Turk J Gastroenterol *2015; 26: 291-6*

Review

Importance of malnutrition in patients with cirrhosis

Hüseyin Savaş Göktürk[1], *Haldun Selçuk*[2]

[1]Department of Gastroenterology, Başkent University Faculty of Medicine, Konya, Turkey
[2]Department of Gastroenterology, Başkent University Faculty of Medicine, Ankara, Turkey

ABSTRACT

Malnutrition is common in patients with chronic liver disease and is associated with poor outcomes. Inadequate intake, poor quality diet, maldigestion, malabsorption, altered macronutrient metabolism, and hypermetabolism all contribute to the development of malnutrition in this patient population. Although it is generally easy to detect, clinicians often overlook malnutrition and its measurement is complicated by the lack of a simple, standardized diagnostic method. Early detection of malnutrition and multidisciplinary treatment approaches greatly increase the probability for successful outcomes.

Keywords: Liver cirrhosis, malnutrition, child score, MELD score

INTRODUCTION

Malnutrition develops when the body receives insufficient nutrients, such as carbohydrate, protein, essential fatty acids, amino acids, micronutrients, and vitamins, to maintain healthy tissues and organ function. The liver plays a crucial role in the regulation of the body's nutritional status. Patients with chronic liver disease are often malnourished, and there is a correlation between the severity of liver disease and degree of malnutrition. Furthermore, there is a correlation between the degree of malnutrition and increased rates of in-hospital mortality, longer hospital stays, higher post-transplant morbidity and mortality, and greater costs (1).

It has been reported that the prevalence of clinically significant malnutrition varies from 65% to 100% among patients with chronic liver disease (2,3). The importance of the nutritional status in patients with cirrhosis is often unappreciated by clinicians. In 1964, Child's score was proposed to predict outcomes after portal hypertension surgery in patients with cirrhosis. Child's score originally included nutrition as a variable; however, because of its subjective nature, malnutrition was removed in subsequent modifications and replaced with prothrombin time (4). The Model for End-Stage Liver Disease score utilizes several factors to assess the severity of liver disease; however, malnutrition is excluded from its calculation. Therefore, patients with reduced skeletal muscle mass and macro- and micro-nutrient deficiencies that negatively affect the outcomes of liver transplantation are frequently referred for liver transplant evaluation. Nevertheless, the impact of malnutrition is not widely recognized in clinical practice (3,5).

Etiology and mechanism of malnutrition

Malnutrition in patients with chronic liver disease results from a variable combination of inadequate intake, poor quality diet, maldigestion, malabsorption, altered macronutrient metabolism, and hypermetabolic state (6,7). These are summarized in Table 1.

Inadequate and/or poor quality oral intake

Patients with cirrhosis usually report poor appetites that may be caused by the anorexigenic effects of inflammatory mediators and hormones. Compared with healthy individuals, patients with cirrhosis have decreased ghrelin levels and increased plasma TNF-α and leptin levels. Furthermore, anorexia may be attributed

Address for Correspondence: Hüseyin Savaş Göktürk, Department of Gastroenterology, Başkent University Faculty of Medicine, Konya, Turkey
E-mail: savasgokturk@yahoo.com

Received: January 22, 2015 **Accepted:** April 13, 2015 **Available Online Date:** June 2, 2015

Table 1. Etiology of malnutrition in liver cirrhosis

I- INADEQUATE INTAKE AND/OR POOR QUALITY DIET
a. Anorexia due to disease
b. Abnormal taste (changes in taste perception)
c. Socioeconomic factors
d. Decreased oral intake (because of hepatic encephalopathy, early satiety, and abdominal distension due to ascites and splenomegaly)
e. Increased gastric emptying time
f. Iatrogenic causes (sodium restriction for the treatment of ascites, increased starvation for tests and procedures, unnecessary protein restrictions for hepatic encephalopathy management, and medications)
II- MALDIGESTION AND MALABSORPTION
a. Decreased intestinal luminal bile salt availability and decreased micelle formation (particularly in cholestatic liver diseases)
b. Portal hypertensive gastropathy and enteropathy
c. Portosystemic shunts
d. Pancreatic insufficiency (particularly in alcoholic liver disease)
e. Medications
III- ALTERED MACRONUTRIENT METABOLISM
a. Protein metabolism
i. Increased catabolism (gluconeogenesis, proteolysis)
ii. Increased utilization of branched-chain amino acids (particularly leucine)
iii. Decreased ureagenesis
b. Carbohydrate metabolism
i. Increased gluconeogenesis
ii. Decreased glycogenolysis
iii. Impaired hepatic glycogen synthesis
iv. Insulin resistance (decreased peripheral utilization of glucose)
c. Lipid metabolism
i. Increased lipolysis
ii. Enhanced turnover and oxidation of fatty acids
iii. Increased ketogenesis
IV- HYPERMETABOLISM

