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Review Article

Internal Medicine Section

# Malnutrition in Liver Cirrhosis: A Review

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## ABSTRACT

Malnutrition is a frequent and integral component of acute and chronic diseases and is most common in patients with cirrhosis and increase the severity of disease. Therefore, every hospitalised patient should have an assessment of their nutritional status. Patient with advanced liver disease commonly have malnutrition but its assessment is confounded by many of the usual indicators of nutritional status. The majority of cirrhotic patients unintentionally follow a low calorie diet, a fact that is attributed to various side-effects observed in cirrhosis. Protein Calorie Malnutrition (PCM) occurs in 50% to 90% of liver cirrhosis patients and progresses as liver function crumbled. This article is based on a selective literature review of protein and sodium recommendations. Higher intake of branched-chain amino acids and as well as vegetable proteins has shown benefits in liver cirrhotic patients. Sodium restrictions are necessary to prevent ascites development.


**Keywords:** Carbohydrate metabolism, Lipid metabolism, Minerals, Protein calorie malnutrition, Protein metabolism, Vitamins

## INTRODUCTION

Liver is the second largest organ in the human body. The liver is responsible for performing many functions in the body which include such as metabolisation, synthesis, detoxification and storage. Essential trace elements, such as iron and copper, and Vitamins A, D, and B12 are also stored in the liver. Liver is the most important metabolic organ that regulates physiological and biochemical processes including protein and energy metabolism. Malnutrition is a stipulation that results from an unbalanced diet in which certain nutrients are inadequate or in the altered ratio. There are several types of malnutrition including undernutrition and obesity (Overabundance of nutrient in diet). Because the major form of malnutrition in patient with cirrhosis is undernutrition or protein calorie malnutrition. The malnutrition in cirrhosis is characterised by decreased lean body mass as well as diminished skeletal muscle weight and reduced fat mass. In case of cirrhosis, malnutrition is the single reversible prognostic marker that accelerates deteriorating liver function [1,2].

## METABOLIC FUNCTION OF THE LIVER

Hepatocytes are metabolic overachievers of the liver and they play significant roles in the synthesis of molecules that are utilised at another place for the support of homeostasis, in converting molecules of one type to another, and also in regulating energy balances.

## CARBOHYDRATE METABOLISM

Carbohydrate metabolism is a key biochemical process that ensures a constant supply of energy to living cells. The most important carbohydrate is glucose, which can be broken down via glycolysis, enter into the Kreb's cycle and oxidative phosphorylation to generate ATP. It is essential for all animals to maintain the concentrations of glucose in blood within a normal range. Maintenance of normal blood glucose levels over both short (means hours) and long (means days to weeks) periods of time are one of the important functions of the liver. Glycogenesis results in the formation of complex glycogen from $\alpha$ D glucose in the cytoplasm of liver and muscle cells.

## DIAGNOSTIC CRITERIA OF LIVER CIRRHOSIS

The natural course of fibrosis begins with a long-lasting instead asymptomatic period, called 'compensated' phase followed by a rapidly progressive phase, named 'decompensated' cirrhosis characterised by clinical signs of the liver function impairment (i.e., ascites, variceal bleeding, encephalopathy, jaundice). Liver cirrhosis represents the final stage of liver fibrosis, the wound healing response to chronic liver injury. Cirrhosis is characterised by distortion of the liver parenchyma associated with fibrous septae and nodule formation as well as alterations in blood flow. Details of the criteria for diagnosis of liver cirrhosis is summarised in [Table/Fig-1-3][3].

Common symptoms in cirrhosis include:

- Cutaneous signs of liver disease.
- A firm liver on palpation.
- Liver biopsy.

| Parameter | 1 | 2 | 3 |
|---|---|---|---|
| Ascites | Absent | Slight | Moderate |
| Encephalopathy | None | Grade 1-2 | Grade 3-4 |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (mg/dL) | >3.5 | 2.8-3.5 | <2.8 |
| Prothrombin Time | PT: 1-3 | PT: 4-6 | PT: >6 |

