Review Article

# Understanding Nutritional Issues in Cirrhosis of Liver

**Anup Kumar Das**[1]

**Cirrhosis of liver is a huge health burden in our country. It has a multitude of problems arising out of hepato-cellular damage and portal hypertension. Although the curative treatment remains liver transplant in cases which are usually advanced when first seen, the majority of cases need multipronged conservative treatment. Being a catabolic condition, malnutrition is very common but often under-evaluated and not adequately treated. It is now established that malnutrition, which has a number of etiologies in this disease, is deleterious in cirrhosis of liver. Understanding the mechanism, extent and degree of malnutrition in cirrhosis is essential to evaluate the condition for formulating a better management strategy as far as nutritional support is involved. This is very important as macro and micro nutrient deficiencies are very common which should be corrected as far as possible in a rationale manner at the earliest, with the help of a qualified nutritionist. Western guidelines exist wherein specific and succinct protocols are detailed. In cirrhosis of liver a compact evaluation of nutritional status should be undertaken so that a better quality of life and disease prognosis is achieved.**

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Nutrition involves assimilation of enteral or parenteral food by a living organism for maintenance, growth, reproduction, and tissue repair, both in health and disease. When the food and nutrient intake is inadequate or unbalanced; or assimilated or utilized improperly, malnutrition results. It can lead to either under or overnutrition, both with adverse health effects, altering body composition and it's biological functions.

Prevalence of malnutrition ranges from 20% in compensated liver disease to >80% after decompensation occurs[1]. In advanced liver disease irrespective of cause, the prevalence reportedly varies from 50%-90%[2,3]. Even in early stages of cirrhosis, malnutrition occurs, and has a poor prognosis and higher mortality[4,5]. Nonetheless, it is under-recognized and possibly under-treated, and the extent of nutritional assessment and support in routine clinical care is unknown[6]. There are few studies on nutritional issues in cirrhosis, especially in Asian population[7].

## Impact of Malnutrition in Cirrhosis of Liver :

Malnutrition in patients with liver cirrhosis during hospitalization is associated with increased morbidity including hepatic encephalopathy, variceal bleeding, refractory ascites, spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS)[8]. Carvalho and Parise[2] found that 21% of Child A patients had moderate or severe malnutrition, versus approximately 52% of Child B and 58% of Child C patients in non hospitalized patients. Therefore, it occurs early in the natural history of cirrhosis and frequently recognized late in chronic liver disease. In cirrhosis, the decompensation risk is 58% over 10 years[9], and 12% per year[10]. The decompensated states involve higher mortality. But it is important to note that prognostic assessments in cirrhosis (especially in early stages) is difficult because several factors influence the natural history, eg, the etiology, the effect of treatment in decreasing the underlying hepatic necro-inflammation/fibrosis, the extent of hepatic dysfunction, the presence/degree of portal hypertension, and the presence of hepatocellular carcinoma[11].

Still, malnutrition is acknowledged as an independent predictor for survival, as shown by a study on 212 hospi-

**Macro and micro nutrient deficiency, especially sarcopenia in cirrhosis is multifactorial, yet very common even in early stages of the disease. Proper understanding of the condition is important so that these deficiencies can be assessed and corrected since malnutrition worsens the prognosis. Correction of malnutrition should be routine part of management protocol but often overlooked and expert dietary consultations should be sought, particularly in advanced stages. Indian guidelines don't exist in this regard which is a necessity now keeping in view of the increasing number of patients.**

Department of Medicine, Assam Medical College, Dibrugarh 786002
[1]MD, Professor and Corresponding author

talized cirrhotics followed up for 2 years[12]. It is interesting to note that the two prognostic scores for chronic liver disease (Child-Pugh and MELD) do not include nutritional status as a parameter.

## Pathogenesis of Malnutrition in Cirrhosis :

The aetiology of malnutrition is multifactorial[13]. Basically three mechanisms are important : Decreased intake, Malabsorptive and Metabolic.

(a) Decreased intake of macronutrients have both disease related and iatrogenic factors[14]. The former include any of a GI symptom like nausea, anorexia, bloating, pain, belching or diarrhea present in upto 80% in cirrhosis. Upregulation of TNFa and leptin can also cause anorexia in cirrhosis, in addition to ascites, lactulose, psychological stress and low serum testosterone, and complications like HE and SBP. Delayed gastric and intestinal transit in cirrhosis has been demonstrated in 25% and 35% cases respectively; and may lead to anorexia or bloating via decreased gastric accommodative power and bacterial overgrowth (SIBO)[15]. Zinc deficiency is common in advanced liver disease and can contribute to anorexia by causing loss of taste and smell. Zinc and magnesium deficiency can occur due to diuretic use and restricted animal protein intake. In-hospital fasting for procedures like endoscopy, radio-imaging and during variceal bleed also contribute to calorie deprivation since the diseased liver has a low glycogen reserve.

