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MINIREVIEWS

Nutritional evaluation in cirrhosis: Emphasis on the phase angle

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Abstract

Protein-calorie malnutrition (PCM) is a common condition in cirrhotic patients, leading to a worse prognosis, complications, poor quality of life and lower survival rates. Among ways of assessing nutritional status, there are anthropometric methods such as the evaluation of the triceps skinfold, the arm circumference, the arm muscle circumference and the body mass index, and non-anthropometric methods such as the subjective global assessment, the handgrip strength of non-dominant hand, and the bioelectrical impedance analysis (BIA). PCM is frequently under-diagnosed in clinical settings in patients with cirrhosis due to the limitations of nutritional evaluation methods in this population. BIA is a useful method, but cannot be indicated in patients with abnormal body composition. In these situations, the phase angle (PA) has been used, and can become an important tool in assessing nutritional status in any situation. The PA is superior to anthropometric methods and might be considered as a nutritional indicator in cirrhosis. The early characterization of the nutritional status in patients with cirrhosis means an early nutritional intervention, with a positive impact on patients' overall prognosis. Among the usually accepted methods for nutritional diagnosis, the PA provides information in a quick and objective manner.

Key words: Malnutrition; Bioelectrical impedance; Phase angle; Sarcopenia; Nutrition

Core tip: Malnutrition in cirrhotic patients is a common clinical condition, but there is currently no nutritional diagnosis method defined as the gold standard. Presently, the only nutritional indicator compatible with the clinical condition through the Child-Pugh score in cirrhosis is the phase angle (PA). The PA has been

a reliable method and is free of influences regarding changes in body composition of cirrhotic patients at an advanced stage. The PA measured by bioelectrical impedance analysis promises to be a significant parameter for early nutritional intervention in patients with chronic liver disease.

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INTRODUCTION

Many factors favor the development of protein-calorie malnutrition (PCM) in cirrhosis, a common condition that leads to serious repercussions regarding the general state and clinical course of patients[1] and that presents a worse prognosis, complications, poor quality of life and lower survival rates[2,3]. However, malnutrition is often underdiagnosed in this situation[4]. It is difficult to evaluate the nutritional status of patients with cirrhosis, as there are particularities due to the clinical condition that make it hard to precisely inform the real nutritional status and its consequent prognosis[5].

Malnutrition can be directly related to a poor survival rate in patients with cirrhosis, and its improvement is a strong indicator of quality of life, especially for those who are on the waiting list for liver transplantation[6]. Early detection of malnutrition in cirrhotic patients is of great clinical relevance and interferes positively in patient recovery[7,8].

The new European Society of Clinical Nutrition and Metabolism (ESPEN) consensus[9], recommends that subjects at risk of malnutrition be identified by validated screening tools, and they advocate two options for the diagnosis of malnutrition: The body mass index (BMI, kg/m^2) lower than 18.5 to characterize malnutrition, and the combined finding of unintentional weight loss and either reduced BMI or a low fat-free mass index (FFMI), or both. Weight loss could be either greater than 10% of habitual weight regardless of time, or greater than 5% over 3 mo. Low FFMI is characterized as lower than 15 or lower than 17 kg/m^2 in females or males, respectively. However, many other tools, such as anthropometric and non-anthropometric methods as well as laboratory tests may be used, classifying the degrees of malnutrition as mild, moderate and severe in different ways - although none of these other tools are widely recognized as a gold standard, and thus must be considered together. Various nutritional parameters has been used to assess the nutritional status such as anthropometry parameters [mid arm circumference, triceps skinfold thickness (TSF)], hand grip, serum albumin level, creatinine height index, and total lymphocyte count[8-10]. Recently electrical bioimpedance has been proposed for body composition analysis of patients with chronic liver disease[8,11-13]. In view of paucity of data on prevalence of malnutrition and its relationship with morbidity and mortality in patients with liver cirrhosis as well as the absence of a gold standard method for nutritional evaluation in these patients, we conducted this study to determine the prevalence of malnutrition by various methods and its clinical importance in cirrhotic patients according the severity of disease.

