Review Article

Nutritional status in cirrhosis; pathogenesis and management

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Summary

Malnutrition is common in patients with cirrhosis. It is associated with worse prognosis and frequent complications including infections, hepatic encephalopathy and ascites. Moreover, malnutrition is associated with the progression of liver failure and high mortality rate. It has many underlying mechanisms including anorexia, vomiting, poor absorption, and increased losses and other gastrointestinal disorders. The objectives of nutritional intervention in cirrhotic patients are the support of liver regeneration, prevention or correction of specific nutritional deficiencies and the prevention and/or treatment of the complications of liver disease. So that, early recognition and treatment of malnutrition in chronic liver disease lead to better disease outcome as well as prevention of the complications of chronic liver disease. The following review discusses approaches for the clinician to overcome some of the difficulties that prevent adequate nutrition delivery in cirrhotic patients.

Keywords: Nutritional status, liver disease, liver transplantation, complications, hepatic encephalopathy.

Introduction

Multiple variables, often interrelated, combine to affect the fluid, electrolyte, and nutritional status of patients with chronic liver disease. Although malnutrition adversely affects outcomes in patients with chronic liver disease, it may not be recognized until late in disease progression. The term malnutrition has different meanings, WHO define malnutrition as deficiencies, excesses or imbalances in a person’s intake of energy and/or nutrients.

Prevalence of Malnutrition in Cirrhosis

A study conducted by Carvalho and Parise, showed that, malnutrition is prevalent in patients with chronic liver disease up to 75% of patients. The malnutrition incidence increased with progression of liver cirrhosis assessed by Child Pugh score. Patients with CPA had a 46% rate of malnutrition compared with 84% and 95% of patients with CPB and CPC respectively. Furthermore, Protein calorie malnutrition was demonstrated in a large analysis of nationwide hospitalized patients with cirrhosis and portal hypertension; it was more frequently associated with ascites (65% vs 48%, P<.0001) and hepatorenal syndrome (5% vs 3%, P<.0001), longer hospitalization, and a 2 fold increase in hospital mortality compared with well-nourished.

Pathogenesis of Malnutrition in Cirrhosis

Multiple factors, tab (1) contribute to malnutrition in CLD, including anorexia, inefficient digestion/absorption, iatrogenic measures or impaired metabolism. The following review discusses approaches for the clinician to overcome some of the difficulties that prevent adequate nutrition delivery in cirrhotic patients.

Table (1) Factors that contribute to malnutrition in chronic liver disease.

<table>
<thead>
<tr>
<th>Inadequate nutrient intake</th>
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<tr>
<td>Early satiety (ascites)</td>
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<tr>
<td>Anorexia</td>
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<td>Dysgeusia (Zinc deficiency)</td>
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<td>Hepatic encephalopathy</td>
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<td>Restricted diet (low protein, low sodium, fluid restriction)</td>
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<td>Alcoholic intake</td>
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<td>Socioeconomic barrier</td>
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<table>
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<tr>
<th>Metabolic changes</th>
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<tr>
<td>Hypermetabolic state</td>
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<td>Increased gluconeogenesis</td>
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<td>Insulin resistance</td>
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<table>
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<th>Malabsorption</th>
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<tr>
<td>Fecal supernumerous stool</td>
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<tr>
<td>Portal venous stasis</td>
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<tr>
<td>Esophagus varices</td>
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<tr>
<td>Malabsorption</td>
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Keywords: Nutritional status, liver disease, liver transplantation, complications, hepatic encephalopathy.
1) Decreased intake of nutrients
Loss of appetite is a frequent complaint in patients with cirrhosis and is believed to be partially attributable to up regulation of multiple cytokines such as tumor necrosis factor-α (TNF-α) and leptin. Moreover, cirrhotic patient usually suffered from early satiety (sometimes related to micronutrients deficiencies, such as zinc or magnesium that may cause dysgeusia) and subsequent inadequate nutrient intake as result of reduced gastric expansion capacity secondary to ascites. In addition, early satiety may be attributed to reduced hepatic release of bile salts with subsequent fat malabsorption. Moreover, sodium restriction, frequent paracentesis or even some drugs, such as diuretics and lactulose, can lead to nutritional deficiencies.