(b) Malabsorptive factors develop due to altered bile flow (causing fat malabsorption), SIBO and pancreatic insufficiency (especially in alcoholics with an 18% prevalence), which are common in cirrhotics. These anomalies also impair food intake. SIBO is 4 times more common in patients with HE than in those without[16]. Another interesting but under-recognized condition is celiac disease which shows a prevalence of 1 in 40 in cirrhosis as compared to controls[17] and needs further studies to recommend a gluten free diet in them. Porta-systemic shunting can lead nutrients to bypass the liver, thus depriving their metabolism and assimilation. Particularly, long-chain fatty acids enter portal circulation instead of micelles (due to bile acid deficiencies) leading to increased hepatic triglyceride concentration which may hamper liver function further in an already diseased liver. 90% of cirrhotics also have Vitamin D deficiency and 29% of them being severe[18]. Use of steroids exacerbates Vitamin D deficiency in autoimmune cirrhosis.

(c) Metabolic factors Hypermetabolism occurs in 15% – 30% cirrhotics, probably due to stimulation of sympathetic system (tachycardia, increased cardiac output, hyperglycemia) and release of pro-inflammatory cytokines like TNF-a, IL1 or IL6[19] which induce high energy expenditure. Hypermetabolism is defined as Resting Energy Expenditure (REE) >120% compared to the predicted value and is the amount of energy an individual uses to perform vital organ functions, without activity and digestion. This sympathic overactivity may result from gut bacterial translocation, chronic inflammatory state, or central neuro-circulatory dysregulation. Insulin resistance, increased neoglucogenesis, protein catabolism and decreased glycogenolysis, are characteristic. These cause a significant depletion of protein and fat reserves, in about 50% of cirrhotic patients[20]. Decreased glycogen reserve in a diseased liver implies that with a short overnight fast, the amount of fat and protein catabolism in cirrhosis is equivalent to 2 to 3 days of fasting of a normal individual. Because in the absence of glycogen, neoglucogenesis uses protein and fats as alternate fuel leading to sarcopenia and adipopenia respectively, defined as hepatic cachexia. In cirrhosis sarcopenia is the primary and predominant consequence, especially in skeletal muscles whose fibers in adults are composed of terminally differentiated myocytes that do not replicate. Overweight and obesity are now endemic in many parts of the world. Cirrhosis may result in simultaneous loss of skeletal muscle and increased adipose tissue,a condition called sarcopenic obesity.This is characterized by a reduction in muscle size but increased proportion of inter- and intra-muscular fat. This is uncommon in Indians[7].

(a) SARCOPENIA (defined as a muscle mass two standard deviations below the healthy young adult mean) leads to a low functional capacity. After the age of 50 years, approximately 1% of skeletal muscle loss occurs per year and therefore is a feature of aging and many chronic diseases including malignancy. It is common in end-stage liver disease and increases it's morbidity and mortality[21]. The factors responsible for cirrhotic sarcopenia includes decreased total energy intake and reduced availability of substrates for muscle mass due to malabsorptive/malnutritional factors mentioned earlier. The skeletal muscles play an important part in controlling raised blood ammonia (due to hepatic dysfunction and porta-systemic shunts) by increasing glutamine synthesis in skeletal muscles and brain which binds to ammonia. This is however, a stop-gap, short term process. If continued, glutamine accumulation occurs which is metabolized again by a (normal) liver. If the liver is dysfunctional, then excess glutamine will be broken down by glutaminase in kidneys and intestines which re-converts one molecule of glutamine to two ammonia molecules, thereby promoting further ammonia generation and HE. Branch Chain Amino Acids (BCAA) is important here, as they act as a substrate of muscles to convert glutamine to glutamate in the muscles. In cirrhosis, serum BCAA is decreased and long-term supplementation of

BCAA has been shown to improve nutritional status and prolong event-free survival and quality of life[13]. Myostatin, a member of the TGF ß superfamily expressed in the skeletal muscle, inhibits protein synthesis. It is increased in cirrhotics. It also inhibits satellite cellular differentiation and proliferation, and found to be increased in muscles of cirrhotics, and may contribute to muscle wasting. Satellite cells are myogenically committed precursor cells that contribute nuclei to the myocytes for maintenance and growth of mature skeletal muscle. In cirrhosis, skeletal muscles may also play a part in release of cytokines like TNF-a by a proteolytic pathway involving ubiquitin leading to sarcopenia[22]. In addition, muscular autophagy and IGF1 anomalies (involved in protein synthesis or degradation in skeletal muscles) are seen in cirrhotics[23]. It may be noted that sarcopenia is not universal in underweight cirrhotic patients, and can be present in patients with any BMI.

