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The Challenges of Nutritional Assessment in Cirrhosis

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Abstract

Purpose of Review—Nutritional status in patients with cirrhosis is very frequently associated with macro- and micronutrient deficiencies. Cirrhosis itself is the cause of malnutrition and nutritional deficiencies but these conditions have to be identified and addressed properly as they can worsen the prognosis of cirrhosis. The goals of this review are to 1) identify and describe the challenges associated with nutritional assessment in cirrhosis and 2) describe recent advancements when using clinical, laboratory, and instrumental tools in the evaluation of malnourished patients with liver diseases.

Recent Findings—The most promising tools for nutritional assessment in cirrhosis include the evaluation of body composition with phase angle obtained by bioelectrical impedance analysis, computed tomography transverse images at the level of third lumbar vertebra. The Royal-Free Hospital global assessment algorithm appears to be helpful but needs further validation.

Summary—Nutritional assessment in cirrhosis is challenging as several factors, including edema, can interfere with it and because of lack of a validated gold standard. Regardless, nutritional assessment methods have been developed in recent years and should gain relevance in the clinical practice.

Keywords

Cirrhosis; Liver; Nutrition; Malnutrition; Assessment

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Introduction

Prevalence and prognosis of malnutrition in cirrhosis

Prevalence of protein-calorie malnutrition in patients in cirrhosis has been estimated between 30-100%, [1, 2, 3, 4]. Malnutrition is an independent predictor of increased mortality and poor outcomes in patients with cirrhosis [3, 5, 6, 7]. There is a higher prevalence of malnutrition among patients with decompensated cirrhosis compared to compensated cirrhosis and the severity of liver disease correlates with severity of malnutrition [8]. Malnutrition has been associated with increased prevalence of complications of portal hypertension including hepatorenal syndrome, ascites, and hepatic encephalopathy [5, 9]. Malnourished patients also have increased pre- and post-transplant mortality, longer hospital stays, increased risk of infection, and decreased quality of life, with associated increased hospital costs [1, 5]. Post-transplant, malnourished patients have longer intensive care and hospital stays and increased risk of infection [1].

Causes and pathogenesis

Causes of malnutrition in patients with cirrhosis are multifactorial. Decreased or impaired intake occurs from anorexia frequently resulting from increased tumor necrosis factor-alpha and leptin levels, alcohol use, early satiety from abdominal distention in ascites, gastrointestinal symptoms such as nausea and vomiting, dysgeusia from zinc and magnesium deficiency, restriction of sodium and fluid intake making food less palatable, altered mental status from hepatic encephalopathy, fasting while hospitalized in anticipation of procedures and diagnostic tests, and complications from advanced cirrhosis such as gastrointestinal bleeding and sepsis [11, 12]. Malabsorption in cirrhosis occurs also from fat malabsorption from chronic pancreatitis, decreased production of bile acids in cholestasis, and small bowel bacterial overgrowth [13, 14].

Micronutrient deficiencies occur from inadequate intake and malabsorption. Commonly seen are hypomagnesaemia and zinc deficiency from diuretic use, decreased levels of fat-soluble vitamins A, D, E, and K from decreased levels of intraluminal bile acids, and folate, thiamine, and vitamin B6 deficiency from malabsorption and alcohol use [15, 16, 17].

Metabolism of glucose and lipids are altered in cirrhosis. Increased gluconeogenesis is caused by impaired hepatic storage of glucose, insulin resistance, and increased circulating beta-androgens. This increased gluconeogenesis causes increased lipid and protein catabolism and abnormal amino acid metabolism and results in an early starvation state after an overnight fast that is comparable to a 26-72 hour fast seen in normal individuals [18, 19].

Cirrhotic patients are in a catabolic and chronic inflammatory state resulting in an increased resting metabolic rate. Increased resting energy expenditure (REE) and hypermetabolism is observed in 18-58% of cirrhotic patients and is seen independently of etiology of cirrhosis or liver function [18, 20, 21, 22, 23]. Increased REE is associated with increased mortality, insulin resistance, increased lipid utilization/lipid oxidation, higher fat free mass, and lower leptin levels [18, 21, 23, 24]. This increased REE and metabolic rate can be explained by an elevated inflammatory state, increased beta-adrenergic activity, and catabolic state [20].

Nutritional assessment in cirrhosis

Uncertainty exists in the area of nutritional assessment among patients with cirrhosis, due to the absence of a validated gold standard in this clinical setting. Therefore, the approach to patient nutritional and metabolic derangements should be based on a combination of practice guidelines, published evidence, and clinical experience [25].

