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Nutritional support in patients with chronic liver disease

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SUMMARY

Malnutrition is highly prevalent among patients with chronic liver disease and is nearly universal among patients awaiting liver transplantation. Malnutrition in patients with cirrhosis leads to increased morbidity and mortality rates. Furthermore, patients who are severely malnourished before transplant surgery have a higher rate of complications and a decreased overall survival rate after liver transplantation. In light of the high incidence of malnutrition among patients with chronic liver disease and the complications that result from malnutrition in these patients, it is essential to assess the nutritional status of all patients with liver disease, and to initiate treatment as indicated. This review addresses the etiologies of malnutrition, methods used to assess nutritional status, and appropriate treatment strategies.

KEYWORDS cirrhosis, liver disease, nutrient deficiency, nutritional status, protein–calorie malnutrition

REVIEW CRITERIA

PubMed was searched in June 2005 using the terms "liver disease", "cirrhosis", "liver transplant", "nutritional status", "malnutrition", "protein–calorie malnutrition", "nutrient deficiency", "enteral nutrition", "parenteral nutrition", and "branched-chain amino acid" in various combinations. The search was restricted to full papers published in English-language journals. Papers in the authors' own collections were also included in the search. The reference list was updated in November 2005.

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INTRODUCTION

Malnutrition is an increasingly recognized complication of chronic liver disease that has important prognostic implications. Malnourished patients with cirrhosis have a higher rate of complications and, overall, an increased mortality rate.[1,2] Malnutrition has significant implications for liver transplantation; it has been shown that patients with poor nutritional status before transplantation have increased complications and higher mortality rates postoperatively.[3–6] Screening all patients with chronic liver disease for nutritional abnormalities can identify those at risk of developing preventable complications.[7] The initiation of nutritional therapy has the potential to reduce the risk of such complications, and to improve the overall mortality rate.

PREVALENCE

Protein–calorie malnutrition (PCM)—a condition of body wasting related to dietary deficiency of calories and protein—is found in 65–90% of patients with advanced liver disease and in almost 100% of candidates for liver transplantation.[8,9] Patients with chronic liver disease also frequently develop micronutrient deficiencies, which can have a more insidious presentation than the overt cachexia seen in patients with PCM. There is a direct correlation between the progression of the liver disease and the severity of malnutrition.[10,11] Malnutrition develops in patients with cirrhosis irrespective of the etiology of their disease[12] and occurs with roughly equal incidence in patients with alcoholic and nonalcoholic liver disease.[13] Patients with cholestatic liver disease are subject to calorie depletion, whereas patients with noncholestatic disease predominantly experience protein depletion.[14] Additionally, cholestatic disease is more frequently associated with a deficiency in fat-soluble vitamins than noncholestatic disease.[15] Malnutrition is not typically a complication of acute liver injury, but manifests with progression to liver failure.

SEQUELAE

Malnutrition is associated with increased morbidity and mortality rates in patients with chronic liver disease. Patients with cirrhosis who are malnourished have a higher rate of hepatic encephalopathy, infection, and variceal bleeding.[3,16] They are also twice as likely to have refractory ascites.[8] Although numerous studies have found a correlation between poor nutritional status and a decreased survival rate, there is debate as to whether the increased mortality rate is caused by malnutrition or by the advanced liver disease itself. Alberino *et al.* identified malnutrition as an independent predictor of mortality in patients with cirrhosis.[1]

Nutritional status has prognostic implications in liver transplant candidates. Malnutrition before transplantation is associated with a higher rate of post-transplant complications, including infection and variceal bleeding.;[4,16,17] Patients who are severely malnourished require more blood products intraoperatively, remain on ventilatory support longer postoperatively, and have an increased length of hospital stay[3,4,9] and a higher incidence of graft failure.[18] Ultimately, patients with poor nutritional status before transplant surgery have a decreased survival rate after liver transplantation.[5,6,9]

ETIOLOGIES

The primary etiology of malnutrition is poor oral intake, stemming from multiple factors. Many patients with advanced liver disease have an altered sense of taste, which might be related to vitamin A and/or zinc deficiency.[19] Patients with cirrhosis often experience early satiety that is related to mechanical compression from massive ascites. Early satiety can also result from an increased serum concentration of leptin, which has been found in patients with advanced liver disease.[20] The dietary restrictions that are commonly recommended to these patients, such as restriction of sodium, protein, and fluids, can discourage adequate oral intake. In addition, weakness, fatigue, and low-grade encephalopathy can contribute to decreased oral intake.

