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TOPIC HIGHLIGHT

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Nutritional assessment in cirrhotic patients with hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) is one of the worst complications of liver disease and can be greatly influenced by nutritional status. Ammonia metabolism, inflammation and muscle wasting are relevant processes in HE pathophysiology. Malnutrition worsens the prognosis in HE, requiring early assessment of nutritional status of these patients. Body composition changes induced by liver disease and limitations superimposed by HE hamper the proper accomplishment of exams in this population, but evidence is growing that assessment of muscle mass and muscle function is mandatory due to the role of skeletal muscles in ammonia metabolism. In this review, we present the pathophysiological aspects involved in HE to support further discussion about advantages and drawbacks of some methods for evaluating the nutritional status of cirrhotic patients with HE, focusing on body composition.

Key words: Hepatic encephalopathy; Liver cirrhosis; Malnutrition; Anthropometry; Muscle strength; Electric impedance; Nutrition assessment; Dual-energy X-ray absorptiometry

Core tip: Ammonia metabolism, inflammation and muscle wasting are relevant processes in hepatic encephalopathy (HE) pathophysiology and malnutrition worsens the prognosis in this condition, requiring early assessment of nutritional status in these patients. Body composition changes induced by liver disease and limitations superimposed by HE make difficult to accomplish exams properly in this population, but there is a growing evidence that assessment of muscle mass and muscle function is mandatory due to the role of skeletal muscles in ammonia metabolism. In this article,

we review HE pathophysiology and discuss the main methods of nutritional assessment, suggesting the best approaches in HE patients.

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INTRODUCTION

Hepatic encephalopathy (HE), a neurological dysfunction affecting primarily the brain, is caused by acute or chronic liver insufficiency and/or by the presence of portosystemic shunting. This syndrome embraces distinct forms of neurological symptoms from subclinical presentations to hepatic coma[1]. Overt HE afflicts 30%-45% of cirrhotic patients, whereas minimal HE may affect more than half of the cases with advanced cirrhosis[2-4]. The estimated incidence in decompensated cirrhosis is 8% per year and the majority of patients with HE episodes are received in emergency care services[5]. In an observational study, the mean hospitalization length of these patients was between 5.7 and 7.1 d[2].

Among cirrhosis complications, HE mortality is higher than the rate caused by variceal bleeding or ascites. After overt episodes, death rates vary between 42% and 64% in one year according to HE grade[6-8]. The relevance of this condition was demonstrated even in patients without overt HE, for whom a mortality index combining electroencephalogram findings and the model of end-stage liver disease score (MELD) had a higher accuracy for predicting 12- and 18-mo survival than the MELD score alone[9].

The role of nutrition in HE physiopathology is well established, and nutritional treatment is an important step in order to improve quality of life (QOL) and survival of patients with cirrhosis and HE. Since HE is a late complication of advanced liver disease, it is not surprising that cirrhotic patients with HE are susceptible to nutrition disorders[10]. Hence, there are many reasons that nutrition and HE cause a great impact on each other.

Ammonia metabolism is probably the most studied of the mechanisms responsible for the nutritional effects on HE, because ammonia production is highly influenced by dietary components. Consequently, many nutritional treatments have been studied in order to modulate ammonia production, to increase survival rates and to improve QOL of cirrhotic patients stricken by HE.

Nutrition status is directly associated with survival of cirrhotic patients[11-14]. Moreover, when these patients also have HE this association can be even more important. Although there are many studies focusing on the nutrition role in cirrhosis, this article specifically aimed to discuss practical nutritional strategies that can be applied to evaluate the body composition of HE patients. With the purpose of giving pathophysiological support to this discussion, the main factors related to HE etiology are presented as ammonia production, inflammation, and muscle wasting - whereas other factors are briefly addressed.

PATHOPHYSIOLOGY OF HE AND NUTRITIONAL STATUS INFLUENCE ON THE MAIN PROCESSES INVOLVED

The pathophysiology of HE is multifactorial and there is a general agreement that ammonia and inflammation act synergistically to cause astrocyte swelling and brain edema[15]. Since body composition affects ammonia metabolism and has a clear impact on cirrhosis and HE, the main pathophysiological point discussed herein is ammonia metabolism.

Ammonia metabolism

Even though ammonia levels are not strictly proportional to neurological impairment, ammonia is of great relevance in HE. High blood ammonia levels are not sufficient to establish the diagnosis of HE in cirrhotic patients; however, a normal value requires diagnostic reevaluation[1]. It means that ammonia blood levels are still valuable when they are related to additional clinical information, but isolated ammonia levels should never be considered sufficient to make a diagnosis. It is also important to consider that the values are influenced by physical activity, the source of the blood collected (arterial or venous), the prandial status and the diet pattern before the test.

In humans, there are three main sources of ammonia: The intestines, the kidneys and the muscles. The total daily production in adults is around 1000 mmol of ammonia[16]. The kidney production is increased in cirrhotic patients during hemodynamic disturbances[17]. The role of intestines in ammonia production is fairly the most frequently cited aspect in prior studies about HE, making the colon one of the main treatment targets.

Studies on non-absorbable disaccharides were the initial evidence that orally ingested substances could be useful in HE treatment. Lactulose and lactitol are the most studied among them in clinical trials of HE treatment. Lactulose is a good example of how a non-absorbable component could be relevant in this setting. Beyond the cathartic property, achieved by increasing intestinal transit, lactulose is also converted to lactic acid and acetic acid, which have the potential of converting ammonia to ammonium. Another interesting effect of disaccharides is that the colon acidification favors the proliferation of nonammoniagenic bacteria[18]. According to this point of view, lactulose also has a prebiotic property, and these effects could be achieved, at least in part, by nutritional treatments.

Colonic production of ammonia is a target in HE treatment, but it is important to notice that three systems are able to convert ammonia into other substances. The liver is the chief organ, and urea synthesis is the main metabolic route for ammonia clearance in normal conditions[19]. Skeletal muscles are a secondary system that can convert ammonia to glutamine, as is the brain tissue. Given the osmotic effect of glutamine, continuous conversion of ammonia to glutamine inside the astrocytes can cause cellular edema. Astrocytes constitute a significant part of the cerebral volume, so any degree of edema in these cells can be relevant to the brain and can lead to decreased excitatory neurotransmission, which is a characteristic feature of HE[20].