Considering the scarcity of data in the evaluation of malnutrition in patients with liver cirrhosis as well as the absence of a gold standard for nutritional evaluation in these patients, the present review was performed, critically addressing the following points: Malnutrition in cirrhosis; sarcopenia; nutritional assessment in cirrhosis; bioelectrical impedance analysis and the phase angle[10].

MALNUTRITION IN CIRRHOSIS

Malnutrition is one of the most frequent complications in cirrhotic patients[11]. However, its frequency in cirrhosis is highly variable, and may affect between 20% of the patients with compensated cirrhosis and more than 60% of these patients with severe hepatic disfunction[12,13].

Alberino *et al*[6] studied 212 hospitalized patients with liver cirrhosis that were followed for 2 years or until death. The severely and moderately malnourished patients had lower survival rates than normal and over nourished patients, and severe depletion of muscle mass and body fat was found to be an independent predictor of survival. This data suggests that malnutrition is an independent predictor of survival in patients with liver cirrhosis. Additionally, a nationwide analysis of the prevalence of PCM in patients with cirrhosis and portal hypertension (PHTN) and its mortality was conducted in the United States[13]. There were 114703 admissions with cirrhosis and PHTN between 1998 and 2005, and the prevalence of PCM was higher among patients with cirrhosis and PHTN compared with general medical inpatients; this prevalence was also associated with higher in-hospital mortality and resource utilization. The authors concluded that PCM may be an indicator of disease severity and should be routinely assessed on admission.

Besides the metabolic changes observed in cirrhosis, there are factors that can contribute to increased malnutrition in this population. Factors such as anorexia and early satiety, triggered by changes in endogenous leptin, mineral deficiencies and reduction in gastric expandability favor a negative energetic balance, with an imbalance between ingestion and energy intake and expenditure, and PCM may develop as a result[14]. The zinc and magnesium deficiencies that may be often seen in the population of patients with cirrhosis contribute to the development of dysgeusia, which aggravates the intake capacity[15,16].

The clinical complications that can occur in decompensated cirrhosis - such as gastrointestinal bleeding,

hepatic encephalopathy (HE) and ascites - can further accentuate the PCM situation[14], alongside the diet offered to these patients, which is restrictive in most cases. Thus, although for a short period of time, a hypoproteic diet may be eventually implemented, especially in cases of HE grades Ⅲ and Ⅳ[4]. It is worth highlighting that the protein restriction has been banned in HE in order to prevent the worsening of PCM, and a diet with 1 to 1.5 g of protein per kilogram of weight is suggested[4].

The recommended low-sodium diet in the treatment of patients with ascites and peripheral edema makes the food intake even more difficult and significantly decreases the daily calorie intake, thus stimulating PCM. A low-sodium diet with a daily intake of 2 g of salt is recommended[17].

It is known that skeletal muscles contribute in the proper metabolic functioning of macro and micronutrients, favoring body homeostasis. In individuals with cirrhosis, there is a significant loss and dysfunction of such musculature, often characterizing sarcopenia[18,19]. This state generates systemic and inflammatory changes associated with the PCM, negatively impacting the patient's clinical status[20].

The classical study by Merli *et al*[21] prospectively evaluated a total of 1053 cirrhotic patients to determine whether malnutrition is a risk factor for mortality in cirrhosis. They found that the cumulative survival was lower in patients with a reduction in muscle mass in Child-Pugh classes A and B.

Montano-Loza *et al*[22] studied 112 cirrhotic patients consecutively evaluated for liver transplantation, and observed that sarcopenia occurred in up to 40% of the patients and was related to the worsening of clinical conditions represented by biochemical and clinical parameters; moreover, by multivariate Cox analysis, the Child-Pugh (HR = 1.85; P = 0.04), the model for end-stage liver disease (MELD) scores (HR = 1.08; P = 0.001) and sarcopenia (HR = 2.21; P = 0.008) were independently associated with mortality. The median survival time for patients with sarcopenia was 19 ± 6 mo, compared with 34 ± 11 mo among non-sarcopenic patients (P = 0.005). Sarcopenia can be considered an indicator of risk of infection in cirrhotic individuals, directly reflecting a decline in immune function, worsening the quality of life and decreasing survival.

SARCOPENIA

Malnutrition in cirrhosis is closely related to the development of sarcopenia, which will be one of the most common complications related to survival in this population of patients. Nevertheless, there is a lack of an optimal index for sarcopenia and of a consensus definition for sarcopenia in patients with cirrhosis in whom ascites and edema may interfere with body composition analysis[23].

Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death[24,25]. The European Working Group on Sarcopenia in Older People recommends using the presence of both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia[26].

Montano-Loza *et al*[19] evaluated a population of 248 cirrhotic patients enlisted for liver transplantation and identified sarcopenia in 45% of patients; sarcopenia was associated with a longer period of hospitalization and higher risk of bacterial infection after transplantation.

Similarly, Tandon *et al*[5] evaluated 142 patients with cirrhosis listed for liver transplantation, and found that 41% were sarcopenic. Male gender, the BMI, and Child-Pugh class C cirrhosis (but not the MELD score) were independent predictors of sarcopenia, which was an independent predictor of mortality after adjustments for age and MELD scores. The authors concluded that sarcopenia is associated with increased waiting-list mortality and is poorly predicted by subjective nutritional assessment tools such as BMI and subjective global assessment (SGA). The objective assessment of sarcopenia holds promise for prognostication in this patient population.

NUTRITIONAL ASSESSMENT IN CIRRHOSIS

Among the different ways of assessing nutritional status, there are anthropometric methods such as determining the TSF, the arm circumference (AC), the arm muscle circumference (AMC) and the BMI, as well as non-anthropometric methods such as SGA, handgrip strength (HS) of non-dominant hand, the adductor pollicis muscle thickness (APMT) and the phase angle (PA) by bioelectrical impedance analysis (BIA).

Classical anthropometry assesses the measurement of body size and its proportions. The results obtained are compared with the points of reference previously described[27].

Cirrhotic individuals present significant changes regarding body weight by hydric retention, making BMI an inadequate method for nutritional diagnosis[28]. Such distortion was observed in the study performed by Gottschall *et al*[29], in which 61.8% of patients were classified as overweight, while other techniques, such as SGA or HS, found malnutrition in 38% and 85.7% in the same population of patients, respectively.

The TSF measurement indirectly estimates fat mass by measuring the thickness of two layers of skin and the adjacent subcutaneous fat. This is a good assessment method, although some studies have found a low prevalence of malnutrition in cirrhosis when comparing this method to others[30-32].

Abbott *et al*[33] and Alberino *et al*[6] described, in their studies, that 54% of the evaluated cirrhotic patients were malnourished when utilizing AC and AMC, supporting the findings of Merli *et al*[21], which suggest

AMC as an accurate indicator of malnutrition in patients in the early stages of cirrhosis. On the other hand, a study performed in our center by Fernandes *et al*[34] showed that AC and AMC are not sensible parameters for the nutritional diagnosis.

As a general rule, the anthropometric parameters may be affected when there is hydric retention; the results are observer-dependent and can be conflicting, becoming inadequate in the nutritional assessment of patients with cirrhosis.

When considering the non-anthropometric methods, SGA is a method of interest that uses easily reproducible parameters such as the clinical history and physical conditions of the individual, focusing on the nutritional aspects and offering a score that provides the nutritional diagnosis[35]. However, this method shows limitations, especially when the patient has some difficulty to understanding or even HE, as patients will not report their nutritional history adequately[36].

Figueiredo *et al*[37] observed that SGA has a sensitivity of only 22% in cirrhotic individuals and underestimates their nutritional status in 57%, while overestimating it in 6%[38]. On the other side, Ritter and Gazzola[38] established SGA as a good option for the nutritional assessment of patients with liver disease.

Although some authors[36,39,40] have suggested that SGA might be useful to assess the nutritional status evolution of cirrhotic patients who are liver transplant candidates, these studies have detected malnutrition in only 25% of cases with this method.

The HS assessment through dynamometry refers to the measurement of muscle strength and of pressure distribution[41], classifying the nutritional status of individuals by gender and age. In dynamometry, there is the assumption that in PCM there is a decrease in muscle mass, hindering one's functional capacity[42]. Studies with cirrhotic patients have shown the superiority of HS assessment when compared to SGA in diagnosing malnutrition; HS is considered a low-cost and simple method that is not influenced by the presence of hydric retention[42]. Curiously, in different studies, HS - while proving to be a good method in assessing nutritional risk - does not present a correlation between malnutrition and the staging of liver disease through the Child-Pugh score, although it is considered that liver disease patients, when classified as Child-Pugh C, are malnourished *per se*[41].