Considered as a potentially modifiable condition, protein-calorie malnutrition may be assessed by a comprehensive nutritional evaluation aimed at determining if cirrhotic patients are at risk of malnutrition or at identifying the severity of already existing malnutrition and its changes overtime [25, 26]. The ideal tool for the nutritional assessment should be easy to use by health care professionals, including untrained physicians and nurses, and it should have reasonable sensitivity, specificity, and reproducibility [27].

Nutrition evaluation in patients with cirrhosis may be based on anthropometric methods, assessing the measurement of body size and its proportions, as well as on non-anthropometric methods, investigating on: 1) body composition assessment, with a specific focus on muscle mass, 2) functional assessment, 3) dietary assessment, and 4) global assessment tools.

Body weight, waist and arm circumference, triceps skinfold thickness, and BMI often provide an inaccurate classification of malnutrition as they are all affected by the fluid retention that often occurs in patients with cirrhosis [25]. Therefore, it appears clinically relevant to have a predictable estimation of the dry weight in patients presenting with fluid retention.

A study by McHugh *et al.* [28] tested linear and volume measurements from abdominal computed tomography (CT) scan to estimate dry weight of patients with end stage liver disease undergoing transplantation using multivariable linear regressions. Specific equations were found to estimate dry body weight (regardless of ascites), offering a more precise representation of size than scale weight in patients with ascites. Equations are not commonly used in clinical practice and should be implemented in larger trials.

In this light, the use of non-anthropometric methods is strongly recommended.

Body composition is an important component of the nutritional assessment in cirrhosis. In particular, the bioelectrical impedance analysis (BIA) allows an easy and rapid assessment of muscle mass and adiposity. However, the results obtained by BIA present low sensitivity as they are highly influenced by fluid retention, especially edema, or shifts, such as ascites, which may give misleading information on muscle and adipose tissues changes. Therefore, its use in cross-sectional and longitudinal evaluation of cirrhosis is not currently recommended [29]. Considering these limitations, a study by Fernandes *et al.* recently analyzed the specific role of phase angle (PA), obtained by BIA, which was studied in different trials. The PA is a parameter obtained through BIA and results from the ratio of resistance (R) and tissue capacitance (Xc). More specifically, R is associated with hydration, whereas Xc reflects cellularity and cells integrity. The PA data correlated significantly with the presence of malnutrition and with the stage of liver disease, indicating that it might be

considered a good prognostic marker in patients with cirrhosis, with and without edema and/or ascites [30]. This information appears clinically relevant and it should be confirmed by larger clinical trials during long term follow-up.

Additional body composition tools are represented by bioimpedance spectroscopy and dual-energy X-ray absorptiometry (DXA) which better discriminate fluid shifts from body composition changes, having higher accuracy and precision [31]. DXA can be used to calculate the appendicular muscle mass index, which is supposed to be more precise in cirrhosis as, focusing only on fat free mass, it is not affected by fluid retention nor overweight status [32]. However, these devices are not widely available in routine clinic due to high costs.

Multiple imaging methods have been tested to quantify body composition compartments and especially to recognize reduced muscle mass, i.e. sarcopenia, considered as one of the most common condition associated with mortality in this clinical setting [33, 34], leading to divergent results.

Computed tomography (CT), acquiring transverse images, can capture, usually at the level of third lumbar vertebra, lean and adipose tissue deposits and define the skeletal muscle index, whose low value can identify a sarcopenic status. This method analyzes only a single or few slices and therefore prediction equations are needed for whole-body lean mass. Patient's follow-up with CT scan is limited by costs, availability, and risk of ionizing radiation and contrast exposure.

Ultrasound imaging may provide measures of changes in muscle density, which may reflect adipose infiltration or muscle damage. Preliminary data showed that BMI and thigh muscle thickness, as documented by ultrasound imaging, are good predictors of sarcopenia in cirrhosis [29].

Nevertheless, it appears difficult to distinguish between muscle and subcutaneous adipose tissue border in overweight and obese individuals, decreasing accuracy and reliability of the ultrasound method. Additionally, ultrasound technique requires specific cutoff points that have not yet been established in cirrhosis, requiring a validation and correlation with clinical outcomes before its reliable use in this clinical setting.

Functional assessment allows to study the quality of lean tissue (muscle strength), and it is useful for the global assessment of patients nutritional status. Muscle weakness may insidiously develop with decompensation and malnutrition in patients with cirrhosis. Several studies have documented an association between altered functional measures (e.g., handgrip, 6-minute walk test, physical frailty, and volume of O₂ peak tests) and worse prognosis [35, 36, 37]. The 6-minute walk test was shown to be a useful tool in assessing physical function, and its modifications were found to be independent predictors of survival in patients with cirrhosis [36]. However, functional measures, in particular the 6-minute walk test and other tests requiring walking or attentive participation, cannot be performed correctly in patients with complications of portal hypertension (i.e. encephalopathy) [38]. Handgrip strength appears to be a valuable option and it consists in an easy-to-perform method that can diagnose or predict sarcopenia with an overall higher sensitivity and specificity with respect

to other tools, thus representing a predictor of complications and decompensation in cirrhosis [39].