Malabsorption is another important factor in the development of malnutrition in this patient population. A number of mechanisms contribute to malabsorption. There might be a reduction in the bile-salt pool in patients with advanced liver disease, leading to fat malabsorption,[21] which is particularly problematic in patients with cholestatic liver disease. Another potential mechanism that contributes to malabsorption in patients with advanced liver disease is bacterial overgrowth resulting from impaired small-bowel motility.[22] The presence of portal hypertension has also been implicated as a cause of malabsorption and gastrointestinal protein loss.[23,24] An additional factor is the administration of medications that lead to malabsorption, such as neomycin, which is used in the treatment of hepatic encephalopathy.[25] Fat malabsorption not only contributes to undernourishment, but also results in a deficiency in fat-soluble vitamins.

Another factor that might contribute to malnutrition, around which there has been considerable debate, is increased energy expenditure. Although several studies have suggested that cirrhosis does not significantly alter resting energy expenditure (REE),[26,27] other studies suggest that patients with cirrhosis are actually hypermetabolic when measurements of REE are corrected for lean body mass.[28,29] Hypermetabolism is found in as many as a third of patients with stable cirrhosis; however, it seems that there is significant variability in REE among patients with cirrhosis. In fact, it has been suggested that up to 30% of patients with cirrhosis are actually hypometabolic.[30,31]

The exact cause of hypermetabolism remains unclear, but certain predisposing factors have been identified. Infection, a common complication in patients with advanced liver disease, tends to induce a state of hypermetabolism. Ascites has also been shown to increase energy expenditure; this effect tends to be reversed with the removal of ascitic fluid.[32] Muller *et al.* demonstrated that hypermetabolism cannot be readily identified by clinical or biochemical markers of liver disease, suggesting that hypermetabolism might be an extrahepatic manifestation of liver disease.[31] It has also been demonstrated that an increase in energy expenditure caused by hypermetabolism seems to be matched by a reduction in activity-related energy expenditure.[33] Successful treatment of portal hypertension with transjugular intrahepatic portosystemic shunt placement results in a reduction of the hypermetabolic state.[34]

Patients with advanced liver disease also have an altered pattern of fuel consumption, in which there is a more rapid transition from the use of carbohydrates to the use of fat stores as a substrate for metabolism. This increased use of lipids is a metabolic pattern that is seen in starvation.[6,35,36] Chang *et al.* showed that, after

GLOSSARY

THIRD-SPACING
A shift of fluid from the intravascular space to the interstitium

ISOTOPE DILUTION
A method of assessing body composition using a tracer dose of stable isotope, which is administered orally and analyzed in body fluids using mass spectroscopy

WHOLE-BODY POTASSIUM
The measurement of whole-body radiolabeled isotope of potassium can be used to calculate fat-free mass by standardized formulas

BIOELECTRICAL IMPEDANCE
An assay of total body water, whereby a weak current is passed through the body: the voltage drop between two electrodes is measured and is proportional to the body's fluid volume in that region

an overnight fast, 58% of the energy used by patients with cirrhosis was derived from fat oxidation, whereas control participants derived 55% of their energy from carbohydrates.[36]

NUTRITIONAL ASSESSMENT

Considering the complications created by malnutrition, a thorough nutritional assessment should be performed for every patient with chronic liver disease. This, however, might not be easily accomplished.

There are several factors that complicate the evaluation of nutritional status in patients with cirrhosis. Many of the commonly used markers of malnutrition are not useful parameters for the prediction of malnutrition in this patient population. Weight, for example, is not a reliable indicator of malnutrition, because the presence of ascites and edema will increase the measured weight, whereas lean body mass might actually be reduced. Also, many of the laboratory tests that are typical markers of nutritional status are less reliable in patients with cirrhosis. For example, concentrations of albumin and prealbumin could be low because of low levels of synthesis, rather than because of poor nutritional status. Other parameters must be used in the evaluation of these patients. A commonly used method is anthropometry. Anthropometric measurements include triceps skin-fold thickness and midarm circumference, which assess fat storage and skeletal muscle mass, respectively. This method is, however, also not without its problems. Potential limitations of anthropometry include poor inter-observer reproducibility and overestimation of these values because of the THIRD-SPACING of fluid.[11]