2) Impaired digestion and absorption
Portal hypertension is believed to be responsible for poor digestion and nutrient malabsorption in cirrhotic patients. It promotes changes in the intestinal mucosa, like increased permeability, contributing to an increased loss of proteins. Intestinal dysmotility and bacterial overgrowth may also lead to an impaired digestion/absorption. Additionally, due to alcohol abuse many cirrhotic patients have chronic pancreatitis that leads to malabsorption. The deficiency of biliary salts (particularly in cholestatic diseases) and advanced degrees of pancreatic insufficiency. In addition to pancreatic insufficiency in alcoholic liver disease, there can be direct ethanol impairment of absorption of nutrients. Similarly, fat malabsorption and fat soluble vitamins deficiency are reported in patients with cholestatic liver diseases (eg, PBS, PSC) due to decreased intraluminal bile salt concentration.

3) Metabolism alteration
Another common problem seen in patients with liver cirrhosis is disrupted protein metabolism. During the early stages of the disease, these patients experience a high proteolysis rate. With further advancement of the disease, the ability of the liver to synthesize and store proteins becomes limited. In the late stages, there is a marked decline in protein synthesis resulting in hypoalbuminemia, sarcopenia and other nutritional problems. Cirrhotic patients have reduced hepatic glycogen reserves due to the reduced synthetic capacity of hepatic cells, and so an overnight fast in these patients is equivalent to approximately 72 h fast in healthy persons. As a result metabolism shifts to fatty acids as a main substrate for oxidation in cirrhotic patient. Certain tissues dependent on glucose will need gluconeogenesis from amino acids, as fatty acids cannot be used for this process. This leads to mobilization of amino acids from the skeletal muscles to synthesis adequate amount of. Repeated and frequent fasting results in recurrent proteolysis resulting in muscle loss in human cirrhotic patients. This contributes to the loss of subcutaneous fat and muscle wasting that is the hallmark of malnutrition.

4) Loss of nutrients
Loss of nutrients is common among cirrhotic patients secondary to recurrent of attacks GIT bleeding and protein-losing enteropathy that lead to malnutrition. Similarly, protein deficiency and malnutrition are induced by iatrogenic interventions such as the use of diuretics, lactulose, and recurrent paracentesis.

General Nutritional Guidelines in Cirrhosis
Suppression of hepatotoxic mediators and providing of optimal supply of both macro and micro nutrient are the main aims of nutritional recommendations for cirrhotic patients. General nutrition guidelines for patients with cirrhosis. It is simplified in the tab. (2).
Clinical Nutrition and Metabolism (ESPEN) guidelines recommend energy intakes of 105 to 147 kJ/kg body weight/d, this being increased to 147 to 168 kJ/kg/d (35 to 40 kcal/kg/d) in the setting of malnutrition. In malnourished patients with chronic liver disease, the oral and enteral nutrition are recommended as initial means to meet caloric needs. Furthermore, patients who cannot meet their caloric goals with oral supplements, tube feeds via nasoenteral tube is recommended. Parenteral nutrition should be reserved only for those with moderate-to-severe malnutrition who absolutely cannot meet their caloric needs by oral or enteral routes. Eating of 4 or 6 meals daily and late evening snack are recommended for cirrhotic patients hoping to achieve high caloric intake and positive nitrogen balance to avoid accelerated starvation state.

Table (3) Energy and Protein Recommendations in Chronic Liver Disease.

### Energy requirement
ESPEN: 35-40 kcal/kg/day

- With acute encephalopathy: 35 kcal/kg/day
- Without encephalopathy: 25-35 kcal/kg/day
- Stable and malnourished: 30-40 Kcal/kg/day

### Protein requirement
ESPEN: 1.0-1.5 g/kg/day

- With acute encephalopathy: 0.6-0.8 g/kg/day
- Without encephalopathy: 1.0-1.5 Kcal/kg/day

