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Title: Nutritional Evaluation Methods and Treatment in Liver Cirrhosis

Context and objective: The focus of nutritional assessment in cirrhosis is to identify the risk that influences in morbidity and mortality, which can be modified by adequate and individualized nutritional therapy. Currently, there is no gold standard to evaluate nutritional status of cirrhotic patients. Due to various factors such as ascites and edema, the precise determination of nutritional status is hampered. This study's objective is to revise the most recent nutritional assessment methods, as well as adequate treatment to such cases.

Type of study and place: Literature review of original articles and books.

Methods: Bibliography review of scientific articles and books that analyzed evaluation methods and treatment of malnutrition in cirrhosis in online open research platforms (Pubmed, LiLacs, SciELo) using the following specific describers: "chronic liver failure", "malnutrition", "nutrition assessment", "liver cirrhosis".

Results: From the searched terms, articles were selected based on their relevance to the subject. Apart from the online search, a bibliographic search on adult malnutrition books was performed to complement the information related to management and treatment in the cirrhotic patient found in online databases. After the research, 25 articles were identified within the determined parameters. The material was analyzed and organized following the article's objective.

Conclusions: Since malnutrition in cirrhotic patients leads to an increase in morbidity and mortality, a staged approach is necessary, starting with simpler and accessible methods and deepening with more complex methods when required. The treatment of malnutrition in cirrhosis was established through goals to be followed towards reducing adverse outcomes.

Mesh Terms: "chronic liver failure", "malnutrition", "nutrition assessment", "liver cirrhosis".

Introduction:

Cirrhosis is a late stage of progressive hepatic fibrosis with distortion of liver architecture and formation of regenerative nodules due to chronic injury, leading, eventually, to portal

hypertension and end-stage liver disease[1]. The prevalence of protein-calorie malnutrition in cirrhotic patients is high, and tends to correlate more with severity than with etiology of the chronic liver disease. Statistics using anthropometric data show protein-calorie malnutrition in 34% to 82% of patients with alcoholic cirrhosis and 27% to 87% with non-alcoholic cirrhosis[2]. In regard of severity of the disease, malnutrition was described in more than 75% of patients with advanced liver disease[3]. The severity of liver disease can be categorized using standard techniques such as Child-Pugh score, *Model for End Stage Liver Disease* (MELD), or distinction between compensated and decompensated liver diseases[1]. The Child-Pugh score uses predictive factors of severity including ascites, hepatic encephalopathy, bilirubin, albumin and INR. The MELD score uses laboratory parameters such as INR, total bilirubin, serum creatinine.

Malnutrition is an independent mortality predictor and correlates to decompensation, reduction of survival rates and complications: ascites, variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome and worse life quality[3]. Despite the high prevalence and prognostic implications, nutritional deficits continue to be underdiagnosed[4]. It is crucial that practitioners have the capability of recognizing and treating such deficits in a way to reduce morbidity and mortality associated[2].

Objective: The study's objective was to review the methods of evaluation of nutritional status and treatment of malnutrition in cirrhosis.

Methods: Bibliography review of scientific articles and books that analyzed evaluation methods and treatment of malnutrition in the cirrhotic patient in online open research platforms (Pubmed, LiLacs, SciELo) using the following specific describers: "chronic liver failure", "malnutrition", "nutrition assessment" and "liver cirrhosis".

Results: Twenty five articles were found within the determined parameters and the main aspects were organized in topics and are described as such.

Etiology of malnutrition

Calorie-protein malnutrition in cirrhosis is multifactorial and mainly due to low dietary intake, impaired digestion and absorption, and metabolism changes[5].