Subjective global assessment (SGA) is a technique that combines multiple elements of nutritional assessment to classify the severity of malnutrition.[37] These components are weight loss during the previous 6 months, changes in dietary intake, gastrointestinal symptoms, functional capacity, metabolic demands, signs of muscle wasting, and the presence of presacral or pedal edema. SGA has been shown to have an interobserver reproducibility rate of 80%,[38] and is useful in predicting outcome following liver transplantation.[3]

The assessment of muscle function measuring hand-grip strength and respiratory-muscle strength has also been used in nutritional evaluation; however, these measurements tend to be more useful when taken serially.[39] Hand-grip strength is a highly sensitive test and might actually overestimate the prevalence of malnutrition. Nonetheless, hand-grip strength seems to be a good predictor of complications in patients with advanced liver disease. A recent study compared SGA, the prognostic nutritional index, and hand-grip strength as predictors of outcome in patients with cirrhosis.[40] In this study, decreased hand-grip strength accurately predicted a poor clinical outcome that was related to a higher rate of complications, including ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome, whereas SGA and the prognostic nutritional index did not. The prevalence of malnutrition was highest when measured by hand-grip strength, suggesting that hand-grip strength could be the most sensitive technique. Figueiredo *et al.* showed that decreased handgrip strength before transplantation is associated with longer stays in the intensive-care unit and more postoperative infections.[17]

Depletion of body cell mass (BCM) is a useful estimation of nutritional status.[41] Decreased BCM before transplantation has been shown to correlate with a threefold increase in post-transplant mortality rates.[5,6] ISOTOPE DILUTION, measurement of WHOLE-BODY POTASSIUM, and *in vivo* neutron activation analysis are arguably the most accurate methods currently available to assess body composition; however, these techniques are costly and labor intensive, making them less practical for routine nutritional screening. BIOELECTRICAL IMPEDANCE is a more readily available tool for estimating BCM. Although this is a reliable tool in many patient populations, the accuracy of these measurements in patients with cirrhosis can be affected by fluid retention.[42] Pirlich *et al.*, however, showed that estimation of BCM using bioelectrical impedance correlated closely with BCM measured by total body potassium in patients with and without ascites.[43] Figueiredo *et al.* studied whether the traditionally measured nutritional parameters correlate with BCM. Although depleted BCM correlated most closely with arm-muscle circumference and hand-grip strength, most parameters, nonetheless, did not correlate well with depleted BCM.[44]

An evaluation of the status of energy metabolism might be a reasonable component of a nutritional assessment, because there seems to be a correlation between hypermetabolism

and malnutrition.[6,31] This evaluation can be accomplished using indirect calorimetry, a widely accepted tool that is used to estimate REE. Indirect calorimetry measures the consumption of oxygen and production of carbon dioxide, and REE is calculated using the Weir equation: [kcal/d = [3.941 × VO_2 (l/day)] + 1.106 × VCO_2(l/day)].[45] The measured REE is compared with the predicted energy expenditure, as calculated using the Harris–Benedict equation.[46] A patient is generally considered to be hypermetabolic if the measured REE is more than 10–20% greater than the predicted REE.[30,31] In transplant recipients, hypermetabolism is associated with a decreased survival rate after transplantation.[5] The use of indirect calorimetry enables the calculation of the nonprotein respiratory quotient, defined as the ratio of energy produced by carbohydrate metabolism to energy generated by fat oxidation, which confirms whether a patient has an altered pattern of fuel consumption.

TREATMENT

The goals of nutritional therapy are to improve PCM and correct nutrient deficiencies. This can be accomplished via oral, enteral, or parenteral methods, or a combination of these modalities.

Intervention in the early stages of malnutrition can improve outcome. Hirsch *et al.* studied the effects of nutritional supplementation in patients with alcoholic cirrhosis.[47] They found that patients receiving a daily supplement of 1,000 kcal and 34 g of protein (given as a casein-based enteral nutrition product) had better outcomes compared with those in the control group; the number of hospitalizations was significantly fewer in the treated group, and additional parameters, including midarm circumference, serum albumin concentration, and hand-grip strength, also improved earlier in the treated group than in the control group. Mendenhall *et al.* studied the effects of oral nutritional support in patients with alcoholic hepatitis. In patients with severe malnutrition, inadequate caloric intake was associated with 51% mortality compared with 19% mortality in patients who received adequate oral nutrition (greater than 2,500 kcal/day).[48] One randomized, controlled trial demonstrated that providing nutritional supplementation to pretransplant candidates did not increase overall dietary energy or protein intake, and did not significantly improve post-transplant outcome. It is thought that the patients who received a nutritional supplement might have compensated for taking the supplement by decreasing their intake of food. This study concluded that regular dietary counseling is as effective in increasing energy intake as providing a nutritional supplement.[49]