Dietary intake assessment can be investigated with a 3-day food diary completed by the patient. It is important to evaluate current calorie and protein intake and to compare them with the habitual intake. The ESPEN guidelines recommend intake of 25-30 kcal/kg dry body weight in clinically stable cirrhosis, to be increased to 30-35 kcal/kg dry body weight in malnourished patients, and to provide 50-60% of calories as carbohydrate, 20-30% of calories as protein (1-1.5 g/kg body weight) and 10-20% of calories as lipids [40, 41]. In addition, it is clinically relevant to evaluate the presence/absence of anorexia, defined as the loss or reduction of the desire to eat, by specific anorexia questionnaires and by the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) score [42, 43]. The FAACT score, based on 12 questions related to appetite and food intake, allows a qualitative and quantitative diagnosis of reduced food intake. As recently shown, a FAACT score ≥ 30 is indicative of the presence of anorexia [43].

A specific anorexia questionnaire, which is a rapid qualitative tool to diagnose anorexia related to several chronic diseases, including cirrhosis, investigates the presence of major symptoms, such as meat aversion, taste and smell alterations, nausea and/or vomiting and early satiety. Patients reporting one or more of these symptoms are considered as anorexic [44].

Calorie and energy intake are also part of the evaluation performed by other tools, such as Mini Nutritional Assessment-MNA, Malnutrition Universal Screening Tool-MUST, Nutrition Risk Screening tool-NRS, aiming at identifying anorexia and the associated protein-energy malnutrition, which have a significant impact on survival and morbidity in chronic diseases. To date, none of these appetite assessment tools have been validated in the setting of cirrhosis [25].

The global assessment tools may be useful in completing nutritional assessment in liver disease, including the Subjective Global Assessment (SGA) which is based on 5 clinical parameters, including weight change in the prior 3-6 months, dietary intakes, gastrointestinal symptoms, functional capacity, metabolic derangements, and 3 physical parameters, including loss of subcutaneous fat, loss of muscle mass, and presence of edema/ascites. The SGA categorizes patients into: well nourished (A), moderately malnourished (B), or severely malnourished (C). The SGA was implemented in cirrhotic patients with and without hepatocellular carcinoma resulting as a good predictor of nutritional status [45], considering that in patients with cirrhosis weight and biochemical values may vary with the severity of the underlying liver disease [46]. Nevertheless, this tool, despite being relatively simple, could be fairly inaccurate, because it underestimates the prevalence of sarcopenia in cirrhosis [29]. In a recent study on 69 patients diagnosed with sarcopenia by imaging technique, only 46% were moderately or severely malnourished according to SGA, indicating the limited capacity of this tool in assessing nutritional status [29]. The Royal Free Hospital SGA represents a modification of the traditional SGA. It consists of an algorithm, which combines a subjective assessment of nutritional status with BMI (estimated dry body weight), mid-arm muscle circumference, and dietary intake [47], ultimately

dividing patients into 3 categories: adequately nourished, moderately nourished (or suspected to be), and severely malnourished. This tool was able to correlate the altered nutritional status with a shorter survival in men, but not in women, raising questions on its application to both genders.

Nutrition assessment in specific etiologies of liver disease and cirrhosis

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) includes various severities of liver disease from fatty liver characterized by hepatic steatosis only to nonalcoholic steatohepatitis (NASH) where steatosis is associated with inflammatory infiltrate, hepatocyte ballooning, and liver fibrosis. NASH is a risk factor for development of cirrhosis and hepatocellular carcinoma. Epidemiologically, NAFLD and NASH are very common conditions. The prevalence of NAFLD in the 1999-2012 National Health and Nutrition Examination Survey (NHANES) was 30% in the 6,000 included subjects and 10.3% of them presented advanced fibrosis [48]. Of note, the same study also demonstrated an increased risk of mortality associated with advanced fibrosis. NAFLD is considered the hepatic manifestation of the metabolic syndrome which is characterized by obesity, diabetes, hyperlipidemia, and hypertension. Interestingly, patients with NASH, despite being typically obese, also present a high prevalence of sarcopenia, or muscle mass loss, also named sarcopenic obesity. This association between sarcopenia and obesity makes the nutritional assessment of this condition particularly challenging [49]. It has been demonstrated that adults with lower muscle mass, also have an increased risk of NAFLD [50]. In a study on more than 300 patients with biopsy-proven NAFLD, the association between sarcopenia and severity of liver disease was studied. Sarcopenia was defined as the ratio between appendicular skeletal muscle mass and body weight. When a subject presented with a ratio value beyond two standard deviations below the mean for healthy young adults, sarcopenia was associated positively with NASH and with the severity of the stage of fibrosis [51]. These findings were confirmed in another study on 225 patients with NAFLD and sarcopenia, which resulted to be associated as well with severity of steatosis and fibrosis [52]. Interestingly, the association between NAFLD and sarcopenia resulted in both studies to be independent from metabolic risk factors, including BMI and insulin resistance. An additional factor associated with sarcopenic obesity and potentially useful in the overall assessment of NASH patients is gamma-glutamyl transferase level (GGT) [53], as elevated GGT levels were associated with increased risk of sarcopenia and sarcopenic obesity in a cohort of patients older than 50 years. Growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were also associated with increased risk of sarcopenic obesity and hepatic fat deposition [54].