to infections, medications, or underlying depression. Sodium-restricted diets, vitamin A and zinc deficiencies, and neurotoxins can lead to taste alteration and cause foods to be unpalatable. Gastroparesis, tense ascites, and small bowel dysmotility also cause nausea and early satiety. Periods without oral intake in preparation for tests and procedures, unnecessary protein and calorie restrictions for the treatment of hepatic encephalopathy (HE), and medications account for some iatrogenic causes of poor oral intake. All of these factors may exist to varying degrees in patients with cirrhosis (8).

Maldigestion and malabsorption

Decreases in intestinal luminal bile salt availability and micelle formation can cause fat malabsorption in patients with cholestasis. As liver function deteriorates, more portosystemic shunts develop, causing nutrients to bypass the liver without metabolic processing. Portal hypertensive gastropathy and enteropathy, medications that affect intestinal flora (e.g., antibiotics and nonabsorbable disaccharides), and pancreatic insufficiency (particularly in alcoholic liver disease) also lead to malabsorption by different mechanisms (6,9).

Altered macronutrient metabolism

Patients with cirrhosis have significantly altered protein metabolism. Increasing proteolysis and utilization of branched chain amino acids (BCAAs) may lead to accelerated protein breakdown from muscle cells as a source of substrate. Glucose metabolism is altered in several ways, including a reduction in the ability of hepatocytes to store, synthesize, and breakdown glycogen; inappropriate degradation of glycogen by the liver

leads to increased gluconeogenesis; and decreased glycogenolysis as fat replaces carbohydrate as a fuel source. Increased lipolysis, enhanced turnover and oxidation of fatty acids, and ketogenesis are because of lipid metabolism alterations. After 2 to 3 days of starvation, healthy subjects demonstrated changes in their rates of fat and protein metabolism; however, similar changes are commonly found in patients with cirrhosis following an overnight fast (3,7).

Hypermetabolism

Resting energy expenditure (REE) is the amount of energy expended during the performance of vital organ functions with the body at rest. It is predictively measured with the Harris–Benedict Equation using the parameters of weight, height, and sex. Increased, decreased, and normal REE can all occur in patients with cirrhosis depending on variables, such as the presence of infection, ascites, and the degree of malnutrition. The respiratory quotient is a unit less number estimated from carbon dioxide production that is used to calculate basal metabolic rate. In advanced liver disease, its value is 0.6–0.7, which is in the hypermetabolic range (9-11).

Assessment of nutritional status

Assessment of nutritional status and the requirement for nutritional support is important because the nutritional state correlates with both prognosis and potential complications of cirrhosis (e.g., ascites and HE). Although malnutrition is increasingly being acknowledged among clinicians and signs of malnutrition may be obvious in many cases of end-stage liver disease, a high index of clinical suspicion is necessary, specifically in patients with compensated liver cirrhosis. Accurate nutrition assessment is also of paramount importance because erroneous estimations of body composition and nutritional status may lead to malnutrition. Because albumin and prealbumin are synthesized by the liver, utilizing them as biochemical markers of nutritional status may lead to inaccurate assessments and erroneous estimations of body composition.

Although traditional anthropometric measures, such as weight, mid-arm circumference, and triceps skin-fold thickness, may be adequate for the determination of nutritional status of patients with cirrhosis, the reliability of these factors is affected by fluid retention, edema, and ascites. Bioelectrical impedance analysis is commonly used to estimate body composition; however, this method is also challenging owing to the prevalence of ascites or edema in this population (8,9,12). Serial measurements with a handgrip strength test have also been used in nutritional status evaluation. However, this heavily relies on patient volition and may overestimate the prevalence of malnutrition, particularly in patients with HE (7,13).

Subjective global assessment (SGA) is a bedside clinical technique that assesses a patient's nutritional status by a focused history (information on dietary intake and weight changes during the previous six months) and physical examination (subcutaneous fat loss, signs of muscle wasting, edema, and ascites) (14,15). Although SGA is an adequate bedside assessment tool, previous studies have reported that it can underestimate the frequency and severity of malnutrition in the earlier stages of cirrhosis. Figuiredo et al. (16) suggested that nutritional intervention should be automatically initiated in patients with Child's class B or C cirrhosis owing to the prevalence of malnutrition in these groups with more extensive nutritional assessments for class A patients in order to provide timely support. The biggest disadvantage of SGA may be the steep learning curve for the operator; the diagnostic value of the test improves with increased repetition and experience. A combination of subjective and objective data is required for a comprehensive analysis of a patient's nutritional status (16-18).