Enteral nutrition

As a general guideline, oral intake should be encouraged; if patients are unable to maintain adequate intake orally, a nasogastric tube should be inserted for enteral feeding. Cabre *et al.* found that, in severely malnourished patients with cirrhosis, enteral feeding improved serum albumin levels and Child–Turcotte–Pugh scores, and decreased in-hospital mortality rates, compared with the standard oral diet.[50] Hasse *et al.* demonstrated the benefit of early initiation of enteral feeding after transplantation.[51] Patients who received enteral feeds had an improved nitrogen balance and fewer viral infections after transplantation. Kearns *et al.* showed that aggressive nutritional intervention with enteral feeding accelerated improvement in alcoholic liver disease; patients who received enteral feeds demonstrated a more rapid decrease in bilirubin levels and improvement in hepatic encephalopathy compared with control participants.[52]

Parenteral nutrition

Parenteral nutrition is a less desirable option than enteral nutrition and should be reserved for patients in whom enteral feeding cannot be achieved.[53] Wicks *et al.* showed that enteral feeding is as effective as parenteral feeding for maintaining nutritional status after liver transplantation, and has the benefit of decreasing complications and cost.[54] There is some evidence to suggest that parenteral feeding might be superior to enteral feeding in patients with portosystemic shunting, because enteral feeding might worsen hyperammonemia in this specific patient population.[55]

Guidelines for meeting nutritional goals

In 1997, the European Society for Clinical Nutrition and Metabolism created guidelines for meeting nutritional goals in patients with end-stage liver disease.[53] They recommend initiation of enteral feeding when oral intake is inadequate. In patients with compensated cirrhosis, the guidelines recommend that patients consume 25–35 kcal/kg body weight per day of

nonprotein energy and 1–1.2 g/kg body weight per day of protein or amino acids. In patients with complicated cirrhosis associated with malnutrition, nonprotein energy should be increased to 35–40 kcal/kg body weight per day and protein intake should increase to 1.5 g/kg body weight per day. According to the guidelines, protein intake should decrease to 0.5–1.5 g/kg body weight/day if stage I or II encephalopathy is present, and to 0.5 g/kg body weight/day if stage III or IV encephalopathy is present. More recent evidence suggests that protein restriction should not be recommended, even in the setting of episodic hepatic encephalopathy.[56]

Distribution of calorie intake

The distribution of calorie intake throughout the day has also been studied. It has been proposed that eating a late evening snack could alleviate the shift towards lipid oxidation by reducing the length of time a patient fasts overnight. Indeed, a late evening meal has been shown to improve the nitrogen balance[57] and raise the nonprotein respiratory quotient.[58] A typical recommendation for patients with advanced liver disease is to consume four to five small meals per day, as well as a late evening snack.

Supplementation with branched-chain amino acids

The usefulness of branched-chain amino acid (BCAA) supplementation in patients with cirrhosis has long been debated. It was proposed that depletion of BCAAs, as seen in many patients with advanced liver disease, might promote the development of hepatic encephalopathy by enhancing the passage of aromatic amino acids across the blood–brain barrier, resulting in the synthesis of false neurotransmitters. For this reason, it was hypothesized that BCAA supplementation might improve hepatic encephalopathy. Early investigations, therefore, focused on BCAAs as a potential treatment for hepatic encephalopathy. Although some controlled trials showed no benefit of BCAAs with respect to mental function,[59] several trials showed a significant improvement in hepatic encephalopathy with BCAA treatment.[60,61] A 2003 review of 11 randomized trials concluded that BCAAs improve hepatic encephalopathy, particularly when administered enterally to patients with chronic encephalopathy.[62]

Although there are conflicting data, there is more evidence of the beneficial effects of BCAAs to support their use in the treatment of malnutrition in patients with advanced cirrhosis. Marchesini *et al.* performed a multicenter, randomized trial examining the role of oral BCAA supplementation in patients with advanced liver disease.[63] The trial consisted of 174 patients with advanced cirrhosis who received 1 year of nutritional supplementation with BCAAs, lactoalbumin, or maltodextrins. BCAA administration was advantageous with regard to rates of mortality, progression of liver failure, and hospital admission. The most significant limitation that the investigators found was poor compliance with the BCAA-enriched diet; in the BCAA group, 15% of patients did not complete the treatment course. Poor compliance was attributed to poor palatability of the BCAA supplement. A recent multicenter, randomized, nutrient-intake-controlled trial demonstrated that oral supplementation with BCAAs for 2 years improved survival, serum albumin concentration, and quality of life in patients with decompensated cirrhosis.[64]

Recent studies advocate the use of nocturnal BCAA administration.[65] It is believed that BCAAs that are consumed during the day are primarily used as a source of energy for physical exercise, whereas when administered at night, BCAAs might be preferentially used for protein synthesis.