Accordingly, in advanced cirrhosis, the liver can be insufficient to accomplish the ammonia clearance as needed. Hence, the only way to avoid glutamine formation inside the neural cells is to convert ammonia to glutamine in skeletal muscles. Conversely, cirrhosis is a catabolic disease, and patients with advanced cirrhosis are commonly affected by muscular wasting, which decreases the amount of muscle tissue available to make this conversion. One of the main reasons for this catabolic state is that changes in the cirrhotic liver impair the glucose metabolism, so that when these patients are in a fasting state they have to use muscular proteins as an energy source. In many of these patients, HE arises as a late complication, developed when their muscles have been affected for a long duration, leading to muscle depletion and malnutrition. It can be difficult to counteract this process in HE patients, and prevention is clearly the best choice to preserve muscle mass in this setting.

It is estimated that nearly half of the total ammonia can be metabolized in muscles through glutamine synthesis. However, glutamine synthesis and ammonia uptake are low during rest[19]. Some studies have hypothesized that in the rest state the muscle might not be significant to ammonia metabolism in healthy subjects, but it could be more important in liver disease[20]. Since muscle is the best means to increase ammonia clearance in cirrhotic patients with HE, physical activity could be very relevant in this setting. However, the role of muscle activity as a way to prevent HE was not verified in clinical trials.

Due to the role of muscle mass in cirrhotic patients, especially those with HE, early nutritional assessment must be performed properly. The early nutritional diagnosis must be followed by an appropriate dietary treatment in order to reduce the process of muscle wasting related to this liver disease. Even so, ammonia metabolism is not the only aspect that should be considered.

Inflammation

The inflammatory process is another significant issue in HE pathophysiology that can also be a target for different forms of treatment, including nutritional strategies. Inflammatory cytokines affect the blood-brain barrier and increase the ammonia diffusion in astrocytes[21]. Cirrhosis is characterized by subclinical increasing of inflammatory cytokines, but it can be difficult to show the correlation between HE and inflammation through peripheral blood cytokine tests[22]. In a double-blind randomized trial comparing the effects of two antibiotics, our group showed for the first time that hospitalization length was associated with C reactive protein levels during HE treatment. This finding illustrates the inflammation impact not only when the patient arrives at the hospital but also during HE treatment[23].

The level of inflammation products found through fecal calprotectin tests is higher in patients with cirrhosis and HE, indicating that the gastrointestinal tract (GIT) is the main source of inflammation in these patients[24]. A further study suggested that there is a global mucosal-immune interface change in these patients that affects the entire GIT[25]. Cirrhosis is often associated to slow gastrointestinal transit and mucosal edema, allowing the passage of bacterial products through the epithelial barrier. These products keep a continuous flow of bacterial particles through the portal vein, promoting the release of tumor necrosis factor inside the liver and causing a long-lasting cellular damage into the organ[26].

Obviously, nutritional management is not sufficient to avoid inflammation caused by acute infections, and reducing this sustained inflammatory state in cirrhotic patients is a challenge. However, when the main source of inflammation is the GIT, nutritional treatments can be useful to limit this process. Cirrhotic patients with HE are frequently stricken by small intestinal bacterial overgrowth, which leads to alterations in intestinal microbiota profile[27,28]. In this context, probiotics, prebiotics and symbiotics ingested can increase GIT transit and alter the microbiota involved in GIT inflammation to achieve a better bacterial profile, similar to the effects obtained by lactulose.

To demonstrate this effect in a clinical trial, Liu *et al*[27] evaluated the results obtained by a symbiotic preparation on minimal HE in patients with cirrhosis. They found that the symbiotic treatment favored the fecal proliferation of *Lactobacilli*, thus reducing the amount of the previous bacterial strains, which were more associated to inflammation. This modulation of GIT microbiota was concomitant to a remarkable decrease in serum ammonia and a significant improvement of HE in half of the subjects. Remarkably, the symbiotic treatment was also associated with endotoxemia reduction, improving the Child-Pugh class in nearly 50% of cases. Treatment with fermentable fiber alone was similarly helpful to many patients. Thus, the authors concluded that treatment with symbiotics or fermentable fiber would constitute an alternative to lactulose for the management of minimal HE in cirrhotic patients[27].

Other mechanisms involved in HE and also in different types of encephalopathy

Besides the fact that ammonia and inflammation

are the most appraised components involved in HE pathophysiology, the evidence supporting the role of oxidative stress and hyponatremia in HE is growing. The increase of blood-brain barrier permeability related to hyponatremia and oxidative stress has been associated to HE development[17]. Hyponatremia in cirrhotic patients is often caused by fluid retention, leading to hypervolemic (dilutional) hyponatremia. Conventional therapy in this setting is a challenge because fluid restriction and loop diuretics are frequently inefficacious[29]. It has been considered as a third hit in HE pathophysiology, because it can worsen the cerebral edema caused by hyperammonemia and inflammation. The management of these conditions in the emergency room is beyond the scope of this review, but nutritional strategies can be convenient in order to avoid or correct some electrolytic disturbances.

Electrolytes and fluid imbalances are commonly associated with several illnesses and have a great impact in cirrhosis and HE. Potassium and zinc deficits can be a consequence of restricted diets, and some enriched supplements can be useful for avoiding or treating them. Hypokalemia should be promptly corrected in patients with HE because it increases ammonia production and excretion by the kidneys[30]. Additionally, zinc deficiency is not rare in HE, and the early diagnosis should be done in this setting[31]. It should always be suspected in the presence of HE associated with malnutrition, especially when a poor diet is maintained for a long duration, as in the case of severe alcohol addiction. In theory, the lack of dietary proteins could be a contributing factor, because they are a significant source of zinc. Zinc deficiency can lead to HE, diarrhea, muscle cramps and skin lesions, complications that can be avoided by the prompt initiation of the disturbance correction.

Many HE patients have high manganese levels, possibly reproducing the effects of hepatocellular failure, as well as impaired biliary flow and the existence of porto-systemic venous shunts[32]. Manganese accumulation in brain tissue is found in severe cases of HE and acquired hepatocerebral degeneration[33,34]. Other electrolyte imbalances found in patients with cirrhosis and HE include hypocalcaemia and hypomagnesaemia, but their role in HE is not so clear. Finally, these patients present severe amino acid imbalances that lead to depletion in branched chain amino acids, which can be supplemented to achieve improvement in HE[35,36].

NUTRITIONAL STATUS IN HE

Among cirrhotic patients, 75% of those who develop HE have moderate to severe malnutrition, which affects their energy reserves and muscle mass[1]. Due to the muscular involvement in ammonia metabolism, malnutrition is associated with a higher incidence of HE[37-39]. The best means to define malnutrition in cirrhosis is protein calorie malnutrition, in which both lean and fat tissue can be depleted[39,40]. Although this reduction in both tissues is recognized as cachexia, the predominant loss of muscle mass in cirrhosis suggests that sarcopenia, or loss of skeletal muscle mass, is the first nutritional deficiency[40].

