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Optimizing nutrition in hepatic cirrhosis: A comprehensive assessment and care approach

Mendez-Guerrero O *et al.* Optimizing nutrition in cirrhosis

Abstract

Cirrhosis is considered a growing cause of morbidity and mortality, which represents a significant public health problem. Currently, there is no effective treatment to reverse cirrhosis. Treatment primarily centers on addressing the underlying liver condition, monitoring, and managing portal hypertension-related complications, and evaluating the potential for liver transplantation in cases of decompensated cirrhosis, marked by rapid progression and the emergence of complications like variceal bleeding, hepatic encephalopathy, ascites, malnutrition, and more. Malnutrition, a prevalent complication across all disease stages, is often underdiagnosed in cirrhosis due to the complexities of nutritional assessment in patients with fluid retention and/or obesity, despite its crucial impact on prognosis. Increasing emphasis has been placed on the collaboration of nutritionists within hepatology and Liver transplant teams to deliver comprehensive care, a practice that has shown to improve outcomes. This review covers appropriate screening and assessment methods for evaluating the nutritional status of this population, diagnostic approaches for malnutrition, and context-specific nutrition treatments. It also discusses evidence-based recommendations for supplementation and physical exercise, both essential elements of the standard care provided to cirrhotic patients.

Key Words: Cirrhosis; Nutritional diagnosis; Treatment; Diet; Guidelines

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Core Tip: Currently, there is a wealth of information on the ideal nutritional treatment for cirrhosis. Yet, a critical gap persists: The absence of a concise clinical document encompassing the entire nutritional care process. The significance of nutritional management is increasing, given its profound influence on both patient prognosis and quality of life. We here strongly emphasize the need to offer a practical foundation for managing nutrition in cirrhosis, grounded in scientific evidence.

INTRODUCTION

Cirrhosis is a globally highly prevalent disease associated with significantly high morbidity and mortality. It is the 14th cause of death worldwide accounting for 1.03 million deaths/year^[1]. This chronic disease is a ¹result of the progression of many forms of necro-inflammatory liver diseases leading to fibrosis, vascular remodeling, development of portal hypertension along with its complications, and ultimately liver failure^[2]. The disease's natural progression involves an asymptomatic phase known as "compensated cirrhosis", followed by "decompensated cirrhosis", marked by rapid progression and the emergence of symptoms including portal hypertension, bleeding, hepatic encephalopathy (HE), ascites, malnutrition, among others^[3].

Cirrhosis is a condition with a longstanding propensity for the development of malnutrition, sarcopenia, and fragility.

Malnutrition in this population is attributed to the interaction of different factors, including: Metabolic alterations^[4], inadequate dietary intake, increased energy requirements as a result of hypermetabolism and systemic inflammation^[5], deficiencies of micronutrients, and anorexia due to hormonal imbalances, among others^[6]. Malnutrition is not simply an accompanying condition but has a significant impact on the progression of the disease that further worsens the patient prognosis. Its direct impact on patient outcomes and complications is widely acknowledged^[7].

Diagnosing malnutrition can be challenging due to its complex evaluation and the potential influence of factors like fluid overload, HE, and obesity, which can mask its effects^[7-9].

As one of the few modifiable factors within cirrhosis, early diagnosis and timely treatment offer the potential to influence positively patient outcomes.

¹ In this review we aim to describe the impact of malnutrition in cirrhosis, the adequate strategies for a thorough nutritional status assessment using validated screening tools. We also discuss evidence-based recommendations of nutritional and exercise intervention that can be used to improve outcomes for patients with liver cirrhosis.

DIAGNOSIS AND TREATMENT

The most useful scores to determine the severity of the disease include ¹³ the Child-Pugh and model for end-stage liver disease (MELD) scores. The Child-Pugh score incorporates biochemical and clinical factors such as total bilirubin, albumin, international normalized ratio (INR), ascites, and HE. However, limitations arise due to the variability in assessing clinical variables like ascites and HE^[10]. Therefore, the MELD score was developed, offering a more objective approach. It relies on a mathematical model involving biochemical parameters like creatinine, total bilirubin, and INR. The MELD score is widely used as a measurement to evaluate and prioritize the organ allocation for transplantation, since it accurately predicts short-term survival (3 months). The cut-off value of 15 is widely used to prioritize candidates to receive a liver transplantation^[11].

Currently, preventing cirrhosis lacks an effective treatment approach. As a result, the present emphasis is on managing liver diseases and their related complications. This involves meticulous assessment of individuals with decompensated disease for potential liver transplantation^[12].