Correcting nutrient deficiencies

Nutritional therapy in patients with chronic liver disease should not only focus on treatment of PCM, but should also aim to correct specific nutrient deficiencies. Patients with advanced liver disease commonly develop micronutrient deficiencies. For example, patients with alcoholic liver disease who continue to consume alcohol are particularly at risk for deficiency of thiamine, folate, and magnesium.[66] Most patients with advanced liver disease, but particularly those with cholestatic liver disease, develop a deficiency of fat-soluble vitamins.[67]

Decreased serum vitamin A levels result from fat malabsorption, as well as defective mobilization of vitamin A from the liver.[68] One of the common complications of vitamin A deficiency is night blindness, which has been shown to improve with vitamin A supplementation, generally at a dose of 25,000 units/day for 4–12 weeks.[69] Persistent problems with dark adaptation, despite adequate supplementation, might result from concomitant zinc deficiency.[70] Vitamin A deficiency typically resolves within

2 weeks of liver transplantation.[69] Vitamin A toxicity is a potential risk of vitamin A supplementation. Vitamin A toxicity typically causes elevated transaminase levels and can eventually lead to cirrhosis, chronic hepatitis, or portal hypertension.[70] Although it was traditionally thought that the development of vitamin A toxicity requires doses well in excess of the recommended range, data now suggest that cirrhosis can develop at therapeutic doses of vitamin A (e.g. 25,000 IU/day for 6 years).[71] Liver disease resulting from vitamin A toxicity can persist for up to 1 year after discontinuation of the supplement.

Vitamin D deficiency is another complication of chronic liver disease, resulting primarily from malabsorption; decreased UV light exposure and inadequate dietary intake might also be contributing factors to vitamin D deficiency. Impaired hepatic 25-hydroxylation of vitamin D is also seen in patients with alcoholic cirrhosis.[72] Calcium deficiency, and eventually osteomalacia or osteoporosis, results from decreased intestinal calcium absorption. Up to 43% of patients undergoing transplant evaluation have osteoporosis.[73] There are conflicting data on whether vitamin D supplementation improves osteoporosis in patients with advanced liver disease. It has been suggested that osteoporosis does not respond to vitamin D supplementation in patients with primary biliary cirrhosis,[62] but it can improve in patients with alcoholic liver disease when 25-hydroxyvitamin D supplementation (25–50 mg/day) is taken.[74] A proposed guideline is to supplement all patients who have chronic liver disease with calcium (1 g/day) and vitamin D3 (800 IU/day).[75,76]

Zinc deficiency commonly occurs in patients with cirrhosis and has been implicated in the pathogenesis of hepatic encephalopathy.[77] Zinc supplementation at doses of 600 mg/day for 3 months has been shown to improve mental functioning in patients with hepatic encephalopathy,[78] although other studies show conflicting findings, and the role of zinc in treating hepatic encephalopathy remains controversial.

CONCLUSION

Malnutrition is a well-known complication of advanced liver disease and is associated with detrimental consequences if left untreated. It is, therefore, of critical importance to assess the nutritional status of all patients with chronic liver disease and to optimize nutritional support in these patients. Treatment should focus on maintaining adequate protein and caloric intake and correcting nutrient deficiencies. Strategies include the consumption of frequent small meals and a late evening snack to reduce protein breakdown. When oral intake is insufficient, early implementation of enteral feeding should be considered. The use of BCAAs remains controversial, but the most recent data promote their therapeutic potential. Malnutrition is a potentially reversible condition that, when identified and treated appropriately, can lead to improved outcomes.

KEY POINTS

- Malnutrition is an increasingly recognized complication of chronic liver disease that has important prognostic implications
- Etiologies include poor oral intake, malabsorption, increased energy expenditure, and an altered pattern of fuel consumption
- The nutritional status of all patients with liver disease should be assessed to identify those at risk of developing preventable complications
- Initiating nutritional therapy can reduce the risk of complications and improve the overall mortality rate

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Competing interests
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