Concurrently, overweight has been cited in cirrhotic patients as another matter of concern. Berzigotti *et al*[41] evaluated 161 cirrhotic patients over a mean follow-up of 59 mo or until cirrhosis decompensation. The incidence of complications in patients was 15% in those with normal body mass index (BMI), 31% in those overweight and 43% in obese patients. In cirrhosis, obesity can be associated with loss of muscle mass, an ambiguous state of excess adipose tissue and muscle wasting denominated sarcopenic obesity, which has accumulated risks for each of the two phenotypes of body composition[41-44].

Thus, the presence of cirrhosis and HE affects nutritional status by many mechanisms, as described in Table 1.

As HE is frequently associated with advanced cirrhosis and this combination of severe conditions can have a substantial effect on food ingestion, the effects are clear in the clinical setting. In a multicentric trial assessing cirrhotic inpatients with jaundice, the spontaneous caloric intakes in the control group were approximately 20-25 kcal/kg per day, considered by the authors to constitute more than expected[45]. A large study aimed to document the impact of malnutrition and nutritional practice in 396 cirrhotic inpatients registered the caloric intake as 35.1 ± 10.0 kcal/kg per day in Child A, 29.0 ± 7.3 kcal/kg per day in Child B and 24.0 ± 8.0 kcal/kg per day in Child C subjects. Of note, changes in dietary and protein intake during hospitalization were related to mortality[46]. In a study of 60 outpatients, in which the majority of whom had compensated liver disease, the caloric intake was between 24 and 40 kcal/kg per day[47]. Another study assessing 300 cirrhotic outpatients obtained a mean value of 32 kcal/kg per day[48]. Unfortunately, the HE rates are not clearly documented, so it is difficult to identify the food intake patterns in this condition.

To analyze this question, our group assessed 60 outpatients with cirrhosis and HE. The majority of them had grade 1 HE (34 patients), while 23 presented minimal HE and only two subjects had grade 2 HE. The mean caloric ingestion was 20.5 ± 8.61 kcal/kg per day (unpublished data). These values were clearly below the recommendations for cirrhotic patients with HE, which range from 35 to 40 kcal/kg per day[32,49]. It is difficult to know whether the presence of HE is the main reason for the disagreement between our data and other results of caloric ingestion obtained in studies that did not evaluate only patients with HE, given the potential relevance of many other differences between the populations assessed. To clarify this hypothesis, we encourage researchers to implement new studies of caloric ingestion in HE patients to contribute with additional data on this topic.

Given all the mechanisms that influence malnutrition in HE, there are no doubts that it is necessary to evaluate

Table 1 Possible causes of malnutrition in patients with cirrhosis and hepatic encephalopathy

Possible causes	Clinical manifestation
Reduced ingestion of foods	Anorexia
	Early satiety
	Ascites
	Confusion and/or excessive somnolence
	Frequent hospitalizations
Impaired absorption of nutrients	Alterations in enterohepatic circulation
	Impaired biliary excretion
	Small intestinal bacterial overgrowth
	Portosystemic shunts
Metabolic disturbances	Protein hypercatabolism/BCAA depletion
	Decreased glycogen stores and gluconeogenesis
	Insulin resistance and enhanced ketogenesis
	Increased lipolysis and fatty acid oxidation
Other factors	Restricted diets (*e.g.*, low sodium diets)
	Protein loss during large volume paracentesis
	Abdominal distention during lactulose therapy

BCAA: Branched chain amino acids.

the nutritional status of cirrhotic patients who develop HE. However, it can be a challenge because patients with HE often have altered body composition, including variations in fluid balance and protein catabolism induced by the liver disease[1,32,50,51]. Moreover, they can be particularly difficult to evaluate through exams requiring extensive patient collaboration.

Some authors have suggested that changes in water homeostasis and compartmentalization can exist even before fluid accumulation is detected, and when these patients have ascites, pleural effusion or edema their evaluation *via* traditional methods can be even less accurate for assessing body composition[52,53]. Additionally, changes in lean mass and fat ratio can also reduce the accuracy of some methods of nutritional evaluation, as in sarcopenic, obese and also sarcopenic obese patients[41,43,44]. These alterations in body composition require more attention to assess patients with advanced liver disease, which can affect some measures obtained by the traditional methods.

Finally, metabolic changes lead to lessening in protein and fat reserves in 50%-75% of cirrhotic patients[1,50]. Furthermore, the degree of depletion in these reserves is related to prognosis and is a risk factor for developing HE, thus necessitating the evaluation of body composition in this population[39].

METHODS TO EVALUATE THE NUTRITIONAL STATUS OF CIRRHOTIC PATIENTS WHO DEVELOPED HE

Detailed body composition assessment is essential in HE patients. It is the first step to define the pattern of tissue loss and to establish nutritional treatment strategies[54]. Therefore, nutritional assessment of cirrhotic patients with HE must combine a good dietary history, body composition data and laboratory exams[1,32,49,55]. In this review, we will focus on body composition evaluation.

Most techniques to assess body composition are focused on differentiating fat mass from fat-free mass, while some methods presume that fat-free mass has constant characteristics, such as hydration fraction and density. Thus, techniques such as anthropometry and bioelectrical impedance could lead to over- or under-estimation of body composition findings when these assumptions are invalid[56]. Despite that, anthropometric and bioelectrical impedance data were associated with prognosis in cirrhotic patients, and their potential lack of accuracy is difficult to quantify.

Herein, we analyze the usefulness of the most widely utilized techniques in the assessment of nutritional status in cirrhotic patients who developed HE, presenting some of the advantages and drawbacks of each method. Given that patients with severe HE can be difficult to evaluate through exams requiring extensive patient collaboration, we suggest some of them that could be suitable in a practical scenario, adding more complex techniques in the initial evaluation and/or to bring more accuracy. Table 2 summarizes some of the findings in this setting.

Subjective Global Assessment

Subjective Global Assessment (SGA) is one of the most widely used methods to evaluate nutritional status in patients during their hospital stay. It gathers information about food intake, weight changes, gastrointestinal symptoms and physical examinations, which are intended to evaluate subcutaneous fat, muscular atrophy, edema and ascites[57].