(b) MICRONUTRIENTS In addition to micronutrient deficiencies mentioned above, rates of deficiencies of fat-soluble vitamins vary among studies, although frequent in primary biliary cirrhosis. Vitamin A,D,E,K deficiency in upto 33%, 13%, 2%, and 8% respectively was reported in one study.24 Hepatitis C virus and its therapy with peg-interferon/ribavarin therapy competes with human cells for vitamins and may disturb nutrient utilization leading to folate, B1, B2 and B6 deficiencies.

## Prognosis :

Several studies have consistently shown that malnutrition, especially sarcopenia, in cirrhosis adversely affects the survival and the development of various complications of cirrhosis[23]. It is interesting to note that till date no study has proven that reversal of malnutrition improves survival. After TIPS (to reverse portal hypertension), however, some patients show reversal of sarcopenia and they show better survival than those whose sarcopenia did not show improvement. Pre-transplant malnutrition shows a statistically significant increased mortality after transplantation, including prolonged ICU stay in a metaanalysis of 13 studies involving 1187 patients[23]. As regards quality of life based on existing data, it is worse in cirrhosis with sarcopenia and adipopenia. Episodes of HE, even after complete recovery, impact the quality of life in patients with cirrhosis[25]. Seven studies[23] (n = 751) studied the impact of malnutrition (prevalence 6.1% to 67.0%) on the complications of cirrhosis ( ascites, SBP, portal hypertension, hepatorenal syndrome, and HE). There was a statistically significant increase in complications in those with malnutrition. Alcoholics are significantly more malnourished than non-alcoholics. Irrespective of etiology, comparatively males show more muscle mass depletion, while female cirrhotics have more fat depletion[1]. This is probably due a larger fat reserve in females, which are utilized before the muscles to meet the catabolic demands of cirrhosis as compared to male counterparts[7].

## Nutritional Assesment in Cirrhosis :

A thorough history and physical examination are imperative (changes in weight, appetite, GI symptoms, peripheral edema, ascites, muscle wasting and subcutaneous fat loss). Various clinical tools are available to assesss nutrition (Table 1). Although Dual-Energy X-ray Absorptiometry (DEXA) is the gold standard, the European Society of Clinical Nutrition and Metabolism (ESPEN2006) guideline recommends the use of the subjective global assessment (SGA), anthropometry, or the handgrip strength test to identify patients with cirrhosis who are at risk of malnutrition[26]. The SGA is commonly used because it is simple and cost-effective but requires clinical judgement, consistency and is time consuming. SGA is a bedside assessment of dietary intake, weight change, and gastrointestinal symptoms; it includes an examination for subcutaneous fat loss, muscle wasting, edema, and ascites. Being essentially a "nutritional review", SGA may underestimate nutritional status in early stages of the disease. Traditional anthropometric measures like weight, midarm circumference, and triceps skin-fold thickness in patients with cirrhosis should be routinely performed. The handgrip test ( classified as malnourished if their grip strength is <2 SD from the mean of the age and sex groups), compared to SGA in cirrhosis was found to be superior in predicting occurrence of complications (65% *versus* 35.7%)[5]. Therefore, there is a need for a comprehensive analysis of patients' nutritional status that should include a combination of subjective and objective tools before nutritional intervention. Biochemical tests for liver function, serum micronutrients, lymphocyte count and serum cholesterol (indicating calorie depletion) can be help-

Table 1 — *Showing different nutritional assessment tools*

| Tool | Advantage | Disadvantage |
|---|---|---|
| BMI | Easy to perform | Inaccurate in edema/ ascites |
| Mid–arm circumference (MAC) | Low cost | Not a strong predictor of malnutrition |
| Skin fold thickness | Low cost, easy | Unclear accuracy |
| Hand Grip strength | Better at predicting complications, simple, quick | Correlates with MELD but not with CP score |
| Bioelectrical impedence | Not limited by compliance | Inaccurate in edema |
| Subjective Global Assesment (SGA) eg, RFH-GA | Systematic and bedside multifactorial tool, simple | Subjective in nature, time consuming |
| DEXA | Gold Standard | Expensive, technically complex |

ful. It must be noted that frequent nutritional assessment is required in any patient with chronic liver disease, as the dynamic nature of the disease may warrant adjustments for different nutrients over time.

## Nutritional Interventions :

The basic goals in cirrhosis are to meet estimated energy requirement and prevent protein catabolism by frequent feeds by the least invasive route. Specialist dieticians review should be sought whenever possible.