Despite liver transplantation being considered a curative treatment, is not always available to everyone, and in some cases, there is ³ a high incidence of recurrence of the liver disease. In a retrospective cohort evaluating risk factors and outcomes associated

with recurrent autoimmune hepatitis (AIH) after liver transplantation, AIH recurrence was found in 20% of patients after 5 years and 31% after 10 years. The authors concluded that AIH recurrence after transplantation is common and is associated with younger age at LT, post-LT use of mycophenolate mofetil, gender mismatch, and elevated pre-transplant IgG levels. They demonstrated an association between disease recurrence and graft impairment and overall survival in patients with AIH, highlighting the importance of continued efforts to better characterize, prevent, and treat recurrent AIH¹². The liver transplant community continues to be challenged by limitations in organ supply, allocation, and quality. As the need for transplantation expands, innovations to safely use and potentially salvage all donor organs are being explored and tested. Many groups are attempting to overcome these obstacles by gradually developing novel techniques and using sound translational science¹³.

IMPACT OF MALNUTRITION AND SARCOPENIA IN CIRRHOSIS

Malnutrition is defined as inadequate nutrient intake, nutrient imbalance, or altered utilization¹⁴. The prevalence of malnutrition varies depending on the assessment method, disease etiology, and patient stage. It is higher (40%-70%) in decompensated cirrhosis often accompanied by disease-related complications such as HE, ascites, and esophageal varices (Child-Pugh B-C). In compensated or asymptomatic phases (Child-Pugh A), the prevalence ranges from 10% to 40%¹⁴⁻¹⁶.

The pathophysiology of malnutrition and sarcopenia is complex and is attributed to the interaction of factors including metabolic alterations caused by a decrease in hepatic glycogen reserves, increased lipid catabolism, and increased proteolysis due to an increased gluconeogenesis^{4,5}. These metabolic changes lead to a 15%-30% increase in energy requirements¹⁵, which if coupled with the insufficient dietary intake arising from cirrhosis-related complications such as ascites, HE, and dysgeusia, are a significant malnutrition-contributing factor.

Ascites in patients delays gastric emptying, resulting in postprandial satiety and reduced appetite¹⁷. Cognitive impairment in HE leads to decreased food

consumption^[18]. Protein intake is often restricted as part of routine clinical management, leading to reduced calorie intake, despite a lack of evidence supporting improvement in HE^[19].

Cirrhotic patients often experience dysgeusia, which is linked to deficiency in micronutrients like zinc^[20] and other minerals that decrease due to both the drugs used for treating the disease and associated comorbidities, including diuretics^[21], and a decreased consumption by the patients.

Following variceal gastrointestinal bleeding, patients may be kept fasting for prolonged periods. Additionally, endoscopic procedures like variceal ligation can induce temporary dysphagia, potentially leading to reduced protein and energy intake^[14,15].

Sarcopenia, another facet of malnutrition, involves muscle mass and strength loss alongside reduced physical performance^[14,22]. This condition contributes to fragility, marked by reduced physiological reserve and increased stress factors^[23].

Furthermore, there is a decline in muscle fiber formation which is attributed to satellite cell differentiation inhibition^[24] and an increased in mTOR signaling pathway activity^[25], promoting proteolysis. This phenomenon is linked to elevated myostatin activity^[26], a member of the TGF- β cytokine family, which is proven to be enhanced in cirrhosis and closely related to disease severity^[27].

Sarcopenia, regardless of hepatic function, has been shown to be an important predictor of pre and posttransplant complications^[28], including higher risk of infections^[29], HE^[30], longer hospital stay^[31], low quality of life^[32] and survival (Figure 1)^[33].

A weak correlation between muscle mass and liver function has prompted the consideration of sarcopenia as a significant addition to the MELD score. The presence of sarcopenia in a patient is equivalent to adding 10 points to the MELD score^[33]. Therefore, prioritizing these patients and implementing a controlled nutritional plan before transplantation becomes crucial to enhance post-transplant outcomes.

NUTRITIONAL CONTROL AND SCREENING

According to Global Leadership Initiative on Malnutrition criteria, a proper diagnosis requires combining etiological and phenotypic patient characteristics (Table 1)^[34].

Implementing the nutritional control protocol outlined by Clinical Practice Guidelines is strongly advised as a fundamental aspect of standard cirrhosis patient management (Figure 2). This comprehensive plan encompasses nutritional assessment, nutritional diagnosis, a personalized nutritional intervention, and monitoring as recommended by the European Association for the Study of the Liver^[35] (Figure 3). Assessing nutritional status, interpreting parameters, and clinically evaluating patients with cirrhosis possesses challenges influenced by numerous non-nutritional factors, therefore, this should be a collaborative endeavor, where nutritionists and hepatologists work together to provide holistic treatment, ensuring optimal outcomes for the patients.

Nutritional screening evaluates characteristics related to nutritional concerns, pinpointing patients who need thorough nutritional status assessment. These screenings should occur within 24 h of hospitalization or within the initial 14 d of long-term care facility admission^[36]. The tools used must be easy to apply, reproducible, capable of detecting changes over time, and validated for the population in which they are being used^[37].

