. In the multivariate analysis, only sarcopenia, myosteatosis and previous episodes of HE, were independently associated to the presence of MHE.

### 2.2. Myosteatosis and Cognitive Impairment

It is well known that the reduction in muscle mass is not the only muscle alteration that can be associated with chronic liver disease. The infiltration of muscle mass by intermuscular and intramuscular fat was first described in 1983 because of ageing [48] and metabolic abnormalities [49] and later defined as myosteatosis [50]. It is associated with poorer muscle strength and physical performance in older persons. As in sarcopenia, it has been demonstrated that this condition can appears also in younger people with chronic disease [51].

Montano-Loza et al. [27] have demonstrated that sarcopenia and myosteatosis increase the risk of mortality by 1.5-to twofold compared with patients without muscular abnormalities. Whereas these are very frequent alterations in cirrhotic patients, it's important to investigate them. In this study, however, they have considered mainly patients with advanced liver cirrhosis (Child-Pugh B-C) and the percent of hepatocellular carcinoma was quite high.

Few studies have analyzed the relationship between myosteatosis and HE. Bhanji et al. have studied a large cohort of cirrhotic patients with an available CT-scan in a retrospective analysis [38]. At multivariable regression analysis, myosteatosis was independently associated with a higher risk of HE. Patients with HE and myosteatosis had worse survival (15 ± 8 months), in comparison to those without these conditions (58 ± 14 months; $p = 0.001$) or with only HE or myosteatosis (31 ± 6 months; $p = 0.02$). Nardelli et al. investigated for the first time the link between myosteatosis and MHE [34], demonstrating that myosteatosis was strongly associated not only with OHE but also with MHE.

**Table 1.** Studies evaluating the relationship between muscle alterations and hepatic encephalopathy in cirrhosis.

| First Author (Year) | Number of Patients | Methods to Identify Sarcopenia and/or Myosteatosis | Prevalence of Sarcopenia and/or Myosteatosis | Results |
|---|---|---|---|---|
| Merli et al. (2013) [40] | 300 hospitalized cirrhotics | Anthropometric measurements (MAMC) and handgrip strenght (HGS) | 48% | Overt HE in 30% with sarcopenia vs. 15% without sarcopenia ($p = 0.003$)<br>Minimal HE in 49% with sarcopenia vs. 30% without sarcopenia ($p = 0.001$) |
| Hanai et al. (2017) [46] | 120 cirrhotics | Bio-impedance Analysis (BIA), handgrip strenght | 27% | Sarcopenia and serum branched-chain amino acids levels were associated with MHE in the multivariate analysis ($p = 0.02$ and $p = 0.03$ respectively). |
| Miwa et al. (2021) [39] | 270 cirrhotics | Handgrip strength | 38% | Multivariate analysis showed that reduced HGS was associated with a higher prevalence of CHE and higher risk for developing OHE |
| Nardelli et al. (2017) [52] | 46 cirrhotics submitted to TIPS | CT scan to evaluate sarcopenia with Skeletal Muscle Index (SMI) | 57% | Twenty-one patients (46%) developed overt HE after TIPS placement; all of these patients were sarcopenic. At multivariate analysis, only MELD score ($p = 0.043$) and sarcopenia ($p < 0.001$) were independently associated with the development of HE after TIPS placement. |
| Kalaitzakis et al. (2007) [45] | 128 cirrhotic patients | BMI, weight loss, MAMC and triceps skinfold | 40% | HE in 46% with malnutrition vs. 27% without malnutrition ($p = 0.03$) |
| Huisman et al. (2011) [30] | 84 cirrhotic patients | Handgrip strength | 67% | Increased complications in cirrhotic patients with lower muscle function, including HE (18% vs. 48%, $p = 0.007$) |
| Nardelli et al. (2019) [34] | 64 cirrhotic patients | CT scan to evaluate sarcopenia and myosteatosis | Sarcopenia 58%<br>Myosteatosis 38% | Both myosteatosis and sarcopenia were more frequent in patients who developed overt HE. On multivariate analysis, only sarcopenia ($p = 0.005$) and myosteatosis ($p = 0.002$) were independently associated to the development of overt HE. |