**[Table/Fig-1]:** Child-Pugh Score.

| Classification | Stages | | | | |
|---|---|---|---|---|---|
| METAVIR score | F0-F3 | F4 | F4 | F4 | F4 |
| HVPG (mmHg) | | >6 | >10 | >12 | >16 and >20 |
| | | Stage 1 | Stage 2 | Stage 3 | Stage 4-5 |
| | | Compensated | Compensated and varices | Decompensated, varices and ascites | Decompensated variceal bleeding ascites other complications |
| 1-year mortality (%) | | 1 | 3 | 10-30 | 60-100 |

**[Table/Fig-2]:** METAVIR Score (this table is modified from ref [3]).
F: Fibrosis stage; HVPG: Hepatic venous pressure gradient

| Ishak score | Fibrosis stage |
|---|---|
| <1 | No Fibrosis |
| 1 | Some portal tract fibrotic±short fibrous septa |
| 2 | Most portal tract fibrotic±short fibrous septa |
| 3 | Portal tract fibrotic with occasional portal to portal bridging |
| 4 | Portal tract fibrotic with marked portal to portal and portal to central bridging |
| 5 | Marked portal to portal and/or portal to central with occasional nodules |
| 6 | Cirrhosis |

**[Table/Fig-3]:** Ishak Score for stage of fibrosis.

- Imaging study of liver [4]:
  - Evidence of decompensation;
  - Ascites;
  - Impaired hepatic biosynthesis.
- Genetic marker [5,6]:
  - Patatin-like phospholipase-domain-containing gene 3 (PNPLA-3);
  - Adiponutrin.
- Certain risk configurations such as:
  - Metabolic syndrome;
  - Heavy alcohol consumption;
  - Exposure to hepatotoxic substances;
  - Use of hepatotoxic medications [7,8].

### Child-Pugh Score for Cirrhosis

The Child-Pugh score was initially developed about 50 years ago to predict the prognosis after surgery for portal hypertension (portocaval shunting, transection of oesophagus) in patients with liver cirrhosis.

CTP scores are graded and have the following implications:

- CTP category A (5 to 6 points): people have a 100% chance of surviving for one year and an 80% chance of surviving for a subsequent year.
- CTP category B (7 to 9 points): people have an 81% chance of surviving for one year and a 57% chance of surviving for a subsequent year.
- CTP category C (10 to 15 points): people have a 45% chance of surviving for one year and a 35% chance of surviving for a subsequent year.

## SCORING SYSTEM OF LIVER FIBROSIS ON LIVER BIOPSY

Liver biopsy is currently the gold standard for assessing liver fibrosis and has been used for the diagnosis of fibrosis, risk stratification, prognosis evaluation, and differential diagnoses. Liver fibrosis is scored in stages and necro-inflammation is evaluated by grade. Liver fibrosis is histologically staged by assessing the amount of fibrosis and level of architectural disorganisation.

## USUAL EVALUATION OF MALNUTRITION IN CIRRHOTIC PATIENT

Nutritional assessment is of crucial importance in the management of patients with liver cirrhosis. Malnutrition is common in liver cirrhosis and has an adverse-effect on prognosis. The usual evaluation of malnutrition includes the following [9,10]:

- The patient's history and aetiology of malnutrition, such as diet and weight changes, socioeconomic conditions and symptoms unique to each clinical setting.
- Physical findings of malnutrition such as unintentional loss of (>10%) usual body weight in the past three months, decreased in temporal and proximal extremity muscles mass (muscle wasting), decrease skinfold thickness by "pinch test" (loss of subcutaneous fat), mouth and muscles membranes (i.e., nasolabial seborrhea for deficiency of essential fatty acids and glossitis for deficiency of riboflavin, niacin, vitamin B12, pyridoxine, folate) skin rashes, ocular changes and neurological changes.
- Laboratory assessment of malnutrition, such as serum albumin and other visceral proteins, assess blood vitamins such as Vitamin A, E, 25(OH)D, B12, folic acid and minerals such as zinc, magnesium, phosphorus and Immune function such as reduced total lymphocytes count and delayed hypersensitivity skin reaction.
- Specialised procedure for nutritional assessment i.e., bioelectric impedance analysis, resting and total energy expenditure and urine nitrogen excretion and nitrogen balance.