In patients with cirrhosis, the validated screening tools are ¹the Royal Free Hospital Global Assessment (RFH-GA) and the RFH-Nutritional Prioritizing Tool (RFH-NPT)^[19].

RFH-GA

This tool evaluates mortality risk in mild/moderate and severe malnutrition stages. It considers objective and subjective factors, incorporating body mass index (BMI). For patients with fluid overload, it considers dry weight, often calculated from post-paracentesis weight or pre-fluid retention weight, or subtracts a percentage based on ascites severity (5% for mild, 10% for moderate, and 15% for severe), plus an extra 5% for bilateral edema^[38]. In this scheme, the corrected mid-arm muscle area (cAMA) is also used along with dietary intake details in a semi-structured algorithmic

construction. The RFH-GA exhibits excellent intra- and inter-observer reproducibility and has been validated against a multicomponent model of body composition^[39,40].

RFH-NPT

Currently there is international consensus to utilize this tool due to its demonstrated clinical correlation with disease severity and efficient application^[41,42]. Taking under 3 minutes to complete, this screening tool is suitable for non-specialized personnel. It boasts remarkable intra- and inter-observer reproducibility and substantial external validity when compared to RFH-GA^[40].

The process involves three key steps: (1) Individuals with **alcoholic hepatitis or on tube feeding** are promptly identified as high risk without further steps; (2) those without **alcoholic hepatitis and not on tube feeding** are assessed for fluid overload's effect on food intake and weight loss; and (3) individuals without **fluid overload** are evaluated for nutritional status (BMI, unplanned weight loss, daily dietary intake). Patients are categorized as low risk (score 0), moderate risk (score 1), or high risk (score 2 to 7)^[42].

NUTRITIONAL STATUS ASSESSMENT

Body composition assessment methods vary in their characteristics, benefits, and drawbacks. Their diagnostic effectiveness hinges on the patient's disease-related complications during assessment. Fluid retention can distort measurements due to physical changes in body compartments. The following outlines the key measurements for assessing body composition, including their respective advantages and disadvantages.

Anthropometry

Anthropometric assessment measures physical dimensions and body composition. It's highly accessible but demands evaluator training and intra-observer evaluations for measurement consistency^[43,44].

The most used anthropometric measures, in addition to weight and height, are mid-arm circumference (MAC) and triceps skinfold thickness (TSF). These measurements are taken as follows.

MAC: When measuring MAC, the subject should be standing upright with arms by their sides and palms facing inward. The measuring area should be uncovered. To find the midpoint of the arm, the person's arm is flexed at a 90-degree angle with the palm upward. The person taking the measurement stands behind and locates the lateral tip of the acromion, palpating along the upper surface of the scapula's spine. The distance between the acromion (end of the clavicle) and the olecranon (end of the humerus) is measured, marking the midpoint between them. After identifying the midpoint, the arm is relaxed, and the measurement is taken in centimeters (cm)^[43].

TSF: To assess TSF, locate the skinfold site on the back of the arm, directly over the triceps muscle. For accurate measurement, have the subject's arm hang to one side to establish the posterior midline. Mark the skinfold site along the posterior midline of the arm, aligning it with the MAC. The person performing the measurement should stand behind the subject, using their left hand to hold the skinfold 1 cm proximal to the marked site. Position the caliper tips 1 cm below the thumb and index finger, maintaining them perpendicular to the skinfold's longitudinal axis. Take three measurements and record the average in millimeters (mm)^[45,46].

cAMA: The cAMA is calculated using the values obtained from measurements of the MAC and TSF with the following formula:

$$\text{Men cAMA: } \frac{[MAC \text{ cm} - (\pi \times PCT \text{ cm})]^2}{4\pi} - 10$$

$$\text{Women cAMA: } \frac{[MAC \text{ cm} - (\pi \times PCT \text{ cm})]^2}{4\pi} - 6.5$$

cAMA measurements below the 5th percentile, as indicated by reference tables for sex and age by Frisancho, suggest malnutrition resulting from low muscle mass^[45,46].

However, these measurements have limitations in patients with fluid retention, as they can lead to overestimation during assessments and show reduced sensitivity to sudden changes. Consequently, their use is advised in the early stages of the disease^[47].

Imaging methods

Radiological imaging analysis is now used to diagnose muscle mass in cirrhosis. These techniques have gained substantial attention primarily due to their diagnostic capability in determining muscle mass and its connection to disease prognosis. Imaging methods are considered objective and reproducible approaches to evaluate skeletal muscle mass, utilizing indices calculated from cross-sectional images obtained *via* computed tomography (CT) or magnetic resonance imaging (MRI)^[16,48]. These approaches are predominantly employed for hepatocellular carcinoma screening or during liver transplant protocols. However, they are not specifically recommended for muscle mass assessment due to their high costs, exposure to radiation, and a shortage of trained personnel for image analysis.