Hyporexia is one of the most relevant factors related to low calorie intake. Some authors suggest that loss of appetite is caused by suppression of appetite stimulating signals in the

hypothalamus due to a reduction in hormones concentration such as cholecystokinin and increase of inflammatory cytokines such as TNF-alfa[6]. Leptin, an appetite regulating hormone secreted from the fat tissue, is increased by two times in cirrhotic patients when compared to healthy individuals[7]. Alcohol consumption can potentiate hyporexia, especially in alcohol related cirrhosis and frequently empty alcohol calories substitute a balanced diet[6]. The early satiety feeling may be present due to ascites leading to gastric compression[6]. Other factors associated with reduction of intake include nausea, encephalopathy, gastritis and low sodium diet[2].

The changes in absorption and digestion can be consequences of bile salts deficiency, exaggerated bacterial overgrowth, changed gut motility, portal hypertension and increased intestinal permeability[2].

Cirrhosis represents an accelerated starvation status leading to usage of alternative metabolism pathways[6]. During the natural course of disease, there is an increase of proteolysis at early stages and reduction of protein synthesis at later stages. Besides, the synthesis and storage functions of the liver are compromised[8]. The glycogen diminished storage lead to gluconeogenesis, transforming amino acids into glucose.

Consequently, the protein increased catabolism lead to muscle depletion and hyperammonemia[8]. Apart from the protein consumption, the abnormal carbohydrate metabolism causes lipids to be preferentially oxidated for energy obtainment. The insulin resistance was also reported in cirrhotic patients, which could contribute to usage of alternative pathways of energy obtainment[3].

Some studies have conflicting results regarding the influence of the chronic liver disease in As the disease progresses, the amount of proteins used in alternative pathways increases, leading to a higher ammonia concentration. Hyperammonemia leads to a neutrophil dysfunction, greater infection risk and a persistent inflammatory status, worsening the nutritional status[6].

It was also proposed ascites may contribute to an increase in energy expenditure. Thus, its removal would result in a significant reduction in resting energy expenditure as measured by indirect calorimetry[9]. However, its mechanism is still unclear[9].

Vitamins and minerals deficiency are frequently related to cholestasis and portal hypertension leading to an impaired absorption of lipids and liposoluble vitamins. Reductions in Vitamins A, D, B12, folate, thiamine, pyridoxine are common[10].

Nutritional Assessment Objective:

The nutritional assessment objective is to identify the risk that influences in morbidity and mortality which can be modified by adequate and individualized nutritional therapy[10]. The nutritional assessment allows determination of macronutrient statuses (energy, protein and water) and micronutrient (electrolytes, minerals, vitamins and trace elements) of a certain individual. There is no gold standard for nutritional status assessment in the patient with chronic liver disease[6]. Most authors recommend a staged approach, starting with a complete anamnesis and physical examination and, then, proceed to more specific exams when necessary[10].

Nutritional status assessment in cirrhosis:

Anamnesis

Clinical history is crucial in evaluating patients with hepatic insufficiency. The beginning, duration and etiology of the hepatic illness and other concomitant diseases must be assessed (renal, cardiac, diabetes). All patients must be asked about their ideal weight, weight losses in the last two weeks and percentage of ideal weight loss in the last six months. Severe weight loss occurs when there is a non-intentional weight loss greater than 10% in a period of six months. Even though this method is useful in compensated cirrhosis, the weight evaluation is less precise in decompensated cirrhosis, mainly due to fluid abnormalities such as ascites[2,10].

Dietary Intake

Dietary intake can be assessed through several methods and its selection depend on population, resources, professional abilities and objectives to be achieved[8]. One of them is the 24-hour reminder. In this method, the patient writes all meals and snacks made during the day. Alcohol and other drinks must also be documented[8,10]. The 24-hour reminder advantages include low cost, feasibility, and the fact that it doesn't need special equipment. However, there is a risk of underestimating or overestimating the intake of such patients since the method's accuracy depend on the ability of patient to remind and estimate the size of the meals[5].

Medical/Surgical History

The duration and frequency of comorbidities that interfere with nutritional statuses must be evaluated. Symptoms persisting for two weeks or more related to low intake are concerning[10]. Many medical and surgical interventions associated impact the inflammatory and nutritional

statuses, which could lead to characteristic malnourishments[2]. Moreover, review of medication history is recommended due to nutritional interactions that some drugs cause[2].

