

Nutrition in hepatic failure and liver transplantation

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SUMMARY. Chronic liver disorders predispose to complex metabolic disturbances that lead to malnutrition, which is universally present in patients with hepatic failure undergoing liver transplantation and is associated with increased morbidity and mortality. The nutritional status is an important factor for survival after liver transplantation. Aggressive nutritional support is essential during all phases of liver transplantation. This review article focuses on nutritional problems seen in patients with hepatic failure, with emphasis on the nutritional assessment and support of patients before and after liver transplantation.

Key words: Chronic liver disorders, hepatic failure, liver transplantation.

RESUMEN. La enfermedad hepática crónica predispone a alteraciones metabólicas que conducen a la malnutrición, la cual se evidencia de manera universal en los pacientes con insuficiencia hepática que se someten a un trasplante de hígado y está asociada con un incremento en la morbilidad y la mortalidad. El estado nutricional es un factor importante para la supervivencia luego del trasplante hepático. El soporte nutricional intenso es esencial durante todas las fases del trasplante hepático. Este artículo de revisión explora los problemas nutricionales que ocurren en pacientes con insuficiencia hepática, poniendo énfasis en la evaluación y el soporte nutricional antes y después del trasplante hepático.

Palabras clave: Enfermedad hepática crónica, insuficiencia hepática, trasplante hepático.

Malnutrition is a common complication of hepatic failure and progressive deterioration of the nutritional status has been associated with poor outcome in patients with cirrhosis.¹

The liver is the metabolic organ that regulates complex biochemical and physiologic pathways that control the metabolism of carbohydrate, fat, and protein. Protein-energy malnutrition (PEM) is highly prevalent in all forms of chronic liver disease² and has been reported to be as high as 100% in patients undergoing liver transplantation (LT).¹⁻³ PEM has been associated with decreased patient and graft survival following LT.³

The pathogenesis of malnutrition in cirrhosis is complex and multifactorial (*Table 1*), and is influenced by metabolic disturbances, increased energy expenditure, reduced calorie intake and inadequate intestinal absorption of nutrients.

METABOLIC DISTURBANCES

Patients with cirrhosis have abnormal carbohydrate, lipid and protein metabolism, which is associated with muscle depletion.⁴ Muscle wasting is an important manifestation of hepatic failure and is always present in patients undergoing liver transplant evaluation.^{5,6}

Cirrhotic patients tend to use fat as a substrate for energy and may develop a fasting catabolic state of starvation because of a lack of adequate glycogen stores,⁷ leading to increased gluconeogenesis, which exacerbates muscle wasting. A late evening snack appears to improve this catabolic starvation phenomenon in cirrhosis.

Patients with ESLD may develop glucose intolerance and insulin resistance, with a reported prevalence of diabetes mellitus in cirrhosis of 38%.^{8,9}

TABLE 1
ETIOLOGY OF MALNUTRITION IN PATIENTS WITH
HEPATIC FAILURE

Decreased oral intake
Anorexia and early satiety
Dietary restriction (sodium and protein)
Taste abnormalities
Ascites/encephalopathy
Gastroparesis, nausea and vomiting
Nutrient malabsorption
Pancreatic insufficiency
Cholestatic liver disease
Drug induced losses
Neomycin, lactulose, diuretics

Protein catabolism is increased in decompensated liver disease. There is an imbalance between branched-chain amino acids (BCAA) (leucine, isoleucine, and valine) and aromatic amino acids (AAA) (phenylalanine, methionine, and tyrosine) as the expected ratio of 3.5:1 falls to 1:1 in patients with hepatic failure, allowing increased cerebral uptake of AAA's, which promote the synthesis of false neurotransmitters (octopamine, phenylethylamine, and phenylethanolamine) that may affect neurocognitive function.