2) **Protein**
The use of dietary protein is the primary strategy in the treatment of malnutrition and prevent further sarcopenia. The protein requirement is estimated at 1.2 to 1.5 g/kg body weight daily by the ESPEN guideline to meet the increased protein requirements in patients with liver cirrhosis especially malnourished. BCAA supplementation may also have a beneficial effect in patients with hepatic encephalopathy. Latter observation was a surprise as BCAA provides a source of energy to the muscle in addition to being substrates for protein synthesis. BCAA also inhibit amino acid deficiency sensor GCN2 and reverse eIF2a phosphorylation which impairs protein synthesis and thereby, improves muscle mass. Leucine is known to activate mTORC1 and facilitate protein synthesis one hand and inhibit autophagy. Protein restriction is not recommended among patients with history of HE disparate to that has been encouraged in the past. Studies have not supported this hypothesis, and protein restriction may actually worsen malnutrition in patients with cirrhosis. The current recommendation for protein intake is 1.2 to 1.5 g/kg/day. Additionally, restriction in protein consumption may aggravate malnutrition leading to an increased muscle degradation resulting in increasing in ammonia levels and deteriorating the prognosis of HE. Only a transitional restriction of protein consumption (0.8 g/kg/d and less than 48 h) can be attempted in patients with severe protein intolerance in HE and not responding to optimal HE treatment but normal protein consumption should be restarted as soon as possible. Furthermore, diets rich in vegetable proteins appear to be better tolerated than diets containing animal protein. This may be due to increased dietary fiber content, a natural cathartic, and decreased aromatic amino acids levels which are thought to worse HE. Vegetable proteins are rich in BCAA which are better utilized by the muscles, and may even have a beneficial effect by removing one mole of ammonia per mole of BCAAs.

3) **Carbohydrates**
When cirrhosis reaches advanced stages at which 80% of hepatocytes are impaired, recurrent attacks of hypoglycemia are happened due to hyperinsulinemia. Therefore, frequent meals are required in order to provide a constant and planned flow of nutrients. Four to six meals with adequate carbohydrates content are recommended. -45-75% of caloric intake or 4/6 meals rich in carbohydrates per day is recommended.

4) **Lipids**
Fat intake amounting from 20% to 40% of daily caloric requirements should be promoted in patient with CLD in absence of steatorrhea and as long as the patient can tolerate this amount. In chronic liver disease, consumption fat calories in the form of MCT's (medium chain triglyceride) are better than LCT's (long chain triglyceride) because they bypass the carnitine pathway and are readily utilized in the tissues. Diets rich in MCT oils have been effectively used in reducing steatorrhea and improving energy balance. MCT oil can be supplemented in a dose of 0.3 gm/kg/day as a cooking medium.
5) Minerals and trace elements

*) Zinc
It is an essential cofactor of the urea cycle through ornithine transcarbamylase (OTC), which assistances in the detoxification of ammonia in the liver. Zinc supplementation reportedly reverses clinical signs of zinc deficiency in patients with liver disease. Furthermore, zinc supplementation produced metabolic effects and trended toward improvements in MHE.\(^{44}\)

*) Magnesium
It is another micronutrient common to be deficient in chronic liver disease. It has been demonstrated that alcohol impairs magnesium transport and homeostasis in brain, skeletal muscle, heart and liver.\(^{45}\)

*) Iron
Daily iron supplementation should not exceed 7 mg/day as long as patients are not severely anemic. Iron overload and excessive alcohol consumption might act in synergy to promote hepatic fibrogenesis. It was demonstrated that transferrin-iron saturation is associated with an increased incidence of cirrhosis, particularly in the presence of alcohol misuse. Also, untreated iron overload can lead to liver cirrhosis.\(^{46}\)