Physical examination

A complete physical examination must be done and signs of macro and micronutrient deficiencies must receive special attention.

The weight must be measured in a standard weight scale, since the reported weight may not be exact. After the weight determination, the Body Mass Index (BMI) can be calculated. The presence of ascites and edema must be described in each weight measurement, knowing that weight is changed by water and salt retention[2]. There are standard values for BMI when applied for patients with chronic liver disease[5,6]. The standard reference values for malnutrition in patients with cirrhosis are:

-No ascites: BMI $\leq 22 kg/m^2$

-Moderate ascites: BMI $\leq 23 kg/m^2$

-Tense ascites: BMI$\leq 25 kg/m^2$

According to Campillo et al., these values have an 86% sensibility and 90% specificity when applied[11].

Micronutrient deficiencies

In regard of micronutrient deficiencies, it is important to look for pallor (iron deficiency), hyperkeratosis (vitamin A), dermatitis (vitamin A), bruising (vitamin C and K), glossitis (vitamin B12, folate and niacin), angular stomatitis (vitamin B12) and reduced tendinous reflexes in lower extremities (vitamin B12 and B1)[2].

Anthropometry

Anthropometric evaluation is essential for any nutritional assessment[6]. The main measurements evaluated in the cirrhotic patient are weight, height, waist and hip circumferences and skinfold thickness[6]. Due to edema and ascites, values of these measurements may be altered, leading to underestimation of malnutrition. The mid-arm muscle circumference in the chronic liver disease patient is calculated by subtracting the tricipital skinfold thickness by the circumference of the non-dominant arm multiplied by a constant (0,3142). This method presented a good inter-rater reliability[6,12].

Handgrip Strength

Handgrip strength is measured by a dynamometer and presents a sensibility and specificity, in general, better than other methods such as electric bioimpedance and Subjective Global Assessment (SGA)[6]. Since it's an easy and reliable method, handgrip strength was considered a good predictor of the nutritional status in the cirrhotic patient[6]. The patient must do an isometric contraction with its maximum strength for three times. The highest of the three measurements is recorded and compared to reference values for age and sex[6].

Subjective Global Assessment (SGA)

The Subjective Global Assessment (SGA) is a clinical method that assesses the patient's nourishment through clinical history and physical examination. The history component is composed by five parts: weight change, diet intake change, gastrointestinal symptoms, functional capacity and metabolic demand and its relation to the disease. The physical examination component evaluates subcutaneous tissue loss (triceps and chest), muscular depletion (quadriceps and deltoids), ankle edema, sacral edema and ascites. After gathering the data, the evaluator classifies the patient in three categories: well-nourished (A class), moderately malnourished (B class) or severely malnourished (C class)[2,6]. The inter-rater reliability was tested in a study with 20 candidates to liver transplant[13]. The evaluators had a similar response in 80% of the times, and the best predictors were muscular depletion and loss of subcutaneous tissue[13].

Resting Energy Expenditure

Patients with chronic liver disease can present severe metabolic abnormalities similar to catabolic statuses in sepsis or trauma[14]. The prediction of resting energy expenditure through the Harris-Benedict equation is not precise in 50% of cirrhotic patients[2].

The gold standard to evaluate resting energy expenditure is indirect calorimetry[15], which is underused due to lack of trained professional and high costs[16].

Laboratory Evaluation

The main laboratory exams requested in compensated liver cirrhosis patients are albumin, creatinine and International Normalized Ratio (INR). In decompensated cirrhosis, the likelihood of getting altered results is higher, reducing the chance of them being independent markers for nutritional status[2].

Plasma Proteins

Many plasma proteins can be used to assess nutritional status such as albumin, pre-albumin, transferrin, coagulation factors (prothrombin time or INR). Due to concomitant liver disease, the synthesis of these proteins can be reduced, even in the presence of a good nutritional status[2]. Thus, this method tends to be more efficient on cirrhosis early stages[2].