INCREASED ENERGY EXPENDITURE

The body composition is represented by two compartments: the lean body mass (LBM), and fat mass. LBM is made by muscle mass, visceral proteins, glycogen, and intracellular water. Body cell mass (BCM) is the active metabolic compartment, which is responsible for the basal energy expenditure (BEE). BEE can be predicted with several formulas, such as the Harris-Benedict equation: Men: $66.5 + [13.8 \times \text{Wt (kg)}] + [5.0 \times \text{Ht (cm)}] - [6.8 \times \text{Age (yr)}] = \text{kcal/d}$. Women: $655.1 + [9.6 \times \text{Wt (kg)}] + [1.8 \times \text{Ht (cm)}] - [4.7 \times \text{Age (yr)}] = \text{kcal/d}$, or can be measured with indirect calorimetry. Predicted BEE from the Harris-Benedict equation may be different from measured values in patients with hepatic failure as the formula is based on weight, which can be altered by fluid retention, therefore, BEE should be measured and not predicted in patients with hepatic failure and ascites.^{10,11}

BEE measurement in liver disorders is variable; hypermetabolism has been described in 34% of patients with cirrhosis and represents a prognostic factor inde-

pendent of the Model of End-stage Liver Disease (MELD) or Child-Pugh scores.^{7,12} Cirrhotic patients who are hypermetabolic have a more rapid progression to liver transplantation or death.¹² Hypermetabolism has been associated with decreased survival after LT.¹³

REDUCED CALORIC INTAKE

Patients with chronic liver disease frequently have early satiety, altered gastric motility, taste abnormalities, nausea and anorexia, leading to an inadequate oral intake.^{14,15} Elevated inflammatory cytokines (tumor necrosis factor, interleukin-1b, and interleukin -6) have been described in patients with cirrhosis and may have an anorexic effect.¹⁶ Other factors associated with the progression of anorexia include unpalatable diets related to sodium and protein restriction.

Patients with tense ascites have reduced postprandial gastric volumes and large-volume paracentesis increases fasting gastric volumes, leading to an improved oral intake.¹⁷

DECREASED INTESTINAL ABSORPTION

Abnormal absorption of nutrients occurs in patients with chronic cholestatic disorders, such as primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune cholangiopathy. Inadequate absorption of fat-soluble vitamins (A, D, E, and K) is most common in alcoholic patients with pancreatic insufficiency.

Celiac disease has been associated with chronic autoimmune hepatitis, primary sclerosing cholangitis,¹⁸ and non-alcoholic steatohepatitis (NASH).¹⁹ Elevated liver enzymes had been described in 40% of patients with untreated celiac disease, which frequently improve after the institution of a gluten-free diet.¹⁸

ASSESSMENT OF NUTRITION STATUS

Assessment of the nutritional status of patients with hepatic failure is challenging because weight changes are affected by fluctuations in fluid retention and traditional parameters such as serum protein concentrations, total lymphocyte count, delayed hypersensitivity testing, and creatinine-height index are affected by liver disease.

A thorough clinical and nutritional evaluation is required in all patients with hepatic failure as malnutrition is multifactorial. A dietary history is essential to assess weight changes, taste abnormalities, early satiety, degree of anorexia and chronic diarrhea. Physical exam may

show stigmata of chronic liver disease, such as palmar erythema, spider angiomas, temporal muscle hypotrophy, loss of subcutaneous fat, and muscle wasting; subtle changes in oral mucosa, skin, and hair may suggest nutrient deficiencies. Zinc deficiency is frequent in decompensated cirrhosis and has been associated with changes in smell, taste, protein metabolism, and hepatic encephalopathy.²⁰

Anthropometric measurements include triceps skin fold and mid-arm muscle circumference are still useful to assess subcutaneous fat and muscle mass.²¹ Mid-arm-muscle circumference and handgrip strength measurements appear to be sensitive markers of BCM depletion.²²

The Subjective Global Assessment (SGA), a nutritional evaluation based on present weight, height, nutritional history, changes on physical examination and existing medical conditions has been found to be a reliable tool to evaluate the nutritional status of cirrhotic patients undergoing liver transplant evaluation.^{23,24} Patients are classified as being well nourished or having mild, moderate, or severe malnutrition.