Both the American and European Societies of parenteral and enteral nutrition (ASPEN/ESPEN) have their own recommendations (Table 2). The ESPEN guidelines stresses more on prevention of malnutrition and is followed commonly. The patient's "dry weight" needs to be determined first because of edema and ascites can affect the actual weight. This is done roughly by subtracting from the patient's total weight by an amount of 2.2 kg, 6 kg and 12 kg (in mild, moderate, severe ascites respectively) and 1kg, 5 kg and 10 kg (in mild, moderate and severe edema respectively). Protein restriction, even in HE, do not confer any benefit and cirrhotics require more protein than normal. BCAA are essential for protein synthesis and turnover, and regulation of energy metabolism. It may be beneficial in improving CP score, improving quality of life and reduced hospital stay[27]. A late night high BCAA diet has recently been reported to improve mortality[28]. Leucine-enriched essential amino acids may be useful in the treatment of sarcopenia as Leucine is a substrate for protein synthesis, plays a key role in the skeletal muscle anabolism, protein synthesis and autophagy regulation[29].

Table 2 — *Nutrition Recommendations*

| | |
|---|---|
| Energy requirement, based on dry weight or determined ideal body weight, for patients with ascites | 25–40 kcal per d |
| **ASPEN :** | |
| Without encephalopathy | 25–35 kcal/kg per d |
| With acute encephalopathy | 35 kcal/kg per d |
| Stable and malnourished | 30–40 kcal/kg per d |
| **ESPEN :** | |
| All stable cirrhosis patients | 35–40 kcal/kg per d |
| **Macronutrients :** | |
| Carbohydrate | 45%–65% of daily caloric intake per DRI |
| **Protein :** | |
| All patients, except acute encephalopathy | 1.0–1.5 g/kg per d |
| Acute encephalopathy | 0.6–0.8 g/kg per d |
| Fat | 25%–30% of daily caloric intake per DRI |
| **Micronutrients :** | |
| Fat-soluble vitamins (vitamins A, D, E, and K); all patients with compensated liver disease | Up to RDA levels[a] |
| Zinc | Up to RDA levels[a] |
| Selenium | Up to RDA levels[a] |
| Folic acid and thiamine; patients with history of alcohol abuse | Up to RDA levels[a] |
| Sodium; patients with ascites and edema | Restricted to <2 g per d |

Nocturnal oral supplementation can shorten the length of overnight fasts and improve protein stores. Carbohydrate restriction is not recommended although cirrhosis is associated with insulin resistance. However, glucose should not be given in doses of more than 5-6 gm/day. Long chain fatty acid containing foods are best avoided as they can not be metabolized in cirrhosis and may lead to steatosis, and many patients also have associated exocrine pancreatic deficiency.

All should receive a multivitamin. Diet supplementation with higher doses fat-soluble vitamins (A,D,E, and K), zinc, and selenium are recommended in advanced disease but deficiencies in these are frequently found in patients with compensated liver disease as well[23]. Alcohol abuse warrants long term folic acid and thiamine supplementation. Due to presence of SIBO, probiotics have been used, but long-term use seems to be useful in HE, and more research is needed to find out the appropriate strains and the dosage.

When indicated, cyclical or continuous nasogastric or nasojejunal feeding is recommended in upright position or with a pro-kinetic to prevent aspiration[30]. Varices are no contraindication of tube insertion, but percutaneous route is best avoided because of possible bleeding or infection, in those with gastric varices or ascites. Generally, high-energy whole protein formulation are recommended in ascetic patients. Diarrhea/malabsorption may result in many, where a trial of medium-chain fatty acids can be given.

Total parenteral nutrition (TPN) is indicated when there are contraindications to oral or enteral nutrition and when adequate oral or enteral caloric intake is inadequate. The formulation contains protein, carbohydrate, fat, electrolytes, minerals and vitamins. Risk of potentially fatal infection, central venous thrombosis and deterioration of hepatic function(cholestasis) increases with TPN. Infection occurs due to endotoxemia, immunodepression, altered intestinal permeability, high glucose infusion and catheter related. TPN is recommended in very advanced disease, for end of life care and after surgery or liver transplant but the lipid content should be <1gm/kg/day.

## Summary :

Malnutrition, especially sarcopenia in cirrhosis, is present in all grades which decreases quality of life, increases mortality and complications. It is multifactorial. Although the inclusion of sarcopenia into cirrhosis prognostic scores has been limited by lack of dependable, simple and objective method to quantify muscle wasting, it should be assessed routinely in clinical practice and corrected. Addition of nutritional indices will add signifi-

cantly to the presently used CP and MELD scores for prognosis in cirrhosis and needs further research. Although malnutrition progresses with worsening liver function and CP score, it is not yet established that improvement of nutrition, particularly sarcopenia will improve survival. Hence early nutritional intervention in cirrhosis is more practical rather than in advanced stages. However, novel therapy like myostatin antagonists are being tried in animal models.

**Conflict of Interest : NIL**

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