Although SGA is useful as a screening tool to be applied upon hospital arrival, it is not sufficient to evaluate cirrhotic patients with HE on account of some methodological limitations. First, SGA depends on personal information that can be difficult to obtain from patients with cognitive impairment or somnolence. Second, the only anthropometric measure utilized is the body weight, which is often changed by ascites and edema[50,51]. Therefore, the guidelines of the International Society for HE and Nitrogen Metabolism (ISHEN) highlight that SGA can underestimate malnutrition occurrence in cirrhotic patients and does not predict outcome accurately[32].

Anthropometry

Anthropometric measurements are objective methods to evaluate the nutritional status. They are rapid, non-invasive and low-cost techniques, specifically suited to assess somatometric characteristics. These measurements have been considered the most useful procedures to assess nutritional status in cirrhotic patients[58]. Nonetheless, they also have limitations when applied in patients with HE and cirrhosis. For instance, ascites and edema can influence body weight and BMI values,

Table 2 Advantages and disadvantages of the main methods of nutritional assessment for cirrhotic patients with hepatic encephalopathy

Method	Advantages	Disadvantages
SGA	Quick application Low cost Can identify patients under risk of malnutrition upon hospital arrival Can be applied in hospital rooms	Requires patient comprehension and collaboration Subjectivity (the only objective measure used is weight) Can underestimate malnutrition Cannot be used as a follow-up method
Anthropometry	Quick application Low cost Demands little collaboration Can be applied in hospital rooms Some measures (CAMA, MAMC, APMT) are less influenced by water retention and overweight/obesity MAMC is widely recommended for liver disease patients MAMC and TSF are associated with outcomes in cirrhotic patients and are related to the presence of HE	Some measures (body weight, body mass index, AC, TSF) can be highly influenced by water retention and overweight/obesity Interobserver variation decreases the data reproducibility Can underestimate malnutrition
Handgrip strength	Quick application Low cost Can be applied in hospital rooms Identify impaired muscle function Is not influenced by either water retention or overweight/obesity Is an independent predictor of cirrhosis decompensation	Cannot identify muscle wasting anatomically Is not so suitable for evaluating cirrhotic women, because skeletal muscle function correlates with muscle mass only in men
Bioelectrical impedance analysis	Quick application Can be applied in hospital rooms when portable equipment is used PA and BCM are associated with outcomes in cirrhotic patients	Controversial applicability in patients with fluid retention Requires patient removal to the equipment room when non-portable equipment is used Can underestimate malnutrition
Dual-energy X-ray absorptiometry	Adequate accuracy to identify muscle depletion Excellent reproducibility Can also identify bone mass reduction as a screening tool Gives detailed analyses of body composition (segmental results), obtaining measures that have prognostic impact in cirrhotic patients FFMI is an independent predictor of HE AMMI can be used to diagnose sarcopenia	High cost Requires patient removal to the equipment room Exposure to ionizing radiation makes routine use less attractive as a follow up method
Computed tomography scan	Adequate accuracy to identify muscle depletion Excellent reproducibility Can be performed retrospectively from images previously obtained Can also identify hepatic nodules, portosystemic shunts and other abnormalities Skeletal muscle thickness in cross-sectional images has prognostic impact in cirrhotic patients L3 SMI can be used to diagnose sarcopenia	High cost Requires patient removal to the equipment room Exposure to ionizing radiation makes routine use less attractive as a follow-up method

The bedside techniques are presented at the top and can be valuable even in conditions of restricted access to technology. The more complex methods are shown at the bottom, and should also be used when technology is unrestrained, providing more accuracy. Methods used only for research purposes and those not applied to patients with hepatic encephalopathy are not included. AC: Arm circumference; AMMI: Appendicular muscle mass index; APMT: Adductor pollicis muscle thickness; BCM: Body cell mass; CAMA: Corrected arm muscle area; FFMI: Fat-free mass index; HE: Hepatic encephalopathy; L3 SMI: Third lumbar vertebrae skeletal muscle index; MAMC: Mid-arm muscle circumference; PA: Phase angle; TSF: Triceps skinfold; SGA: Subjective Global Assessment.

underestimating the prevalence of malnutrition among these patients[51]. Although there is a specific classification of BMI for cirrhotic patients that categorizes the presence of ascites, this reference is not fully applied in clinical trials, and presents a clear limitation of having a single cutoff value to diagnose malnourished patients, precluding the diagnosis of eutrophic or overweight patients[59]. Most studies still use the dry weight, which is estimated by subtracting the weight of ascites and edema that is known from information obtained during clinical assessment, weight values formerly registered, ascites volume drained and references previously established[32].

Skinfolds and body circumferences are less affected

by water retention than BMI. Skinfolds are mainly used to estimate the body fat. Fiore *et al*[60], evaluating 40 cirrhotic subjects without overt fluid retention, found that the percentage of body fat assessed by skinfolds had a difference of less than 5% in comparison to the values obtained by dual-energy X-ray absorptiometry (DEXA). The authors evaluated body composition measures in patients who did not present any degree of edema or ascites. Moreover, most subjects had compensated cirrhosis (Child-Pugh A/B/C = 24/16/0) while the rate of patients with HE is not mentioned in the article, hampering extrapolation of the findings to patients with HE and/or more advanced liver disease.

Two of the most recommended measures to evaluate the nutritional status of cirrhotic patients with HE are triceps skinfold (TSF) and mid-arm muscle circumference (MAMC)[55]. MAMC is calculated through TSF and mid-arm circumference (AC). In a study of 212 cirrhotic inpatients monitored for 2 years, the authors suggested that MAMC and TSF could be included in the Child-Pugh classification in order to improve the predictive accuracy of this score, although the prognostic power of TSF was lower than that of MAMC[11]. Another study of 300 subjects showed that MAMC values were expressively more affected in male than in female cirrhotic patients, while loss of fat deposits based on TSF was more significant in females[48]. In a study evaluating 143 patients before liver transplantation, the authors considered MAMC to be the best reliable anthropometric tool[61]. In a study of 102 patients submitted to orthotopic liver transplantation (OLT), AC and TSF were used to categorize patients according to the values before OLT; those below the 25th percentile had an increased incidence of hepatic tests result abnormalities, suggesting a higher incidence of complications in this group[62].

A method in which MAMC and BMI were combined with SGA information as a new way to evaluate the nutritional status of cirrhotic patients was previously validated[63]. The proposed algorithm showed prognostic value in this population and we encourage its use as a screening method for patients in their hospital admission. However, there is no information whether this algorithm could be useful during the patient follow-up, or whether variations in weight/BMI could impair the accuracy found by the authors. Thus, a simple and precise technique for assessing malnutrition in cirrhotic individuals is not available yet[64].