Some authors as well as the European Society for Clinical Nutrition and Metabolism (ESPEN) 2006 guidelines recommend the use of SGA, anthropometric analysis, or the handgrip strength test to identify patients with cirrhosis who are at risk of malnutrition (9,19).

Nutritional recommendations

Energy

Energy requirements of patients with cirrhosis should be based on the stage of cirrhosis, presence of ascites, and degree of malnutrition. Most guidelines recommend an intake of 35–40 kcal/kg/day. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend 25–35 kcal/kg per day for patients without encephalopathy and 35 kcal/kg/day for those with acute encephalopathy. The 2006 ESPEN guidelines recommend a much higher energy intake of 35–40 kcal/kg/day for all patients with stable cirrhosis. The ESPEN recommendations appear to focus on the prevention and treatment owing to the prevalence of malnutrition among patients with cirrhosis. Furthermore, the ASPEN guidelines recommend 30–40 kcal/kg/day for stable and malnourished patients. Although estimating energy requirements with predictive equations is a common clinical practice, it is important to continuously monitor weight trends and other clinical parameters to maintain the nutritional status (19,20).

Macronutrients

There is an increased prevalence of diabetes mellitus and insulin resistance in patients with cirrhosis. These patients also have limited glycogen stores that is responsible for an increased risk of hypoglycemia. However, carbohydrate restriction is not recommended for patients with cirrhosis, and they are advised to have frequent small meals and snacks to reduce the risk of hypoglycemia. Guidelines of ESPEN recommend that carbohydrates account for 45%–65% of the total daily calories, the same as for healthy adults (8,19).

Historically, restriction of dietary protein was a mainstay of management for patients with cirrhosis and HE and was

thought to improve prognosis and mental status. Recent studies have demonstrated that protein restriction can lead to nutritional deterioration and worsening of HE. Current consensus for recommended protein intake for patients with cirrhosis is between 1.2 and 1.5 g of protein per kilogram of body weight per day. This is higher than the 0.8 g/kg/day recommended for healthy individuals because of increased gluconeogenesis, muscle catabolism, and decreased absorption that occur in patients with cirrhosis. The type of protein (vegetable vs. animal) is less important than the amount of protein in the diet. Some patients tolerate vegetable proteins better than animal proteins; vegetable proteins may increase intraluminal pH and help in preventing constipation. However, meat protein is more bioavailable; if the patient is not constipated or intolerant of animal protein, it is safe and may be more compatible with his or her usual premorbid diet (3,6).

In protein intolerant patients with severe acute HE (grade III-IV), protein intake may be reduced (0.6–0.8 g/kg/day) for short periods until the cause of encephalopathy is determined. For all other conditions, the current recommended protein intake is 1.0–1.5 g/kg/day (9,21). Leucine, isoleucine, and valine are BCAAs and are essential for protein synthesis. However, these cannot be synthesized de novo and must be obtained from dietary sources. Plasma concentrations of BCAAs decrease in patients with cirrhosis, portosystemic shunts, and hyperammonemia. Ammonia and the aromatic amino acids (AAAs) phenylalanine, tyrosine, and tryptophan are metabolized by the liver and accumulate because of impaired hepatocyte function and portal shunting. Because BCAAs and AAAs compete for the same blood–brain barrier transporter, it has been suggested that a decreased plasma ratio of BCAA to AAA may cause HE. Some studies have demonstrated improvements in HE with improved nutritional parameters. Unfortunately, BCAA preparations have important limitations: poor palatability, high cost, and lack of availability in Turkey (22,23). Moreover, alterations in lipid metabolism occur by several mechanisms, and guidelines suggest that fat should be provided at a minimum of 25%–30% of the total daily calories (8,19).

Frequency of food intake is as important as the quantity and quality of foods consumed. Frequent small feedings similar to that recommended in the diabetic diet can prevent a metabolic shift to starvation in patients with cirrhosis (3). The tolerance of patients with cirrhosis to starvation is considerably lower than that in healthy subjects. After only several hours of fasting, there is an early shift from carbohydrate to fat metabolism. This shift does not occur until after 2 to 3 days of fasting in healthy subjects. Patients with cirrhosis are very susceptible to early morning hypoglycemia. Several studies have demonstrated that bedtime supplementation with a late-night snack containing carbohydrate and BCAA-rich protein can help prevent hypoglycemia and improve protein stores (24,25).