The half-life of plasma proteins must be considered when used in nutritional assessment. Albumin's half-life is approximately 20 days, reflecting less acute changes in the nutritional status, whereas pre-albumin 2 to 3 days' half-life is more affected by acute changes in nutritional status[17,18].

Creatinine

The urine 24-hour creatinine gathering is a method to determine muscle mass in the patient with liver cirrhosis. Results less than 18 mg/kg of ideal weight in women and 23 mg/kg of ideal weight in men indicate diminished muscle mass[2]. This technique is limited to patients with normal renal function and can be challenging to be done at an outpatient setting[2].

Adiponectin level

Patients with liver cirrhosis usually present increased levels of adiponectin according to severity of disease. Adiponectin is a polypeptide expressed almost exclusively on fat tissue and some studies showed that its serum levels can predict decompensation in cirrhosis[6].

Cytokines level

When adiponectin is increased, a systemic inflammatory response mediated by pro-inflammatory cytokines (IL-1, IL-6, IL-10, TNF-alfa) is generated, leading to a hypercatabolic status[6].

Imaging Methods

The gold-standard for body composition evaluation is *Dual Energy X-Ray Absorptiometry* (DEXA)[8]. DEXA assesses with precision the amount of fat mass in patients with liver diseases, but is not as precise in regard of lean mass[19,20]. Like other evaluation methods, the inaccuracy of DEXA is probably due to increase of extracellular water in decompensated liver cirrhosis patients[21,22].

Other imaging method that be used is L3 skeletal muscle index[6]. This index is calculated by dividing the transverse skeletal muscle area to the L3 level, quantified by computerized

tomography, by the patient's weight. By this method, sarcopenia is defined by an index $\leq 38,5$ cm^2/m^2 in men and $\leq 52,4$ cm^2/m^2 in women[6]. Some studies demonstrated that sarcopenia defined by this method was an independent mortality predictor in the patients with liver cirrhosis[23,24].

Bioelectric Impedance

There are many studies proposing the validity of Bioelectric impedance phase angle (PA) as a prognostic marker in various clinical and surgical situations, including liver cirrhosis[25]. Bioelectric impedance is a reliable, low cost and non-invasive method which indirectly measures body composition according to its resistance and reactance when an electric current is applied[6].

The vectorial analysis method (graphic resistance/reactance) classifies the hydration status of an individual through a percentage scale, one impedance vector and one PA. From this classification, the results are compared to the reference values for general population[6].

In a study with 305 patients with cirrhosis, the mean PA was 5,4°, with no statistical difference between Child-Pugh classifications. However, there was significant relation when PA was compared to muscle mass and muscle strength[25,26]. Thereafter, it was defined that PA $\leq 5,4°$ were characterized as malnutrition and lower survival rates[2526]. Besides, patients with PA $\leq 4,4°$ had an even lower survival rate in this study[26].

Nutritional recommendations:

American Society of Parenteral and Enteral Nutrition (ASPEN) recommendations[2]:

1) Early evaluation of nutritional status with regular follow-up.

2) Divide the diet in three main meals: with the first meal being early in the morning three snacks and a bedtime supplement.

3) Protein need: 1,0-1,5 g/kg/day

4) Lipids need: 30%-40% of protein calories.

5) Vitamins and minerals replacement when needed (for example, zinc, vitamin D, avoid excessive intake of iron and copper.

6) Enteral supplementation (for example, feed tube) to complement other enteral intakes. Parenteral nutrition can be used for the shortest time possible, when needed.

7) Hepatic encephalopathy must be treated with drugs approved by FDA such as lactulose or rifaximin, when needed.