Other noninvasive methods include bioelectrical impedance analysis (BIA), it evaluates the body electrical conductivity and resistance (impedance). Although BIA determines lean body mass and fat in patients with hepatic failure, it's accuracy in patients with edema and ascites is questionable.²⁵

Dual-energy x-ray absorptiometry (DEXA) has been used to measure total body bone mineral, fat and fat free mass (FFM), however, it is also influenced by fluid retention.²⁶ In patients with hepatic failure, DEXA has been found to be a good method to assess both fat mass and fat-free mass, however, it cannot provide accurate information about the quality of the FFM, particularly in re-

lation to its water content.²⁷

MALNUTRITION BEFORE LIVER TRANSPLANTATION

Liver transplantation (LT) revolutionized the management of liver disease.²⁸ The nutritional status of patients with hepatic failure undergoing liver transplant evaluation continues to deteriorate, therefore, once malnutrition is diagnosed, efforts should be made to correct any vitamin and mineral deficiencies present and prevent further complications (*Table 2*).³

The main purpose of nutritional support before liver transplantation is to prevent further nutrient and muscle depletion. Improvement in nutritional status influences liver metabolism and immune status and may decrease the risk of infection.¹¹

The energy needs of cirrhotic patients are highly variable and can be determined by indirect calorimetry. In patients with decompensated cirrhosis, BEE can be calculated with the Harris-Benedict formula using ideal body weight; the total amount of calories provided should be at least 1.2 times the BEE (30 to 35 kcal/kg/d) and 60 % should be administered as simple and high complex carbohydrates.¹¹

Protein restriction should not be routinely established in all patients with hepatic failure. Protein intake should be at least 1 g/kg/day, and 24-hour urinary urea nitrogen can be measured to assess the catabolic rate in patients with preserved renal function. Further protein intake can be adjusted accordingly, with progressive increments in protein supplementation up to 1.8 to 2.0 g/kg/day as tolerated.

Liver osteodystrophy (osteopenia and osteoporosis) is highly prevalent in patients with cirrhosis and repre-

TABLE 2
NUTRITIONAL RECOMMENDATIONS FOR PATIENTS
WITH HEPATIC FAILURE UNDERGOING LIVER TRANSPLANT EVALUATION

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- Hepatic encephalopathy should be treated aggressively before protein restriction is instituted.
 - Protein restriction should not be performed routinely to prevent aggravating protein deficiency.
 - Smaller and more frequent meals are better tolerated.
 - Monitor calorie count and consider enteral feeding supplementation if oral intake is suboptimal.
 - Water restriction is not recommended unless serum sodium is less than 125 mEq/L.
 - Dietary sodium restriction to less than 2 gm/day in patient with ascites.
 - BEE should be measured and not predicted in patients with edema and ascites.
 - Energy needs are variable and best determined by indirect calorimetry.
 - Cirrhotic patients should take a daily multivitamin.
 - Calcium supplementation (1200-1500 mg/day) in patients with osteopenia.
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TABLE 3
NUTRITIONAL RECOMMENDATIONS AFTER LIVER TRANSPLANTATION

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- Correct nutritional deficiencies in the immediate post-transplant phase
 - Early dietary consultation to prevent excessive weight gain
 - Screening for metabolic bone disease, bisphosphonates in patients with osteoporosis
 - Tight glucose control in patients with diabetes mellitus
-

sent a major cause of morbidity after LT.²⁹ Osteoporosis has been described in 12%-55% of patients with cirrhosis and increase the risk of vertebral fractures.³⁰ Serum vitamin D measurements should be performed in patients with osteoporosis and replaced if deficient. Calcium supplementation is recommended in patients with osteopenia (1,200-1,500 mg/day) and in combination with bisphosphonates in patients with osteoporosis or history of fractures.³¹