CT: A tomographic scan is taken at the L3 lumbar vertebra level, and specialized software is employed to delineate tissues based on hounsfield unit thresholds. Muscles within the L3 region encompass the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis. Cross-sectional areas (cm²) are automatically computed by summing tissue pixels and multiplying by pixel surface area^[30,49].

The resulting muscle and adipose tissue cross-sectional areas are then adjusted for height (cm²/m²), yielding the L3 Skeletal Muscle Index (L3 SMI)^[50].

Recent years have seen the development of specific cutoff values for cirrhosis. Presently, it is advised to utilize the cutoff values established by the North American expert consensus, which are validated and interpreted according to gender: L3 SMI < 39 cm²/m² for women and < 50 cm²/m² for men^[51]. This method offers the advantage of maintaining diagnostic accuracy even in the presence of ascites. However, its practical

application is restricted due to factors such as radiation exposure, costs, and the necessity for standardized personnel to conduct measurements and interpretation.

MRI: This method utilizes an L3 vertebral level image, outlining areas expressed in pixels that are then converted into an area measurement (cm^2). This measurement is adjusted for the patient's height and shares the same interpretation as the L3 SMI since it uses the same cutoff points^[51].

Similar to CT scans, it remains unaffected by ascites and offers the advantage of avoiding ionizing radiation, while also assisting in quantifying intrahepatic fat. However, limitations include its limited availability, cost, and the requirement for standardized personnel to analyze the images, rendering it less practical for routine monitoring.

Dual-energy X-ray absorptiometry: This method evaluates fat mass, lean mass, and bone mineral content. Using this data, muscle mass in the upper and lower limbs is calculated to eliminate the influence of ascites. After adjusting for height, the Appendicular SMI (ASMI) is derived^[52]. A value below two standard deviations from the mean indicates muscle mass loss. Limitations involve potential overestimation of lean mass and inaccuracies due to edema. Nonetheless, the method's advantage is assessing bone mineral density, aiding in tailoring the dietary plan if osteopenia or osteoporosis is detected in the patient^[49,53].

Other methods

Bioelectrical impedance analysis: Bioelectrical impedance analysis (BIA) is a common method for assessing body composition, including lean mass, fat mass, and body fluids. It works by measuring the resistance of body tissues to alternating current. However, the equations used in this method are derived from healthy populations and can be affected by fluid retention. Consequently, its use is not recommended due to its tendency to underestimate lean mass^[39].

Vector analysis of bioelectrical impedance: This analysis was developed to enhance the diagnostic capabilities of conventional impedance. It utilizes direct data from BIA and standardizes them based on the patient's height. The process involves using software created by Piccoli *et al*^[54], which graphically represents the data as a vector. Unlike predicting body composition, this analysis visually represents it as a bivariate vector, assessing both body composition and hydration status. The correlations between these variables lead to an elliptical distribution known as the RXc graph. This graph's normal distribution is derived from a healthy population, yielding three reference percentiles or tolerance ellipses at 50%, 75%, and 95%, specific to each gender. Values beyond the 95th percentile are considered abnormal. Hence, in clinical practice, the 50% and 75% ellipses are used as ranges of normality. Within the graph, there are quadrants with distinct values that offer qualitative insights. These values can be depicted as vectors and interpreted as follows: Hydration variations (edema or dehydration) without tissue structure changes align with the major axis of the tolerance ellipses. Changes in soft tissue quantity (lean and adipose) correspond to vector shifts along the minor axis of the ellipses. The method's advantage lies in its ability to simultaneously assess fluid presence and malnutrition, facilitating nutritional monitoring and diuretic treatment evaluation. It also enables comparisons of a patient's visits to the nutritionist and aims to position the patient within the ellipses of normality^[55,56].

Phase angle: The phase angle (PA), derived from bioelectrical impedance measurements, relies on the body's conductivity properties, specifically the resistance and reactance. This metric mirrors the integrity of cell membranes and their ability to resist impedance currents. It is considered a useful tool that indicates the balance between cellular hydration and body mass, ultimately translating into tissue homeostasis and nutritional status. Low levels of the PA have been associated with inflammation and loss of muscle and fat mass in patients with conditions like cancer^[57], human immunodeficiency virus^[58] among others^[59]. It has been validated in patients

with cirrhosis from the Mexican population, where a PA of ≤ 4.9 has been observed to be associated with worse clinical outcomes^[60,61].

Dynamometry: Dynamometry is a nutritional assessment method that measures muscle function by measuring grip strength with a dynamometer, often using a hand dynamometer. This approach has been verified across diverse populations, as weak grip strength has been linked to functional constraints, diminished quality of life, and heightened morbidity and mortality^[62-64]. Grip strength reflects changes occurring in prominent muscle groups, even during the early phases of malnutrition, and likely isn't directly influenced by liver disease. There are specific cutoff points for men and women in different populations^[65], where measurements below the mean are indicative of malnutrition or reduced functionality^[64,66]. However, in individuals with cirrhosis, its reliability is hindered, particularly in patients with HE, even in mild forms, or those undergoing benzodiazepine therapy, due to cognitive and motor impairments that may skew the outcome^[64].