Alcoholic liver disease

Malnutrition and sarcopenia are among the most important and frequent clinical manifestations of alcoholic liver disease (ALD). ALD encompasses conditions characterized by different severity. Alcoholic fatty liver is present in virtually all drinkers and is reversible after prolonged abstinence from alcohol drinking. Alcoholic hepatitis is associated with high risk of mortality within 6 months, whereas alcoholic cirrhosis is ultimately associated with complications of portal hypertension and risk of hepatocellular carcinoma. Malnutrition and

sarcopenia are present in up to 90% of patients with ALD [55]. Micronutrient deficiencies, including folate, S-adenosylmethionine, cyanocobalamin, vitamin B1 and B6, zinc and selenium, have been extensively shown in this condition. Some of these deficiencies are also considered possible contributors to the liver damage. Therefore, micronutrient assessment and adequate supplementation is recommended in ALD [41, 56].

Previous studies focused on the assessment of malnutrition in ALD as determined by anthropometric measures (ideal body weight, skinfold thickness and estimates of body fat deposition at multiple body sites, midarm muscle area) and visceral protein levels (albumin, transferrin, prealbumin, retinol binding protein) [6, 9] but imaging studies specific for ALD are lacking. As reported in the previous review from Desarathy [57], various factors affect nutritional status in ALD and those factors are often not taken into consideration in clinical studies. For example, the duration of alcohol use, the timing of the most recent alcohol use and interval of abstinence, the amount of alcohol consumed in the short and long term, the type of ALD (fatty liver, alcoholic hepatitis, and cirrhosis, whether this is compensated or decompensated) as well as presence of other comorbidities. In particular, the combination of alcohol drinking and obesity have detrimental effects on the progression of liver disease [58] but the consequences on nutritional status and the specific modalities of its assessment are not known.

Cholestatic liver diseases

Special attention should be devoted to the assessment of nutrition status in cholestatic liver diseases, including primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). PSC is a rare cholestatic liver disease characterized by the destruction of medium to large-size intra- and extrahepatic bile ducts caused by autoimmune and inflammatory processes [59]. PBC is also a chronic inflammatory autoimmune condition but the targets of the damage are the interlobular bile ducts [60]. Even though there are major histopathological and epidemiological differences between these two conditions, they share some of clinical manifestations mainly due to the chronic bile stasis. Chronic cholestasis and related fat malabsorption causes fat-soluble vitamin deficiency and high risk of developing osteoporosis. One study evaluated the prevalence of fat-soluble vitamins deficiency in PSC, showing that vitamin A deficiency was present in 40% of patients, vitamin D deficiency in 14%, and vitamin E in 2%. When evaluating the patients with more advanced liver disease undergoing evaluation for liver transplant, the prevalence of these vitamin deficiencies was much higher, ranging from 82% to 43% [61]. A study on eighty-one patients with PSC evaluated the presence and progression of osteopenia over a 5 year follow up period. The major findings were that about 8-9% of patients presented severe osteoporosis and this was associated with advanced liver disease and presence of inflammatory bowel disease [62].

Therefore, the bone density examination is recommended at 2-3 year intervals in the assessment and long term management of PSC patients [63]. The prevalence of osteoporosis is much higher in PBC, described in up to 30% of patients [64]. As far as fat-soluble vitamin levels, the prevalence of vitamin A, D, E, and K deficiency was 33%, 13%, 2%, and 7.8 %, respectively, in a study involving 180 PBC patients [65].

Conclusion

The assessment of nutritional status in cirrhosis is challenging but anthropometric, functional, dietary intake, and global assessment tools are available and should be implemented. In addition, special attention should be devoted to specific etiologies and differences should potentially be considered when developing new tools. Physicians and patients education is needed to increase awareness of malnutrition, to prevent and/or mitigate poor outcomes, especially those potentially modifiable, and to obtain a positive impact on patients' overall prognosis. A practical, validated, and unified nutritional assessment strategy needs to be implemented into routine clinical practice.

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