Enteral nutritional supplementation (oral or by tube) should be initiated if the patient is unable to maintain sufficient dietary intake. Oral intake is commonly restricted in patients in preparation for tests and procedures. It has been suggested that feeding tubes (not nasogastric tubes) can be placed even in the presence of esophageal varices (3,26).

The use of total parenteral nutrition (TPN) should be reserved for patients with contraindications to oral or enteral nutrition, such as prolonged ileus, intestinal ischemia, and severe malabsorption. TPN does not correct malnutrition faster or more completely than tube feedings or enteral supplementation. In addition, TPN may increase the risk of infection, particularly catheter-related infections, because patients with cirrhosis have impaired immunity. Recent ESPEN guidelines for Child's grade C cirrhosis include the recommendation that TPN be considered after surgery for patients who cannot tolerate oral and/or enteral nutrition. Nutritional support is indicated following liver transplantation with TPN being a clear second choice to enteral nutrition (19).

Micronutrients

Micronutrient deficiencies are common in cirrhosis because the liver is involved in micronutrient transport, storage, and metabolism. Although water-soluble vitamin deficiencies are more common in alcoholic liver disease, they have also been reported in cirrhosis of a non-alcoholic etiology. Impairment of enterohepatic circulation and recurrent antibiotic courses for HE or infections can cause folate, vitamin B 12, and vitamin A deficiencies. Recent studies have demonstrated that both deficiency and insufficiency of vitamin D are highly prevalent in patients with cirrhosis with the degree of deficiency related to the degree of liver dysfunction and to mortality (3,27).

Probiotics/Synbiotics

In patients with cirrhosis, disrupted intestinal microbiota and bacterial overgrowth are implicated in the development of intestinal wall permeability, bacterial translocation, secondary infections, and fat malabsorption (9,28). Observation of changes in gut micro flora in patients with HE led to treatment with modulation of gut flora with probiotics, prebiotics, or synbiotics. Several studies have demonstrated improvement of HE symptoms with synbiotic and probiotic treatment, and some have demonstrated improvement in liver function as well. If side effects occur with the use of probiotics or synbiotics, they tend to be mild, leading to their increased use in clinical practice in an effort to manage HE and reduce infections (6,29).

General nutritional recommendations are summarized in Table 2.

CONCLUSION

Malnutrition is common in patients with chronic liver disease and is associated with poor outcomes. Inadequate intake, poor quality diet, maldigestion, malabsorption, altered macronutrient metabolism, and hypermetabolism all contribute to the development of malnutrition in this patient population. Although it is generally easy to detect, clinicians often overlook malnutrition, and its measurement is complicated by the lack

Table 2. Recommendations for the nutrition of patients with liver cirrhosis

GENERAL PRINCIPLES
Assume that all patients with liver cirrhosis have malnutrition.
Educate patients regarding nutrition (frequent small feedings, carbohydrate-rich bedtime snacks, food diaries, and dietary consultation).
Avoid prolonged periods of fasting.
Avoid unnecessary protein restrictions.
DIETARY GOALS
MACRONUTRIENTS:
ENERGY: 25–40 kcal/kg/day
PROTEIN: 1.2–1.5 g/kg/day (for medically refractory hepatic encephalopathy: 0.6–0.8 g/kg/day)
CARBOHYDRATE: 45%–65% of the total daily calories
FAT: 25%–30% of the total daily calories
MICRONUTRIENTS:
FAT SOLUBLE VITAMINS: up to the recommended dietary allowance
ZINC: up to the recommended dietary allowance
FOLIC ACID: up to the recommended dietary allowance
PROBIOTICS: undetermined

of a simple, standardized diagnostic method. Impaired hepatocyte functions disrupt nutrient balance and metabolism that, in addition to ascites, protein catabolism, and nutrient deficiencies, can lead to HE. Studies have demonstrated that early detection and the treatment of malnutrition is imperative to improve patient outcomes.