The APMT has been suggested as a promising marker of muscle mass[43,44]. The adductor pollicis muscle is the only muscle that allows direct thickness assessment, as it is anatomically well defined and flat in shape[45]. However, few have looked into it as a marker of nutritional status[46].

BIOELECTRICAL IMPEDANCE ANALYSIS

The BIA is a method for assessing body composition that has shown good results regarding the nutritional state, as it shows fat mass, lean mass and basal metabolic rate, in addition to total body water in healthy subjects[47]. The distribution of body fat has an important influence in the severity of certain diseases, such as in cardiovascular disease and depending on the type of fat mass distribution, may pose a higher risk of developing tumors[48]. Thus, in addition to providing a nutritional status assessment, BIA can also be a good prognosis method that is characterized as a practical, quick, non-invasive and low-cost method[48,49].

In the clinical nutritional assessment of a cirrhotic patient, it is possible to perform compartmentalized body assessment through BIA not only in the classical model that is normally used (fat mass and fat-free mass), but also in a quantitative manner, obtaining cellular distribution and providing information on body composition[50].

In the past, there were restrictions on the use of BIA for individuals with abnormal body composition; that is, amputations, electrolyte disorders (edema and ascites), obesity, dystrophies and pregnancy, because the BIA assumes that the human body resembles a cylinder of constant hydration and invariably lean mass[47,51].

Some tissues with high water and electrolyte composition - such as cerebrospinal fluid, blood or muscles - are high electrical conductors. On the other hand, fatty tissues or bones are highly resistant to electric current[47]. The conductivity of biological tissues is virtually ionic, meaning that electric charges are transferred by the ionization of the salts, bases or acids in body fluid. Thus, organic conductivity is directly proportional to the quantity of body fluid volume. Therefore, if the patient is in a state of overhydration, the amount of lean body mass is overestimated, modifying the result of the body assessment, which is one of the limitations of this method[47].

For the assessment of nutritional state by BIA, there are monofrequencial or multifrequencial portable equipment, differing on the options of the amperage of the electric current to allow greater sensitivity of the examination. The patient remains in dorsal decubitus position, with hands and legs parallel to the body. One electrode is placed on the dorsal hand, at the middle finger level, and one in the wrist joint, both on the right side. Another pair of electrodes is placed on the dorsal foot, at the middle toe level, and in the ankle joint, also on the right side. The electrical current enables measuring resistance and reactance and obtaining the PA value.

THE PHASE ANGLE

In view of the limitations of BIA, the clinically established bioelectrical impedance parameter is the PA. The PA was originally described by Baumgartner *et al*[51] for the diagnosis of metabolic disorders. The data is obtained through BIA and is directly calculated through the arc tangent formula (Xc/R). The tissues' capacitance (Xc) is related to cellularity, cell-size and integrity of cellular membrane. The resistance (R) is dependent on the hydration state of the tissues. The ratio of components results in a geometric graphic, where the ratio of R and

Xc results in an angle called the PA.

BIA is represented by the vector Z, which is a combination of the perpendicular vectors R and Xc. The vector Z has a module M, and the horizontal axis defines the PA[52].

The PA reflects the cellular vitality and integrity, where normal values (according to gender and age) indicate preserved cellular activity[34,53,54], being highly predictive of clinical progression in a number of diseases[55].

It has been suggested that the PA can become an important tool in assessing nutritional status in any situation, being superior to anthropometric and biochemical methods[44].

There are reference values according to age and gender[8], and some authors prefer to establish cutoff points according to the disease being studied[47].

The PA has also been studied as a prognostic marker in different clinical situations, such as tumors, acquired immunodeficiency syndrome, and heart and liver diseases[54].

In a review, Llames *et al*[55] concluded that the PA may be sufficient to monitor the nutritional status of an individual. In a population-based study, they observed a higher PA in men than in women, except in individuals over 70 years of age. When stratified by age and gender, the values tend to increase as BMI increases in values of up to 35 kg/m^2; however, there is a decrease in PA in groups with BMI above 35 kg/m^2[55].