Liver frailty index: To assess frailty, the Liver Frailty Index (LFI) is utilized, previously validated in the population with hepatic cirrhosis^[23,67,68]. This index takes into account the following assessments: (1) Grip strength: It considers the average of three measurements taken on the subject's dominant hand using a hand dynamometer^[65,66]; (2) Timed chair stands: Measured as the number of seconds it takes to perform five chair stands with the subject's arms crossed over their chest^[23]; and (3) Balance test: It is evaluated by counting the number of seconds the subject can balance in three positions (feet placed side by side, semi-tandem, and tandem) for a maximum of 10 s each^[23].

The results of each test are incorporated into the following formula (calculator available at <http://Liverfrailtyindex.ucsf.edu>): $(-0.330 \times \text{gender} - \text{adjusted grip strength}) + (-2.529 \times \text{number of chair stands per second}) + (-0.040 \times \text{balance time}) + 6$. A patient is considered frail when they score > 4.5 .

BIOCHEMICAL MARKERS

Biochemical markers play a crucial role in the clinical assessment of cirrhosis, including parameters like prothrombin time (INR), albumin, creatinine, and more^[69]. However, the usefulness of these markers in nutritional evaluation is limited. The compromised hepatic synthesis in cirrhosis leads to reduced levels of ¹serum albumin, prealbumin, transferrin, and prolonged INR, potentially leading to an overestimation of malnutrition prevalence. Moreover, creatinine, commonly used as a measure of malnutrition, can be inaccurate due to its sensitivity to renal function changes often present in these patients^[70]. Additionally, the lymphocyte count is influenced by the disease, with lymphopenia often caused by hypersplenism due to portal hypertension in cirrhosis, making it an unreliable indicator of the patient's nutritional status.

CLINICAL EVALUATION

In the context of the nutritional care process, it is necessary to assess the presence of complications of cirrhosis, such as ascites and HE, as they can lead to deteriorated nutritional status. Timely identification of these complications allows for necessary adjustments in nutritional treatment.

Ascites

Ascites occurs due to disruptions in renal sodium excretion, resulting in a positive sodium balance, and subsequent fluid retention. This accumulation of fluids leads to an increase in extracellular volume. Decreased sodium excretion is primarily attributed to arterial vasodilation triggered by portal hypertension. This, in turn, activates the renin-angiotensin-aldosterone system and the sympathetic nervous system, causing renal vasoconstriction and sodium retention. Consequently, ascites and edema develop as a consequence of these physiological responses^[71].

Ascites is classified into the following grades: ¹⁵Grade I: Mild, detectable only through ultrasound; Grade II: Moderate, evident by symmetrical abdominal distension; and Grade III: Severe and marked abdominal distension.

The cornerstone of ascites treatment is dietary sodium restriction in combination with loop diuretics and aldosterone antagonist diuretics, aiming to create a negative sodium balance that enhances urinary sodium excretion beyond dietary sodium intake^[72]. However, dietary sodium restriction is effective in only around 14% of patients due to the poor adherence associated with such diets.

HE

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HE is a condition characterized by brain dysfunction due to hepatic insufficiency or portosystemic shunting. It manifests as a wide range of neurological and psychiatric abnormalities, spanning from subtle or minimal presentations to a coma state. The West Haven Criteria serve as the standard for categorizing HE. The overt form encompasses minimal HE and West Haven grade I, whereas West Haven grades II to IV fall under the overt or clinically evident HE category^[73]. In the minimal form of HE, observable signs and symptoms are absent, prompting the need for various psychometric and electrophysiological tests for diagnosis. These psychometric tests are straightforward to conduct, and a nutritionist with training in this domain can periodically administer them during consultations to identify the complication when it's not readily apparent. This facilitates necessary adjustments in nutritional treatment. While inadequate diet, low muscle mass, dehydration, and constipation play roles in HE development, early detection is crucial. However, it's important to note that many other unspecified nutritional factors can also contribute to the manifestation of this complication^[74,75].

Other complications of cirrhosis

Additional important complications arise during the evaluation of patients with cirrhosis. Dysgeusia and/or dysphagia are frequently encountered in cirrhosis, influencing the patient's dietary intake and demanding consideration during nutritional interventions. For cases of dysgeusia, investigating deficiencies in zinc and B complex vitamins, which could contribute to this issue, is crucial. If deficiencies are identified, supplementing these micronutrients is advisable. Moreover, assessing the diet's

palatability is essential, as stringent restrictions on seasonings and salt can affect consumption.