Adequate oral intake should be monitored with calorie counts, if suboptimal, enteral feedings should be initiated. The efficacy of tube-feeding formulas has been evaluated in patients with chronic liver disease, and the best results were seen in patients with moderate to severe PEM treated with aggressive nutritional intervention.¹⁶ Feeding tubes do not increase risk of esophageal variceal hemorrhage, but may be associated with an increased risk of sinusitis with long-term use. Standard amino acid formulas are usually well tolerated, which contain a significant proportion of BCAA's, preparations with higher concentrations should be reserved for patients with refractory hepatic encephalopathy.¹¹ Late evening snacks with a BCAA mixture have been suggested to improve serum albumin levels, nitrogen balance and energy metabolism when compared to ordinary food in patients with cirrhosis.³²

Total parenteral nutrition (TPN) should be considered when enteral feeding is contraindicated to provide adequate nutritional support and maintain the metabolic needs of hospitalized cirrhotic patients. TPN is more expensive and has been associated with higher incidence of infections and electrolyte imbalances than enteral nutrition.

NUTRITIONAL MANAGEMENT AFTER LIVER TRANSPLANTATION

Liver transplantation leads to a significant improvement of nutritional deficiencies and metabolic disturbances in patients with hepatic failure; however, several factors

such as preoperative malnutrition, stress from surgery and immunosuppressive medications enhance the need for nutritional support after transplantation.³³

Protein catabolism is increased immediately following liver transplantation.³⁴ Due to increased nitrogen losses, liver transplant patients should receive 1.5 to 2.0 grams of protein per kilogram of dry weight in the immediate post-transplant phase.²³ Energy requirements are not significantly higher in the uncomplicated patient after transplantation; calories should be provided at approximately 120%-130% of the calculated BEE.²³

Early after transplant, oral nutritional supplements or nasoenteric tube feedings can be provided and are preferred over TPN, unless the patient has a nonfunctional gastrointestinal tract. Enteral feedings have been associated with decreased post-operative infection rates,³⁵ and less metabolic complications following transplant when compared to TPN.³⁶

Patients should be advanced from nutritional support to oral diets as soon as tolerated after liver transplantation. Smaller and more frequent feedings are helpful. Nasoenteric feeding tubes should not be discontinued until the patients are able to maintain an adequate oral intake. Electrolyte disturbances in the acute post-transplant period are common and may be related to abdominal drains, gastrointestinal losses, fluid overload; serum potassium, phosphorus, and magnesium levels should be monitored closely and replaced if needed.

Prevention is the main goal of long term nutritional support after liver transplantation (*Table 3*). Metabolic complications such as diabetes mellitus, hypercholesterolemia, obesity and hypertension are common following liver transplantation, increasing morbidity and mortality.³⁷

Obesity is common after liver transplantation; the greatest weight gain occurs after the first 6 months.³⁸ Nutritionist consultation with dietary modifications should be implemented early to minimize the long-term morbidity and mortality associated with obesity.

Hyperlipidemia also occurs frequently in post-liver transplant patients³⁹ and represents a modifiable risk fac-

tor for cardiovascular disease. Pre-transplant serum cholesterol level is an independent risk factor for post-transplant hypercholesterolemia; the incidence of elevated cholesterol after liver transplant has been reported to be 43%.⁴⁰

The incidence of new onset diabetes mellitus after liver transplantation has been reported between 7 to 33 %, and is higher in individuals older than 45 years and in patients with chronic hepatitis C (41, 42).

Bone mineral density (BMD) decreases after liver transplantation (31). Risk factors for bone loss include prolonged steroid use, malnutrition, muscle wasting, pre-transplant osteopenia and immunosuppression therapy. Rapid bone loss occurs 3 to 6 months after liver transplantation, with the highest incidence of fractures seen in 20 to 30% of patients in the first year.³⁰ Bisphosphonate therapy may prevent bone loss after LT and represent the most effective agents for the treatment of post-transplant osteoporosis.^{43,44}

CONCLUSIONS

Nutritional therapy is essential in patients with hepatic failure. An early and multidisciplinary approach involving clinicians, gastroenterologist/hepatologists, dietitians and nurse practitioners should be established. Nutritional support in the acute post transplant phase can reduce complications; long-term management should aim prevent metabolic complications. Adequate nutritional support will lead to improved outcomes and better quality of life after liver transplantation.

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