Another anthropometric measure that may be used for diagnosing muscle wasting in cirrhotic patients is the adductor pollicis muscle thickness (APMT). APMT is a simple tool, with little influence from such body composition changes as edema, ascites and overweight. It has been applied to evaluate the nutritional status in normal populations as well as surgical, renal failure and cancer patients[65-68]. However, we have not found studies specially aimed to evaluate cirrhotic patients.

Specific data of anthropometric measurements in patients with HE were presented in a study of 300 cirrhotic patients (200 men and 100 women). The authors confirmed that the prevalence of overt HE during hospitalization was significantly higher in patients with muscle depletion assessed by MAMC and TSF, as well as in those with decreased muscle strength, showing the relevance of anthropometric measures and muscle strength in HE[39]. Of note, the diagnosis of muscle wasting and fat store depletion was based on MAMC and TSF < 5th percentile, respectively, in relation to normal values.

In a comprehensive review about nutrition in HE, the authors suggested that parameters not affected by ascites or edema include MAMC, AC, and TSF. They also proposed that the diagnosis of malnutrition in advanced liver disease could be done when MAMC and/or TSF values were lower than the 5th percentile in individuals aged 18-74 years, using the 10th percentile for those aged more[64].

Indeed, these measurements were the most widely used for a long time, so there is more evidence that they can be used in cirrhotic patients. Even without such a well-known scientific basis, we suggest that corrected arm muscle area (CAMA) and APMT should also be documented in these patients as supplementary data. Both could be useful to identify muscle wasting, which is extremely relevant for cirrhotic patients with HE. CAMA is calculated through AC and TSF values. As the others measurements proposed by Bémeur *et al*[64], CAMA and APMT are also easy to perform, given that they do not require much cooperation from patients. These advantages are important in cases with somnolence and/or confusion. Additionally, we recommend that the diagnosis of malnutrition in cirrhotic patients with HE should not be based only on anthropometry, unless it is the only method available.

Since anthropometric classifications were not based on cirrhotic patients, it is difficult to establish cutoff values according to the aforementioned studies because most of these values were obtained from standard measures for healthy subjects in different populations. Likewise, other limitations must be considered: The inter-observer disagreement in some procedures, the variations in skin compressibility and hydration, and the fact that in many cases the overweight can preclude the diagnosis of cirrhosis-related muscle loss. Anthropometric measurements should be confirmed by a skilled professional in order to increase their reliability[58]. Therefore, whether evaluations of cirrhotic patients with HE are based only on anthropometry, these issues can be a significant drawback. Given the severe disease found in this population, other methods should be used to support anthropometric findings whenever possible to provide greater accuracy for the data obtained.

Bioelectrical impedance analysis

Bioelectrical impedance analysis (BIA) measures are safe and relatively accurate for estimating fat mass and fat-free mass. The water component of the body is appraised according to the capacity of the body to conduct an

electrical current[69]. Thus, the basic principle of BIA is that electrical conduction is faster through water and slower through fat tissue due to the resistance imposed by fat deposits, thus estimating the percentages of fat and fat-free tissues. The procedure takes less than 2 min to measure body electrical conductivity and resistance (impedance). This resistance value is then applied to the determination of total body water.

BIA has been applied in evaluations of cirrhotic patients for many years[70-77]. Among the results obtained, phase angle (PA) and body cell mass (BCM) deserve particular attention.

PA values are decreased in advanced cirrhosis. Furthermore, a prior study confirmed that PA was associated with muscle strength and muscle mass in cirrhotic patients. Moreover, a phase angle value less than or equal to 5.4 degrees was predictor of reduced survival[72]. Of note, Peres *et al*[75] found that the median PA was 4.17° (3.19°-7.42°) in a HE subpopulation, expressively worse compared to cirrhotic individuals in which HE was not present (5.04°).

BCM is a lean tissue compartment that is diminished in protein-calorie malnutrition. It estimates the body cellular elements, and has been considered one of the best nutritional references for appraising metabolic pathways like protein turnover and energy expenditure[58]. Thus, low BCM is often observed in advanced liver disease.

Analyzing 150 potential candidates for OLT equally divided into two categories (validation group and study group), Selberg *et al*[78] showed that hypermetabolism and low BCM proportion (< 35% of body weight) were related to short survival. Of note, when the authors compared the subjects who died with those who survived, HE and edema severity were expressively worse in the former group, and CAMA measures were correlated with BCM[78]. Figueiredo *et al*[79] evaluated 69 cirrhotic patients using SGA, anthropometry, handgrip strength, lab tests and dual-energy X-ray absorptiometry. Most of the methods applied were weakly associated with BCM measurements, but the authors showed that handgrip strength and MAMC values obtained in this study were the most sensitive markers of depleted BCM. Combining the cutoff points of 30 kg obtained by handgrip strength test and 23 cm obtained by MAMC, the authors showed that these methods could be used together in order to identify BCM depletion accurately in most patients[79].

Müller *et al*[80] in a study with 123 cirrhotic patients found that post-transplantation mortality was higher in patients with low BCM. The authors concluded that hypermetabolism was not present in all patients, but could be a cause of malnutrition, thus contributing to worsen prognosis[80].

As BIA results can be altered by physical activity, dehydration, diuretic use, fluid retention, as well as liquid and food ingestion before the test, the usage of this method for assessing cirrhotic patients has been controversial[56,81-84]. According to a prior study, total body water was comparable in compensated cirrhosis and in non-cirrhotic subjects, but was higher in patients with ascites[52]. Other studies assessing the changes caused by ascites have shown that fluid overload can be a cause of imprecision in BIA results[82,85,86].

In contrast, another research group postulated that ascites exerts an irrelevant influence on BIA measures since chest and abdomen together represent only 11% or less of the body resistance, showing that BCM appraised by BIA was associated with the same measure evaluated by the total body potassium count, regardless the presence of ascites[87]. However, it must be noticed that 72% of the subjects used diuretics.

Ascites should be viewed as a marker of fluid overload and not as a simple liquid accumulation. Accordingly, the instillation of 2-3 L of fluid into the peritoneal cavity has minimal effect on total body resistivity in patients submitted to peritoneal dialysis, and assessments of fat mass and fat-free mass do not vary significantly whether these patients are dry or filled[88,89]. According to ascites pathophysiology, it is a clinical sign that the patient presents diffuse water retention and not only in the abdomen. The controversial point is how much ascites can change BIA results.