6) Vitamins
Vitamin deficiencies in liver disease are related to disorders of hepatic function and diminished reserves and, with increasing severity of the disease, to inadequate dietary intake and/or malabsorption. Fat soluble vitamin deficiencies are common manifestations of malnutrition and liver disease.\(^{47}\) Fat soluble vitamin deficiencies are common manifestations of malnutrition and liver disease. So that, diet supplementation with fat-soluble vitamins (A, D, E, & K), is recommended for patients with liver cirrhosis even with compensated liver disease.\(^{48}\) Chronic liver disease commonly results in vitamin D deficiency. Vitamin D deficiency has also been linked to poor outcomes in patients with hepatitis C. Recently, it was demonstrated that extremely low serum levels of vitamin D are associated with increased mortality in patients with chronic liver disease. Low vitamin D levels are also associated with poor survival, and with the degree of liver dysfunction and severity of the disease as assessed according to the Child-Pugh system.\(^{49}\) Not only low intake of calcium is the cause of hypocalcaemia in cirrhotic patients but also other factors as malabsorption (obstructive jaundice or concomitant pancreatitis), loop diuretics, hypomagnesemia (urine calcium loss), coexistent renal disease, recurrent infusions with citrated blood products, and paraneoplastic calcitonin (hepatic carcinoma).\(^{51}\) In the presence of cirrhosis, supplementation with 1200 to 1500 mg of calcium per day and also 400 to 800 IU of vitamin D is recommended with additional interventions needed for in case of true osteoporosis.\(^{52}\)

7) Electrolytes Sodium (Na)
The standard therapy of ascites secondary to cirrhosis includes a moderate sodium restriction (80-120 mmol sodium/day or 4.6-6.9 g salt/day).\(^{53}\) More restricted sodium intake is not recommended because this may make food less palatable and actually contribute to malnutrition.\(^{54}\) A strict salt control (less than 5 g NaCl per day) was associated with rapid decrease of ascites and a higher spontaneous diuresis. However, strict salt limitation in some studies was correlated with a higher incidence of hyponatremia and diuretic induced renal impairment. With moderate salt restriction (5-6 g/day), increased the dose of diuretics required, but the progress of hyponatremia, renal impairment and hyperuricemia was less frequent. Therefore, salt restriction to 5-6 g salt per day is recommended for the handling of ascites in most current guidelines.\(^{55}\)

8) Fluid
Limitation of fluid up to 1-1.5 liters/day is recommended in patient with ascites. Once serum sodium declines to less than 120 to 125 mEq/L is considered standard practice but with caution to avoid hypovolemia and hypo perfusion which would finally lead to deterioration in kidney function. However, in most patients fluid restriction does not need to be considered until hyponatremia is severe.\(^{56}\)

Nutritional Status Assessment in Cirrhosis
The aim of a nutritional status evaluation is identifying nutritional risk affecting morbidity and mortality which may be modifiable with nutritional therapy. Also, help in determination of the micronutrient and macronutrient state of the patient.\(^{57}\) The most widely used and recommended tools for nutritional assessment include the following:

- Anthropometry
- Bioelectrical impedance analysis (BIA)
* Biochemical parameters
* Subjective Global Assessment (SGA)
* Hand-grip strength
* L3 skeletal muscle index.

**General Nutritional Recommendations in Cirrhosis**

Nutritional recommendations for cirrhotic patients overall emphasis on suppression of hepatotoxic agents and the running of optimal macronutrient supply in terms of energy, protein, carbohydrates and lipids together with micronutrients such as vitamins and minerals.\(^2\),\(^3\). Energy, macro-and micronutrient supplies should be depend on the results of individual nutritional assessments and adjusted for weight maintenance and/or repletion. General recommendations are concise in table (4).\(^6\)

Table (4) A typical prescription to improve nutrition in patients with cirrhosis. therapies marked with* are not recommended for routine use but may be tried in context of controlled trials.\(^6\)

1. Abstinence from alcohol (take psycho-social and psychiatric help if required)
2. Diet
   1.2-1.5 g of protein per kg of body weight per day (a third from dairy, vegetable protein and animal protein each). Total 35-40 healthy meals per day.
   Support late evening snack and early breakfast consisting of complex carbohydrates and protein
   Supplement branched chain amino acids
   Use tube feeding (overnight continuous drip) or parenteral nutrition in critically ill patients
3. Exercise regime consisting of resistance and aerobic exercise, gently increased in a graded manner as per patient’s capacity
4. Normalization of portal pressure, nonselective beta-blockers or TIPS as indicated
5. Ammonia lowering measures: Rifaximin, haloperidol, L-68G, BCAA
6. Hormonal therapy: Testosterone, testosterone, growth hormone\(^6\)
7. Innovative therapies: IFP-1, myostatin inhibitors, follistatin, interferons, DBP inhibitor\(^6\)
8. Liver transplantation\(^7\)

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