| First Author (Year) | Number of Patients | Methods to Identify Sarcopenia and/or Myosteatosis | Prevalence of Sarcopenia and/or Myosteatosis | Results |
|---|---|---|---|---|
| **Bhanji et al. (2018) [38]** | **675 cirrhotic patients** | **CT scan to evaluate sarcopenia and myosteatosis** | **Sarcopenia 36% Myosteatosis 52%** | **Both myosteatosis (70 vs. 45%, $p < 0.001$) and sarcopenia (53 vs. 32%, $p < 0.001$) were more frequent in patients with hepatic encephalopathy. By multivariable regression analysis, both myosteatosis and sarcopenia were associated with a higher risk of hepatic encephalopathy, independent of the MELD score.** |

## 3. Liver-Muscle Axis and Hyperammonemia: A Link to Explore

It has long been known that liver cirrhosis is a systemic disease which, especially in the advanced stages, affects different organs and systems. Although suspected for a long time [53], it has only recently become evident that the relationship between liver and muscle is very close, where one affects the other. Data collected until now show that both muscle synthesis and lysis can be altered in cirrhosis.

Regarding the synthesis of muscle, several factors reduce the potential of the organism to synthesize muscle mass. First, cirrhotic patients are known to have a reduced calories intake; the presence of ascites can lead to early satiety due to increase in abdominal pressure. In turn sarcopenia contributes to fatigue and limits exercise tolerance, reduces performance status and activities of daily living; reduced physical activity obviously contributes to reduced anabolic stimulation [54], which is already altered in the patient with liver cirrhosis [55]. Notably, contrary to what is always claimed, the low-sodium diet could be counterproductive in cirrhotic patients with ascites, making food less palatable and therefore leading the patient to take less calories. Moreover, cirrhotic patients have different causes of malabsorption, such as reduced bile flow with malabsorption of fat-soluble vitamins and fats, pancreatic insufficiency in alcoholic related liver disease with alteration in absorption of fats, bacterial overgrowth due to impaired intestinal motility and portal hypertension [56]. Second, testosterone is an anabolic hormone that increases muscle mass by improving levels of insulin-like growth factor-1 (IGF-1), also called mechano-growth factor [57]. Through IGF-1, testosterone is able to activate mammalian target of rapamycin (mTOR), which is a crucial point in the activation of muscle synthesis. As is well know, cirrhotic patients have low testosterone levels [58]. Finally, leucine-enriched BCAAs have an important role in the synthesis of muscle mass [59]. All these mechanisms, through the stimulation of mTOR, lead to the activation of satellite muscle cells. These cells live in a state of quiescence and when stimulated allow the restoration of muscle mass [60].

On the other hand, proteolysis is upregulated in cirrhotic patients. Above all, cirrhosis is a hypermetabolic condition due to proinflammatory state. In this way, the organism uses gluconeogenesis to compensate for glycogen deficiencies, already altered in the cirrhotic, by consuming proteins and muscle mass. In this perspective, prolonged fasting should be avoided. Chronic inflammation induces autophagy by activating the ubiquitin-proteasome system [61]. Finally, a fundamental regulator of proteostasis is myostatin, a TGFB superfamily member that induces muscle loss. This regulation is due to the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) [55].