To estimate this effect in cirrhotic patients with HE, we evaluated 50 patients with HE that were submitted to BIA and DEXA exams to compare the percentage of fat mass obtained in each exam (non-published data). The median of their Child-Pugh classification scores was 8 (Child-Pugh A/B/C = 11/33/6), 32% of them had ascites and 38% had edema. The mean fat mass according to BIA and DEXA exams were 29.3% ± 7.7% and 29.8% ± 7.1%, respectively. Pearson's r was used to test the correlation and Bland-Altman analysis to evaluate the agreement between the fat percentages obtained by BIA and DEXA[90]. Pearson correlation indicated good agreement (P = 0.0000882 and r = 0.526). However, we found some discrepancies when the differences were observed on the scatter graph and through Bland-Altman analysis (Figure 1). The results obtained by DEXA seem to be similar to the values previously found in cirrhotic patients without fluid retention (29.6 ± 9.2)[60]. Even so, it is important to notice that DEXA exams can also be affected by fluid alterations, as addressed below in this review[54,91].

These limitations and controversial issues must be pondered when a cirrhotic patient with HE has been evaluated, because the precision of BIA results could be affected by all the body changes induced by the liver disease. Nevertheless, when there is not a single sign of fluid retention that could be clinically detected, BIA can be used for predicting total body water in cirrhotic patients, but precision is somewhat worse than in normal conditions[92]. Taking in account these limitations, when more accurate methods are not available and the patient has no signals of fluid overload, we consider that BIA results are still valuable in cirrhotic patients with HE because phase angle and BCM convey prognostic information[72]. Finally, multi-frequency BIA should be

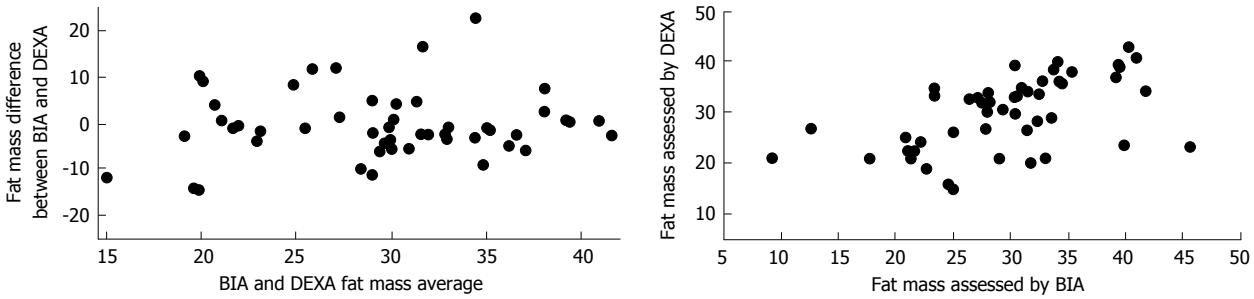

Figure 1 Bland-Altman analysis and scatter graph of fat mass percentages obtained from 50 cirrhotic patients with hepatic encephalopathy. Despite the correlation obtained between the two methods, the differences were also significant. DEXA: Dual-energy X-ray absorptiometry; BIA: Bioelectrical impedance analysis.

preferred in order to achieve more accurate results.

Handgrip strength

There is a growing interest in muscle activity evaluation for nutrition assessment. Walking tests and other tests requiring extensive collaboration could not be fully applied in patients stricken by severe illnesses like HE. Thus, handgrip strength (HS) can be a good option for patients with low-grade HE. Muscle strength is closely related to muscle activity, which is another valuable parameter for cirrhotic patients with HE, because HE tends to decrease physical activity.

A probable reason for decreased muscle activity in these patients is that hyperammonemia is related to fatigue, which is frequently reported in HE[19,93,94]. As previously mentioned in this review, in healthy adults the muscle role in ammonia clearance is minimal during rest, so the physical activity can be very important for ammonia metabolism. Accordingly, a previous study postulated that walking at least 5000 steps daily could be recommended for patients with compensated cirrhosis[95]. Although techniques of muscle activity evaluation are not considered to be methods of nutrition assessment, the information obtained would be of great value in patients with HE and more studies are needed in this setting.

HS has been suggested as a good indicator of nutritional status in liver disease patients by several guidelines[1,32,49]. The test is simple and a significant advantage is that the grip strength value is an independent predictor of cirrhosis decompensation[38,79,96,97]. As commented above, Merli *et al*[39] found that the prevalence of overt HE was higher in patients with decreased HS, suggesting a connection between strength and HE.

However, according to the ISHEN Consensus, skeletal muscle function is well associated with muscle mass only in men, and handgrip dynamometry would not be a reliable tool for appraising nutritional status in cirrhotic women. The degree of muscle loss caused by liver disease is different in each gender[32].

DEXA

The DEXA exam has received special attention because it is widely used to validate the results of body composition obtained by other methods, such as anthropometry and BIA. The procedure is based on measurement of body composition according to a model dividing the body elements in bone, fat, lean and bone-free lean masses, which can be distinct according to the energy photons passing through the body[98]. Additionally, radiation exposure is minimal with this technique[54,99]. The current guidelines recommend DEXA as a specific method for the diagnosis of malnutrition in liver diseases[1,32,49].

The DEXA exam allows assessment of fat-free mass and lean mass, which are technically different. Fat-free mass is composed by non-fat constituents of the body, including a small part of the adipose tissue. On the other hand, lean mass is composed by non-adipose constituents, which includes the lipids found in the nervous tissue and in cell membranes[100].

Riggio *et al*[101] evaluated 22 cirrhotic patients without ascites and 16 matched healthy controls using the DEXA exam. The authors found that the patterns of soft tissue loss in cirrhotic patients vary according to the gender. In women, the fat stores are more reduced, while lean tissue is maintained, as in early starvation. In men, the loss of lean tissue is more prominent, as seen under conditions of stress[101]. This finding could explain the poor correlation between muscle mass and muscle strength in cirrhotic women, making HS not so adequate for evaluating cirrhotic women according to the ISHEN Consensus[32]. Furthermore, it is in agreement with the finding of a prior study in which MAMC values were dramatically more affected in male than in female cirrhotic patients, while loss of fat deposits based on TSF was more significant in females, as formerly presented in this review[48].

Another study employed DEXA to evaluate 53 cirrhotic subjects, of whom only 30 seemed to be free of fluid retention. Results obtained by DEXA were compared with measurements from total body potassium, BIA and skinfold anthropometry. The authors found a good association between total body fat obtained from anthropometry and DEXA, regardless the existence of ascites. Even so, they found some discrepancy between DEXA and the other methods[102].