In summary, healthcare providers should assume that all patients with cirrhosis are malnourished to some degree, and SGA could be used as a first line diagnostic method. Early detection of malnutrition and multidisciplinary treatment approaches greatly increase the chance for successful outcomes.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - H.S.G.; Design - H.S.G.; Supervision - H.S.; Resource - H.S.G.; Materials - H.S.G.; Data Collection &/or Processing - H.S.G., H.S.; Analysis &/or Interpretation - H.S.G.; Literature Search - H.S.G.; Writing - H.S.G., H.S.; Critical Reviews - H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. Liver Int 2009; 29: 1396-402. **[CrossRef]**
2. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: results of a prospective study. Nutrition 2003; 19: 515-21. **[CrossRef]**
3. Sasaki A. Nutrition in patients with cirrhosis. In: Zaman A, ed. Managing the Complications of Cirrhosis: A Practical Approach. 1st ed. Thorafore, NJ, USA: Slack Incorporated; 2012; 19-27.
4. Child CG. Surgery and portal hypertension. In: Child CG, ed. The Liver and Portal Hypertension. Philadelphia, PA: WB Saunders; 1964; 50-72.
5. Tsien C, Garber A, Narayanan A, et al. Post-liver transplantation sarcopenia in cirrhosis: a prospective evaluation. J Gastroenterol Hepatol 2014; 29: 1250-7. **[CrossRef]**
6. Bémeur C, Desjardins P, Butterworth RF. Role of nutrition in the management of hepatic encephalopathy in end-stage liver failure. J Nutr Metab 2010; 2010: 489823. **[CrossRef]**
7. Saunders J, Brian A, Wright M, Stroud M. Malnutrition and nutritional support in patients with liver disease. Frontline Gastroenterol 2010; 1: 105-11. **[CrossRef]**
8. Mouzaki M, Ng V, Kamath BM, Selzner N, Pencharz P, Ling SC. Enteral energy and macronutrients in end-stage liver disease. JPEN J Parenter Enteral Nutr 2014; 38: 673-81. **[CrossRef]**
9. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol 2012; 10: 117-25. **[CrossRef]**
10. Kondrup J, Müller MJ. Energy and protein requirements of patients with chronic liver disease. J Hepatol 1997; 27: 239-47. **[CrossRef]**
11. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr 2007; 85: 1257-66.
12. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr 2010; 34: 156-9. **[CrossRef]**
13. Alvares-da-Silva MR, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical

outcome in cirrhotic outpatients. Nutrition 2005; 21: 113-7. **[CrossRef]**
14. Hasse JM. Diet therapy for organ transplantation. A problem-based approach. Nurs Clin North Am 1997; 32: 863-80.
15. Mahan LK, Escott-stump S. Krause's food nutrition and diet therapy. 10th ed. Philadelphia, PA: WB Saunders Company, 2000.
16. Figueiredo FA, Perez RM, Freitas MM, Kondo M. Comparison of three methods of nutritional assessment in liver cirrhosis: subjective global assessment, traditional nutritional parameters, and body composition analysis. J Gastroenterol 2006; 41: 476-82. **[CrossRef]**
17. Taniguchi E, Kawaguchi T, Itou M, et al. Subjective global assessment is not sufficient to screen patients with defective hepatic metabolism. Nutrition 2011; 27: 282-6. **[CrossRef]**
18. Morgan MY, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. Hepatology 2006; 44: 823-35. **[CrossRef]**
19. Plauth M, Cabré E, Riggio O, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr 2006; 25: 285-94. **[CrossRef]**
21. Bianchi GP, Marchesini G, Fabbri A, et al. Vegetable versus animal protein diet in cirrhotic patients with chronic encephalopathy. A randomized cross-over comparison. J Intern Med 1993; 233: 385-92. **[CrossRef]**
22. Les I, Doval E, García-Martínez R, et al. Effects of branched-chain amino acids supplementation in patients with cirrhosis and a previous episode of hepatic encephalopathy: a randomized study. Am J Gastroenterol 2011; 106: 1081-8. **[CrossRef]**
23. Koretz RL, Avenell A, Lipman TO. Nutritional support for liver disease. Cochrane Database Syst Rev 2012; 5: CD008344. **[CrossRef]**
24. Nakaya Y, Okita K, Suzuki K, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition 2007; 23: 113-20. **[CrossRef]**
25. Plank LD, Gane EJ, Peng S, et al. Noctural nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology 2008; 48: 557-66. **[CrossRef]**
26. Purnak T, Yilmaz Y. Liver disease and malnutrition. Best Pract Res Clin Gastroenterol 2013; 27: 619-29. **[CrossRef]**
27. Lim LY, Chalasani N. Vitamin D deficiency in patients with chronic liver disease and cirrhosis. Curr Gastroenterol Rep 2012; 14: 67-73. **[CrossRef]**
28. Gupta A, Dhiman RK, Kumari S, et al. Role of small intestinal bacterial overgrowth and delayed gastrointestinal transit time in cirrhotic patients with minimal hepatic encephalopathy. J Hepatol 2010; 53: 849-55. **[CrossRef]**
29. Liu Q, Duan ZP, Ha DK, Bengmark S, Kurtovic J, Riordan SM. Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004; 39: 1441-9. **[CrossRef]**