8) When encephalopathy persists despite drug therapy in maximum doses and other causes of mental status alterations are discarded, the protein intake can be reduced to the maximum tolerated and an enriched branched-chain amino acids formula can be used.
9) Patients with decompensated liver cirrhosis, defined as cirrhosis with ascites and/or encephalopathy, that do not meet the required need of 35 to 40 kcal/kg and 1,0 to 1,5 g/kg of protein, must consider enteral supplementation through nasogastric or orogastric tube.

ESPEN Guidelines for Liver Cirrhosis[27]:

I) General

A) Use simple bedside methods such as Subjective Global Assessment or anthropometry to identify patients at risk of undernutrition.
B) Use phase angle or body cell mass measured by bioelectric impedance analysis to quantitate undernutrition, despite some limitations in patients with ascites.
C) Recommended energy intake: 35-40 kcal/kg/day (147-168 kJ/kg/day).
D) Recommended protein intake: 1.2-1.5 g/kg/day.

II) Application

A) Use supplemental enteral nutrition when patients cannot meet their caloric requirements through oral food despite adequate individualized nutritional advise.

III) Route

A) If patients are not able to maintain adequate oral intake from normal food, use oral nutritional supplements or tube feeding (even in the presence of esophageal varices).
B) PEG placement is associated with a higher risk complications and is not recommended.

IV) Type of formula

A) Whole protein formulas are generally recommended.
B) Consider using more concentrated high-energy formulas in patients with ascites.
C) Use BCAA-enriched formulas in patients with hepatic encephalopathy arising during enteral nutrition.
D) The use of oral BCAA supplementation can improve clinical outcome in advanced cirrhosis.

V) Outcome

Enteral nutrition improves nutritional status and liver function, reduces complications and prolongs survival in cirrhosis and is therefore recommended.

Discussion:

Calorie-protein malnutrition in cirrhosis has a high prevalence, especially in the patients with advanced disease and, unfortunately, is still neglected by health care professionals, despite its impact in morbidity and mortality of such patients[2-4]. The etiology of malnutrition in the context of liver cirrhosis is multifactorial and the main aspects related to low diet intake, impaired digestion and absorption, as well as metabolism changes, were discussed in this article[5].

The evaluation of nutritional status in these patients is considered complex and there is no gold-standard method for its diagnosis. The anthropometric measures can be used, but edema and ascites must be considered, which are frequently present. The use of BMI is limited, and the use of specific calculations as proposed by Campillo et al. has a better sensibility and specificity for taking ascites into account[11]. The handgrip strength is a functional reliable method of nutritional assessment with better sensibility and specificity than bioimpedance and SGA.

The SGA can be asked in its applicability in cirrhotic patients in regard of weight loss estimation, because water retention can falsely perceive the real weight gain, making it difficult to get an objective response.

Various laboratory exams in nutritional evaluation can be altered due to liver disfunction in advanced cirrhosis. Thus, its results must be cautiously interpreted[2,17,18].

DEXA may not be as precise in liver cirrhosis due to extracellular water present in such patients[21,22]. The phase angle determined through bioelectric impedance is associated with malnutrition diagnosis and reduction of survival rates in cirrhotic patients[25,26].

Considering the substantial impact of malnutrition in morbidity and mortality of cirrhotic patients, it is crucial that health care professionals are attentive and adequately approach the nutritional status of such patients in order to detect malnutrition and risk when installed. The European and American societies published recommendations and guidelines to be followed when taking care of such patients[2,27].

Conclusion

Evaluation of nutritional status in cirrhotic patients can be done through many ways, and there is still no gold standard for that. Presence of ascites and edema can make it more difficult to

characterize malnutrition in cirrhosis. Therefore, it is necessary to initiate evaluation with simpler methods such as SGA, anamnesis and physical examination and deepen the investigation with more complex methods when needed.

It is known through several studies that nutritional status directly impacts morbidity and mortality of such patients. Thus, malnutrition in patients with cirrhosis must be taken into account by physicians and must be considered as important as the traditional prognostic factors of chronic liver diseases. European and American societies determined reference values to be followed in the treatment of such patients in a way to reduce unfavorable outcomes.

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