According to a prior review about the role of DEXA in the evaluation of cirrhotic patients, one of the main advantages of this exam is the high reproducibility of the measurements, with fat variations of less than 1% in

normal individuals. Accuracy errors are minor, amounting to 1.5% for quantifying lean mass. Additionally, the findings estimate the body compartments properly. Even so, a disadvantage is that fluid imbalances can change the X-ray passage, leading to an inappropriate appraisal of the lean mass[54].

DEXA allows obtainment of the ratio of the lean mass content divided by the square of the height, which is named fat-free mass index (FFMI). In a study of 108 cirrhotic liver transplant candidates, muscle wasting detected by FFMI was an independent predictor of HE[103]. Estimating the content of body segments (upper and lower limbs and trunk), DEXA can also be used to calculate the appendicular muscle mass index (AMMI), which is obtained by dividing the sum of appendicular muscle mass of the four members (free of fat and bone tissue) by the square of the height[100,104]. The AMMI provides a precise estimation of muscle mass because it does not use bone density, which varies with age, ethnicity, and response to drugs[100]. It also disregards the trunk mass, which is commonly affected by fluid retention in cirrhotic patients.

According to AMMI values, the diagnosis of sarcopenia can be made when individuals present less than 2 standard deviations from the healthy adults. The cutoff points were established as 7.26 kg/m^2 and 5.45 kg/m^2 for men and women, respectively[43,44,104]. In the presence of sarcopenia associated with fat mass percentages higher than 27% for men or higher than 38% for women, the diagnosis of sarcopenic obesity can be made[44,104,105]. AMMI is supposed to be very useful in studies about cirrhosis because it is not altered by fluid retention nor overweight status, focusing only on the fat-free mass[95,106].

Additionally, DEXA screening is also important for assessing bone mass before the incidence of fractures in patients with cirrhosis, because bone mass reduction is frequent among them. Thus, AMMI and body composition analysis can be obtained in the same exam performed to evaluate the bone mass.

Computed tomography scan

Recently, there has been a growing interest in employing a computed tomography (CT) scan to assess cirrhosis-related lean mass depletion. One of the reasons is that cirrhotic patients are commonly submitted to this exam to evaluate liver nodules or other alterations previously detected by ultrasonography screening exams. In addition, CT can also be used to evaluate portosystemic shunts in HE patients in order to plan hemodynamic corrections, and another advantage is that CT allows obtainment of information on abdominal muscles that are not commonly accessible. In theory, it could be possible to assess body composition retrospectively from images previously registered. For instance, in a recent CT-based study to assess nutritional status of cirrhotic patients who are candidates for OLT, the authors commented that the CT scan is often implemented in such patients to appraise the blood vessels distribution into the liver, to study the biliary tree and for hepatocellular carcinoma screening[106]. Furthermore, another aim of employing CT to evaluate body composition is that the transversal muscle thickness is associated with prognosis in these patients[107,108].

The measures are recorded by a single cross-sectional image at the level of the third lumbar vertebra or between the vertebrae L3 and L4[106,109]. Skeletal muscle tissue can be identified among other tissues by density limits: A cutoff of 35 Hounsfield units (HU) is used to distinct muscle and fat, whereas the maximum of 150 HU is used to separate muscle and bones, although the former limit can vary between the studies[91,106].

Thus, the exam allows calculating the third lumbar vertebra skeletal muscle index (L3 SMI), established as the muscle area contained in this axial plane divided by the square of the height. The cutoffs for sarcopenia in cirrhotic patients are 42 cm^2/m^2 and 50 cm^2/m^2 for women and men, respectively[110].

Hanai *et al*[109], in a retrospective study of 130 cirrhotic patients submitted to CT exams, found that sarcopenia was significantly associated with mortality. Of interest, the authors suggested that the use of branched-chain amino acids could improve survival of such patients, although the latter finding should be evaluated in prospective studies[109].

The possibility of measurements using previous exams make this method very attractive as a means of bringing more precision to the evaluations of body composition in cirrhotic patients. However, the use of ionizing radiation, the costs and the fact that the patient needs to be removed to the CT equipment are considerable limitations, especially when applied to patients with HE and/or CT is proposed to be repeated during the patient follow-up.

To facilitate choosing appropriately among the methods presented above according to the HE grade, Figure 2 summarizes some of the main points discussed about each method in relation to its advantages and limitations.

Other methods of nutritional assessment

In addition to the aforementioned methods for the assessment of body composition, other multi-compartmental techniques have been applied to cirrhotic patients, especially for scientific research.

Strauss *et al*[111] analyzed the usefulness of DEXA compared with a multi-compartmental model as a gold standard technique for evaluating body composition in 198 cirrhotic patients. The fat-free mass in this model was calculated adding bone content obtained from DEXA plus body water quantified by D_2O dilution and whole body protein quantified by *in vivo* neutron activation analysis (IVNAA). Consequently, fat mass was obtained subtracting fat-free mass from body weight. DEXA showed good accuracy and proved to be a suitable technique to evaluate fat-free mass and fat mass. The only restriction was that DEXA could not provide details on the water amount inside of the fat-free mass. It is