Following endoscopic variceal ligation, patients often experience recurring dysphagia. In such instances, a recommended approach involves softening, chopping, or pureeing solid foods to facilitate safe oral consumption while the patient recovers from dysphagia. Commercial thickeners can provide a valuable alternative by altering food texture and augmenting nutritional content, thus offering a solution for managing complex cases of dysphagia^[76].

ASSESSING DIETARY INTAKE, FOR APPROPRIATE NUTRITIONAL INTERVENTION

Assessing dietary intake is crucial for determining the quantity of energy and nutrients a patient regularly consumes, as well as for identifying early signs of inadequate intake. Properly identifying the specific needs of each patient and tailoring follow-up according to the disease stage will yield better outcomes. Various methods can be employed for dietary evaluation, including the use of 24-h recalls, food frequency questionnaires, or 3-d food diaries. The information gathered from these assessments serves to pinpoint potential obstacles to proper dietary consumption, personalize meal schedules, and implement strategies to ensure adherence to the prescribed diet plan. In general, opting for a 3-d food diary is preferred over a single 24-h recall or food frequency questionnaire, as it yields more comprehensive and less biased information that can be both quantitatively and qualitatively assessed. These tools allow for the estimation of the patient's energy and protein intake, while also facilitating the monitoring of sodium, fluid, and micronutrient consumption^[77].

Nutritional intervention must be individualized, addressing not only the primary liver disease but also any concurrent health issues (Figure 4). Patients with liver disease often have additional conditions like diabetes, chronic kidney disease, and dyslipidemia. Therefore, a comprehensive nutritional strategy should consider these

factors. Following global guidelines and current scientific evidence for treating chronic hepatitis, the following recommendations are proposed:

Energy

The energy intake recommendations set forth by prominent international societies suggest a range of 30 to 40 kcal/kg/d^[78]. However, the importance of tailoring this intake to the specific clinical context cannot be overstated. For patients without malnutrition, an appropriate range is 30 to 35 kcal/kg/d, while malnourished individuals may require 35 to 40 kcal/kg/d. In critically ill patients, the preferred method for determining energy expenditure is indirect calorimetry. In cases where this is not feasible, a minimum intake of 35 kcal/kg/d is advised. In instances of obesity and liver cirrhosis, an energy deficit of 500 to 800 kcal/d has been linked to weight loss^[72].

When calculating nutritional requirements, the current weight is used for patients not experiencing fluid retention. However, in the presence of ascites or edema, the ideal or dry weight is considered. The dry weight corresponds to the weight after paracentesis, or the weight documented before fluid retention occurred. In cases where this data is unavailable, a percentage of weight is subtracted based on the severity of ascites (mild, 5%; moderate, 10%; and severe, 15%). An additional 5% reduction is applied if bilateral lower limb edema is present^[78].

Macronutrients

Protein: The controversy surrounding protein intake is prominent in macronutrient recommendations. Current evidence suggests that protein restriction is not necessary, even in the presence of HE. Protein intake is determined at 1.0 to 1.5 g/kg/d, varying based on the level of malnutrition. For mild malnutrition, the suggestion is 1.0 to 1.2 g/kg/d, 1.3 to 1.4 g/kg/d for moderate malnutrition, and 1.5 g/kg/d for severe malnutrition. To enhance tolerance, it is recommended that 60% to 70% of the protein comes from plant sources^[78,79].

Carbohydrates y lipids: In terms of carbohydrate recommendations, it is advised that they make up 45% to 65% of daily caloric intake. The remaining calories are suggested to be supplied by lipids^[78,79].

Micronutrients

Micronutrient deficiencies are prevalent in cirrhosis. Nevertheless, it's advisable to provide vitamin and mineral supplementation solely to patients with either clinical suspicion or confirmed deficiency^[21]. The goal is to restore normal serum levels.

Sodium: Managing sodium intake is crucial for patients with ascites or edema. The recommended approach involves limiting sodium consumption to 2000 to 2600 mg/d, which corresponds to 5.0 to 6.5 g/d of sodium chloride (NaCl)^[80]. However, stricter limitations are not recommended due to the unpalatable nature of such diets, potentially leading to reduced calorie and protein intake and an increased risk of malnutrition^[81]. Reducing sodium intake can lead to a 10%-20% reduction in fluid retention, particularly in patients experiencing initial episodes of fluid overload with adequate sodium excretion^[17]. It's important to exercise caution when using salt substitutes, as they are high in potassium and could result in hyperkalemia. Offering proper nutritional guidance to patients and their families, including information about salt-to-sodium equivalencies, is essential. Additionally, identifying and limiting the consumption of high-sodium foods is crucial for effective management^[82].

Zinc: Zinc deficiency in patients with cirrhosis has been linked to the development of HE due to its role in ammonia detoxification within the urea cycle. Moreover, inadequate zinc levels have been linked to weakened immune responses during bacterial infections and sepsis episodes^[6,83,84]. Potential causes of zinc deficiency in cirrhosis include disrupted absorption in the digestive tract and heightened urinary excretion, often caused by diuretic usage that elevates urine output and lactulose contributing to gastrointestinal losses^[85].