There are few studies evaluating the PA in cirrhotic patients.

Selberg *et al*[56], in a prospective study of 305 patients with cirrhosis, correlated the PA with muscle mass, muscle strength, and survival rates. They observed that patients with a PA equal to or lower than 5.4 degrees showed lower survival rates than those with PA values above 6.6 degrees. In those with PA under 4.4 degrees, survival was even (and significantly) lower. Variables such as total body potassium, anthropometric measurements and BIA were evaluated separately; however, only the PA proved to be an isolated predictor of survival. The authors concluded that the PA appears to be superior to conventional methods in the clinical assessment of patients with cirrhosis.

In a retrospective study, Pirlich *et al*[53] evaluated the cellular mass composition of 41 cirrhotic patients (20 with ascites and 21 without) through BIA, which was considered the reference method. The study shows that the PA is a tool that is able to detect body cellular mass and to identify its decrease in cirrhotic patients. The PA offers reliable PCM estimates even in patients with large amount of ascites, proving to be superior to commonly used techniques.

In a cohort that assessed 66 cirrhotic patients stratified by their clinical condition through the Child-Pugh score and followed-up during a 17-mo period, the established PA for this population was 5.18 degrees. Patients with values below this angle were considered to have poor prognosis and shorter survival rates. It is worth highlighting that as the patients' clinical situation worsened, the PA decreased, showing a prognostic value[57].

Corroborating these findings, we assessed the nutritional status of 129 cirrhotic patients through different methods and demonstrated that the only method that is able to correlate malnutrition with the staging of liver disease, evaluated through the Child-Pugh classification, was the PA. We set the PA cutoff point as 5.4 degrees, and patients with values below this discriminatory level showed a worse prognosis. We should point out the discrepancies between the results of different evaluation methods (anthropometry, HGS and BIA) used to diagnose PCM, once the diagnosis for malnutrition may vary from 5.4% to 69.3% in the same population, depending on the assessment method employed[34]. The PA evaluated through the BIA presented a sensitivity and specificity of 68.9%-70.0% and 49.2%-56%, respectively, when compared to the HGS[34].

Later, another study performed in our center evaluated 195 cirrhotic patients, reinforcing the idea that the PA is a good prognostic marker when compared to other methods, as it is the only one that correlates with the real clinical condition of the patient[58].

Recently, Ruiz-Margáin *et al*[59] assessed 249 compensated cirrhotic patients in a prospective cohort study with a 48-mo follow-up period. The PA cutoff point for malnutrition was lower than or equal to 4.9 degrees. This study also concluded that the PA is a good prognostic marker, associating the PCM with mortality rate.

A cohort study conducted in our center evaluated 32 cirrhotic patients enlisted for liver transplantion[36]. The patients were interviewed and evaluated on the day of or on the day before the transplant, and 1, 6, and 12 mo after surgery. The assessment of nutritional status was performed applying diagnostic procedures in sequence: Anthropometry, HS, APMT and PA. Methods that better demonstrated the real prevalence of malnourished patients before transplantation were PA (25%), AMC (21.9%) and AC (18.8%). The percentage of malnourished patients was significantly higher after 1 mo of transplantation when compared to the percentage in 6 mo and 1 year after transplantation. It was suggested that the PA could be widely used with this population, since the results are consistent, reliable and reproducible.

Wagner *et al*[60] evaluated nutritional methods that informed the nutritional status of 71 post-transplantation patients. Patients were divided into 3 groups according to time since transplantation: 5 years, between 5 and 10 years, and over 10 years. They used the PA cutoff point as below 5 degrees in order to diagnose malnutrition. The PCM diagnosis was made in 81.2%, 31.6% and 31.7% in each group, respectively (P = 0.008). In this study, the PA showed a higher prevalence of malnutrition among the population of patients in the first years after liver transplantation.

CONCLUSION

The cirrhotic patient is malnourished *per se*, regardless of etiology and the severity of the disease. The early characterization of the nutritional status in patients with cirrhosis means an early nutritional intervention, with a positive impact on patients' overall prognosis. Compared to the usually accepted methods for nutritional diagnosis, the PA obtained through BIA is the only appropriate method to evaluate the nutritional status of cirrhotic, providing safe information in a quick and objective manner as a prognostic index.

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