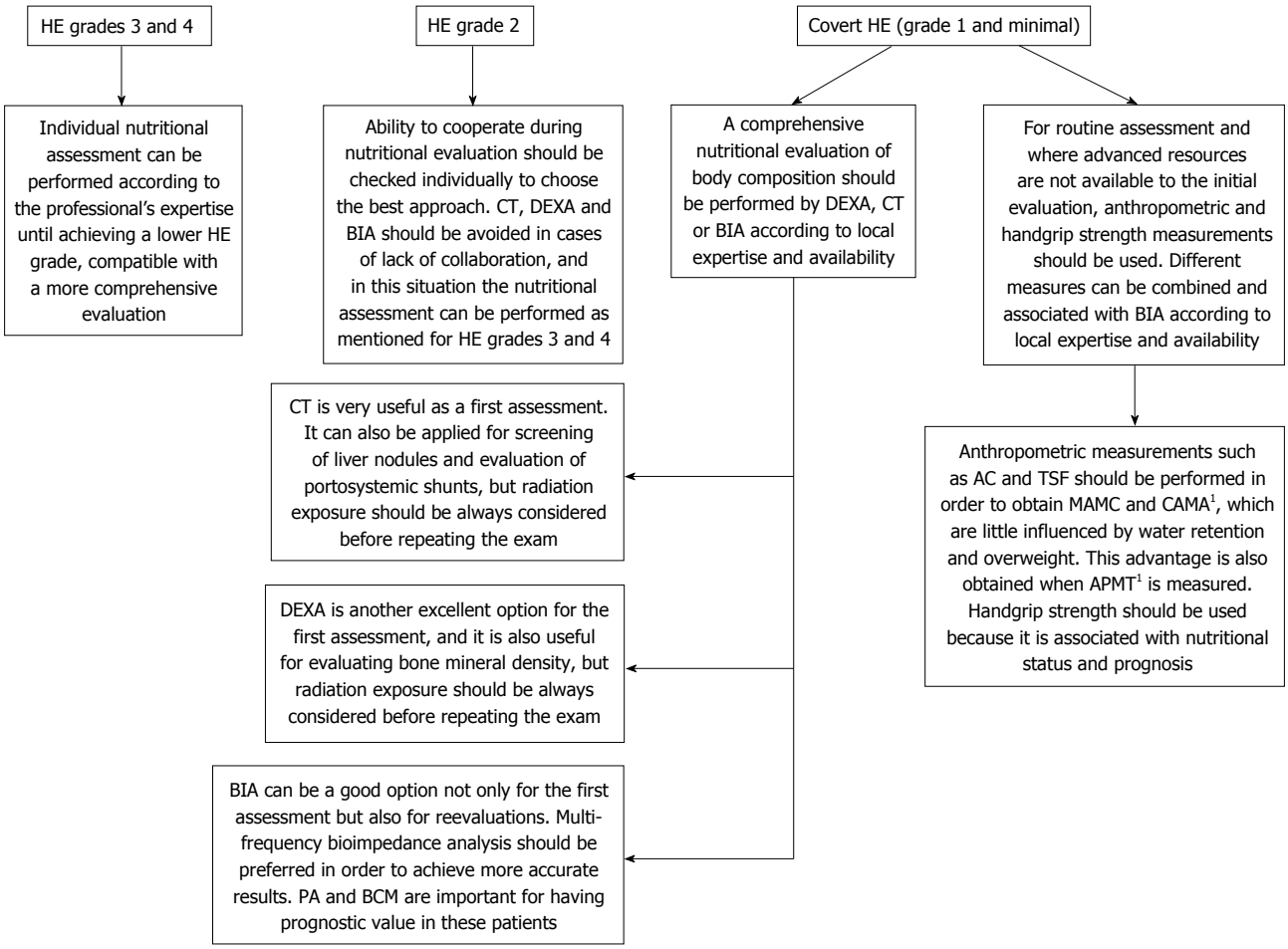

Figure 2 Proposal for choosing the best approaches during nutritional assessment of cirrhotic patients with hepatic encephalopathy. [1]APMT and CAMA are also associated with nutritional status in many conditions, but were not well evaluated in patients with cirrhosis and HE. AC: Arm circumference; APMT: Adductor pollicis muscle thickness; BCM: Body cell mass; BIA: Bioelectrical impedance analysis; CAMA: Corrected arm muscle area; CT: Computed tomography scan; DEXA: Dual-energy X-ray absorptiometry; HE: Hepatic encephalopathy; MAMC: Mid-arm muscle circumference; PA: Phase angle; TSF: Triceps skinfold.

noteworthy that these patients presented overhydrated fat-free mass in both sexes, especially in women[111].

Figueiredo *et al*[112], in a study of 79 cirrhotic patients and 17 controls, compared nutritional evaluation based on anthropometry, SGA, albumin and lymphocytes with a multi-compartmental model combining DEXA and methods of dilution spaces (bromide and deuterium). The multi-compartment model was composed by total bone mineral mass, total body fat, extracellular water and body cell mass. Accordingly, the sum of these four variables corresponded to the body weight. The authors found that the two-compartment assessment was not sufficiently accurate to diagnose malnutrition nor to estimate the severity of this complication in cirrhotic patients[112].

The guidelines from the European Society for Clinical Nutrition and Metabolism in liver disease published in 1997 and 2006 encourage the use of total body potassium count, IVNAA and isotope dilution for accurate quantification of changes in body composition in cirrhotic patients[49,113]. The ISHEN consensus also recommends the usage of magnetic resonance imaging. However, the guidelines warn that while these methods are not biased by hepatic impairment and fluid imbalance, they can involve radiation and can be difficult to repeat during the patient follow up[32,49,113]. Additionally, specific studies employing these other methods in HE patients are still lacking.

Finally, in spite of the usage of methods based on laboratory tests to estimate the degree of liver impairment of cirrhotic patients with HE, they are inadequate to assess their nutritional status. For instance, in such patients the creatinine height index is less accurate, because muscle wasting can reduce creatinine levels whereas renal impairment can increase them[114].

CONCLUSION

HE is associated with many pathophysiological changes induced by liver disease and influenced by nutrition, such as ammonia accumulation and muscle wasting. Likewise, nutritional status has a big impact on outcomes of HE patients. The alterations in body composition induced by liver cirrhosis and the limitations superimposed by HE hamper the obtainment of an accurate nutritional assessment of these patients by a simple test. Fluid

retention, metabolic alterations and depletion in muscle and fat deposits should be carefully investigated, whereas sufficient knowledge on the advantages and drawbacks of the main methods used in this population is essential to achieve consistent results by combining different techniques to assemble detailed data. Furthermore, for each method applied, it is important to recognize which measures are more trustworthy and which should be interpreted with caution due to possible bias. Prior studies in cirrhotic populations indicated that some anthropometric, BIA, DEXA and CT data convey prognostic information, whereas other measures remain controversial when obtained in patients with fluid overload. Most of these studies in cirrhotic patients did not mention the HE rate among the subjects included, so that specific data from patients with HE are scarce.

Knowledge on HE pathophysiology and evidence of the prognostic impact of muscle wasting on cirrhosis make muscle mass and muscle function some of the main points to evaluate in cirrhotic patients with HE. Ideally, a comprehensive assessment should gather information on food intake, anthropometric data not influenced by fluid overload, measurement of lean mass and tests of muscle function. The addition of complex techniques to measure body composition in HE patients increases the need for patient collaboration, the time spent, the demand for health professionals and the cost, but is useful to validate bedside measurements and should be encouraged. According to the local availability of each method and the patient condition, nutritional evaluation should be frequent during the patient follow-up, but the need to remove patients to the equipment room, the exposure to ionizing radiation and the costs can make the repetition of some of these methods less attractive. Therefore, some techniques can be combined to offer HE patients the safest and most cost-effective options, while maintaining the best accuracy in each nutritional evaluation.

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