Vitamina D: Serum vitamin D levels decline with disease progression, and levels below 20 ng/mL are linked to an increased risk of hepatocellular carcinoma, disease decompensation, and increased mortality^[86].

Therefore, regular monitoring of serum 25-hydroxyvitamin D levels is recommended. In cases of deficiency, supplementation is necessary to attain levels exceeding 30 ng/mL. For this purpose, a recommended dosage is 600 to 4000 IU/d of cholecalciferol (vitamin D3)^[86]. Patients with a T-score lower than -1.5 standard deviations are advised to begin supplementation with calcium (1000 to 1500 mg/d) and vitamin D (400 to 800 IU/d)^[87].

Others: Strategies have been devised to counteract fasting periods, and one such strategy involves incorporating a snack into the diet^[88]. This approach not only enhances nutritional metabolism but also improves glucose tolerance and nutritional status^[89]. By reducing fasting periods and minimizing the extent of gluconeogenesis, this strategy enhances the utilization of substrates for energy production. One of the supplementation methods employed is the use of formulas containing branched-chain amino acids (BCAAs), which have demonstrated remarkable effectiveness in improving both nutritional status and the management of associated complications. While a unanimous agreement on dosage does not yet exist, tested doses for BCAAs typically range from 0.15 g to 0.25 g per kilogram of body weight, which corresponds to 8 g to 20 g per day^[90].

Fiber

Due to its positive effects on microbiota and gastrointestinal motility, a daily fiber intake of 25 g to 45 g is recommended^[19].

Fluids

Avoiding general water restriction for all cirrhosis patients is crucial. Fluid intake should only be restricted to 800 to 1000 mL/d in cases of severe hyponatremia, where sodium levels are below 125 mmol/L. Imposing fluid limitations on patients undergoing diuretic therapy can elevate the risk of dehydration^[81].

Exercise

Physical exercise is a key component in clinical practice due to its widely recognized benefits in improving the prognosis of various chronic degenerative diseases. Initially, evidence discouraged exercise recommendation for cirrhotic patients due to its potential elevation of portal pressure. However, these findings were observed in a limited patient group and only during exercise routines; this effect normalized afterward, posing no elevated risk of complications linked to portal hypertension. Presently, clinical trials offer compelling evidence of exercise's positive impact, showing a reduction in portal pressure of around -2.5 mmHg^[91,92]. Exercise guidelines for cirrhosis patients encompass a blend of aerobic and resistance training lasting 30 min to 60 min per session, at least thrice weekly^[93]. For frail individuals with sarcopenia, prioritizing balance and flexibility training is advisable, concentrating on bolstering postural muscles and expanding range of motion before delving into aerobic and resistance training^[87]. Physiotherapists, especially those specializing in geriatrics, should be integrated into multidisciplinary teams to ensure comprehensive care for this patient population.

ALCOHOL-RELATED LIVER DISEASE

Alcohol-related liver disease (ALD), or alcoholic liver disease, encompasses a range of conditions starting with fatty liver and progressing to alcoholic hepatitis and cirrhosis. Patients with ALD exhibit a higher incidence of malnutrition, reported in at least 50% of both outpatients and hospitalized patients^[94]. The compromised nutritional status can be attributed to various factors, including altered olfactory and taste perception^[95],

changes in appetite-related hormonal^[96], lower absorption of nutrients^[97] and alterations in intestinal microbiota^[98].

Moreover, individuals with ALD commonly experience malnutrition, characterized by protein-energy malnutrition and deficiencies in specific nutrients^[99].

One of the key contributors to the development of protein-calorie malnutrition is accelerated catabolism, primarily induced by patients who reduce their energy intake from food while relying on the caloric value of alcohol to meet their basal metabolic expenditure, thereby limiting the contribution of essential macronutrients and micronutrients^[100].

Another significant factor is the loss of appetite, linked to the upregulation of inflammatory cytokines (IL-1b, IL-6, and IL-8), tumor necrosis factor (TNF- α), and leptin levels. This upregulation leads to decreased appetite and early satiety, playing a crucial role in the cachexia observed in various acute and chronic diseases^[95]. TNF- α further influences metabolism by directly impacting the central nervous system, altering the release of neurotransmitters. This modulation slows intestinal motility and gastric emptying, influencing the patients' food choices^[101].

Alcohol interferes with the absorption, storage, metabolism, and activation of certain water-soluble vitamins (thiamine, riboflavin, pyridoxine, ascorbic acid, and folic acid)^[102]. Additionally, individuals with alcohol-related issues frequently exhibit zinc deficiency, a consistent biochemical/nutritional manifestation resulting from poor intestinal absorption^[103]. In alcohol-related cirrhosis, along with reduced enteric absorption and increased urinary excretion of zinc, patients often adhere to diets lacking in protein and zinc. Zinc deficiency is a common cause of dysgeusia^[104].