Within this complex system of regulations, hyperammonemia has one of the most important roles. Ammonia is a compound of nitrogen and hydrogen, mostly a gut-derived toxin produced by bacterial metabolism of urea from proteins that are consumed in the human diet (urease-producing bacterial organisms). With the progression of liver disease, the microbiome enters a dysbiosis state, leading to greater inflammation and cholestasis. So, the composition of gut microbiota becomes altered and plays an important role in the pathogenesis of HE [62]. Moreover ammonia is generated from the continuous amino acid catabolism and purine turnover. From the catabolism inside the enterocytes and from the bacterial production, ammonia enters the portal system and then reaches the liver. Within the liver, ammonia passes through two filter systems, periportal hepatocytes and perivenous hepatocytes. Ammonia is used in the first system as a substrate of the urea cycle. However, in the perivenous hepatocytes there is a strong expression of the enzyme glutamine synthetase which removes the remaining part of toxin to prevent it from entering the systemic circulation [63]. When the liver is damaged and subverted by chronic injury and/or when collateral circles are established that pass the liver filter, ammonia passes directly into the systemic circulation and produces its cytotoxic effects at the level of the central nervous system. At this point the mechanism leading to hepatic encephalopathy is established. What is the role of the muscle within this liver-brain link? Skeletal muscle also expresses glutamine synthetase, although its activity is very low. However, considering the entire muscle extension, it is possible that the muscle is a good buffer system to dispose of excess circulating ammonia [64]. From this, if the skeletal muscle is reduced it has a lower ability to absorb circulating ammonia

and therefore the risk of hepatic encephalopathy increases. Merli et al. have demonstrated that venous blood ammonia levels were significantly higher in patients with muscle depletion and in patients with a decreased muscle strength [40].

In this context, hyperammonemia has a direct negative effect on muscle turn-over. Its action is polyhedral and acts both on synthesis and on muscle lysis. Moreover, hyperammonemia induces a cellular stress response and mimes cell responses activated by amino acid deficiency. In particular, it inhibits the translation of mRNA and protein synthesis into skeletal muscle through activation of general control non-depressed 2 (GCN2) and inhibition of mTORC1 with unknown mechanisms [65]. In addition, the disturbance of the tricarboxylic acid cycle, linked to the loss of alpha-KG (necessary for the conversion of ammonia into glutamate) leads to loss of ATP, mitochondrial dysfunction, reduction of contractile function and finally to sarcopenia. Ammonia also can potentially cause post-translational modifications, including protein nitration and oxidative stress-induced carbonylation of contractile proteins with impaired actomyosin interactions. That is why ammonia-mediated nitration is a potential molecular mechanism of impaired contractile function [20].

It has also been widely demonstrated that hyperammonemia leads to increased activation of myostatin in cirrhotic patients [66], inhibiting protein synthesis. Nishikawa et al. [67] have demonstrated that higher levels of myostatin is associated with hyperammonemia and muscle loss in cirrhotic patients; moreover, patients with increased myostatin had worse prognosis, suggesting the importance of muscle in the prognostic overview of the patient with liver cirrhosis. This concept echoes the above-mentioned idea of considering sarcopenia in the predictive mortality model for cirrhotic patients in liver transplant evaluation [16].

Finally, it has been demonstrated that hyperammonemia increases autophagy in cirrhotic patients with unclear mechanisms [19].

Regarding myosteatosis, the physiopathological association with hyperammonemia and HE is more complex and partially unknown. Myosteatosis seems to derive from a complex mechanism involving the metabolism of fatty acids and glycogen; the pivotal point of this process is mediated by the proinflammatory state that is present and that leads to muscle depletion [26]. Nardelli et al. have demonstrated the association between myosteatosis and HE, hypothezing that fat infiltration, by reducing the fat-free mass, may contribute to the reduction of leads to partial loss of function of glutamate synthetase, expressed in the muscle cell. The significant correlation between ammonia, SMI, and muscle attenuation seems to support this hypothesis [34].

In summary, the set of these mechanisms activates a vicious circle in which cirrhosis induces muscular depletion with multiple mechanisms; the muscular deficiency on the other hand reduces the capacities of absorption of circulating ammonia. Hyperammonemia in turn alters proteostasis and induces further muscle loss. It is now known that muscle depletion reduces survival in cirrhotic patients. The biochemical link of the liver-muscle axis is probably more complex than said and given its prognostic importance it must be further investigated to find therapy targets that can block this vicious circle.

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