The consequences of zinc deficiency can manifest as acrodermatitis, anorexia, hypogonadism, impaired immune function, poor wound healing, night vision problems, diarrhea, issues with mental function, and an increased incidence of HE^[20,105].

Wernicke encephalopathy can develop in patients with depleted thiamine stores, and clinically, it presents as confusion, oculomotor dysfunction, and ataxia. If left untreated, patients may develop Korsakoff syndrome, which is permanent and results in marked

memory deficits^[106,107]. Additionally, deficiencies in vitamin B12 and folic acid are prevalent and can lead to macrocytic anemia^[108]. Moreover, chronic alcohol consumption disrupts vitamin A metabolism as it relies on the same pathways as alcohol metabolism. This alteration in metabolism results in the depletion of retinoid-binding proteins and increased excretion of retinoids into the bile, ultimately causing vitamin A deficiency^[109].

For the management of ALD patients, it is crucial to advise and provide guidance on lifestyle habits such as diet and the cessation of alcohol consumption^[99]. Routine nutritional assessments, dietitian involvement, and supplementation are recommended to enhance clinical outcomes in these patients^[110]. Additionally, vitamins and trace elements should be consumed at least in the recommended daily amounts. Nutritional support has been demonstrated to improve nutritional status and abnormal liver tests^[111].

In summary, nutritional therapy plays a vital role in addressing the complex nutritional needs of individuals with alcoholic liver disease, with the goal of improving clinical outcomes and addressing the challenges associated with this condition.

CONCLUSION

Patients with cirrhosis are at high risk of malnutrition, these patients should have adequate and timely nutritional evaluation, diagnosis, intervention, and monitoring. Dietary management of liver cirrhosis is complex and may require a multipronged approach to address issues of protein-energy malnutrition, muscle wasting, complications of fluid retention, and HE along with other symptoms that can impact nutritional intake. Currently the limited data support patients with liver cirrhosis receiving early nutritional intervention that is high in energy, protein, and carbohydrates, and incorporation of frequent meals, particularly with an additional late evening nutrient-dense snack. Unnecessary dietary restrictions in these patients should be minimized as much as possible. In addition, nutritionist involvement earlier on in the treatment algorithm is an important step to provide aggressive nutritional

intervention and ameliorating the high rates of malnutrition in this patient population. Finally, there is an urgent need to bridge the evidence gap between dietary intervention trials and clinical practice, with a bigger focus on the manipulation of whole diets.

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Figure Legends

Figure 1 Impact of sarcopenia in cirrhosis. The presence of sarcopenia has been shown to be associated with reduced quality of life and survival. It is a predictor of pre and posttransplant complications, including higher risk of infections, ascites, hepatic encephalopathy, and longer hospital stay. HE: Hepatic encephalopathy. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)^[112].

Figure 2 Assessment in patients with cirrhosis. Implementing the nutritional control protocol outlined by Clinical Practice Guidelines is strongly advised as a fundamental aspect of standard cirrhosis patient management. HE: Hepatic encephalopathy; INR: International normalized ratio; CBC: Complete blood count; CT: Computed tomography; DEXA: Dual energy X-ray absorptiometry; BIA: Bioelectrical impedance analysis; BMI: Body mass index; RFH-NPT: Royal Free Hospital Nutritional Prioritizing Tool. The consent was adapted by Clinical Practice Guidelines^[41]. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)^[112].

Figure 3 The nutritional care process includes the following steps. (1) Nutritional assessment; (2) nutritional diagnosis; (3) nutritional intervention; and (4) monitoring. LFI: Liver frailty index; RFH-NPT: Royal Free Hospital Nutritional Prioritizing Tool; CT: Computed tomography; DEXA: Dual energy X-ray absorptiometry; BIA: Bioelectrical impedance analysis; BMI: Body mass index. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)^[112].

Figure 4 General recommendations for nutritional intervention in patients with cirrhosis. BCAAs: Branched-chain amino acids. Citation: The authors have obtained the permission for figure using from the BioRender.com (Supplementary material)^[112].

Table 1 Global leadership initiative on malnutrition criteria for the diagnosis of malnutrition

Phenotypic criteria			Etiological criteria		
Unintentional weight loss	Low body mass index	Reduction of muscle mass	Decreased intake or assimilation of foods	Inflammatory load	
> 5% in the last 6 months or > 10% in more than 6 months	< 20 in < 70 years or < 22 in > 70 yr	Evaluated by validated body composition techniques	≤ 50% > 1 wk or ≤ 100% > 2 wk or any chronic condition that alters food assimilation	Acute injury/inflammation; chronic inflammatory pathology	

Diagnosis requires at least 1 phenotypic criterion and 1 etiological criterion. GLIM: Global leadership initiative on malnutrition.

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