## PROTEIN CALORIE MALNUTRITION

Protein-Calorie Malnutrition (PCM) or Protein-Energy Malnutrition (PEM) refers to a form of malnutrition where it is inadequate calorie or protein intake. Types include: Kwashiorkor (protein malnutrition predominant); Marasmus (deficiency in calorie intake); Marasmic Kwashiorkor (marked protein deficiency and marked calorie insufficiency signs present, sometimes referred to as the most severe form of malnutrition) [9]. Nutrition status of liver disease patients include PCM occurs as a result of a deficit in calorie and protein intake: 1) Poor nutrition intake in liver disease; 2) metabolic changes in liver diseases; 3) hyperactivity of β-adrenergic system; and 4) malabsorption of fats [10-12]. Because liver is incapable to produce sufficient amounts of bile, and because of decreased micelle formation, fatty acid malabsorption occurs which contributes to PCM by decreasing the amount of calories available for the body's use.

## POOR NUTRITION INTAKE IN LIVER DISEASE

A 90% of patients with advanced alcoholic liver disease experience anorexia. Many patients also experience other Gastrointestinal (GI) symptoms such as early satiety, nausea, vomiting, diarrhoea, constipation, indigestion, abdominal pain/distension, ascites and reflux [13], all of which leads to decreased oral intake. Decreased intake of foods high zinc as well as increased GI and urinary losses. Since zinc is bound to albumin and patients with liver disease typically have low albumin levels. Zinc deficiency plays a role in the development of both anorexia, as well as dysgeusia and taste/smell changes, both anorexia dysgeusia further contribute to a decreased food intake [11,14].

## PROTEIN REQUIREMENTS IN CIRRHOTICS PATIENTS

Researchers have recommended that the simple addition of a carbohydrate and protein-rich evening snack may also help nitrogen balance, improve muscle cramps and prevent muscle breakdown by supplying the body with overnight carbohydrate energy, and preventing gluconeogenesis [11,15]. The Branched Chain Amino Acids (BCAA) leucine, isoleucine, and valine as well as the Aromatic Amino Acids (AAA) tryptophan, phenylalanine, and tyrosine are all essential amino acids. In liver disease, due to the altered amino acid metabolism, the body's amino acid profile and the ratio of BCAA: AAA changes to a higher AAA and lower BCAA [11,16]. Supplementation with BCAA has been used to normalize this ratio. One of the most common limiting amino acids in vegetable proteins is methionine, a sulfur-containing amino acid that is broken down and metabolised in the intestines and liver, producing mercaptans or the sulfur analogue of alcohols (thiols) [17]. According to Greenberger NJ et al., these intestinal byproducts of methionine are known to be important in the pathogenesis of Hepatic Encephalopathy (HE) [18]. Since vegetable proteins are low in methionine, it is therefore thought that they may be better protein

sources for patients with HE or those at high risk of developing hepatic encephalopathy [17,18].

## VITAMIN AND MINERAL REQUIREMENT IN LIVER CIRRHOSIS

Cirrhotic patients often have multiple micronutrient deficiencies. Poor nutritional intake is often seen in cirrhotic patients, especially in patients with alcoholic liver disease, which is a large cause of cirrhosis in worldwide. Nutritional therapy in patients with liver cirrhosis should not only focus on treatment of protein energy metabolism, but should also aim to correct specific nutrient deficiencies [Table/Fig-4] [19].

| Micronutrient Deficiency | Signs/Symptoms |
|---|---|
| Magnesium | Insulin resistance, muscle cramps |
| Selenium | Myopathy, cardiomyopathy |
| Vitamin B1/thiamine | Wernicke-Korsakoff syndrome, neurologic symptoms |
| Vitamin B2/riboflavin | Glossitis, cheilitis, lingual papillae atrophy |
| Vitamin A/retinol | Abnormal dark adaptation, rough skin |
| Vitamin C | Scurvy with purpura and petechiae |
| Vitamin D | Altered bone metabolism, altered gut barrier/immune function |
| Vitamin E | Oxidative stress |
| Niacin | Skin photosensitivity, confusion, pellagra |
| Folate, s-adenosylmethionine | Anemia, altered methylation, epigenetic effects |

**[Table/Fig-4]:** List of micronutrient deficiencies and their manifestations in patients with cirrhosis [19].

### Vitamin D

Nutritional therapy in patients with liver cirrhosis should not only focus on treatment of protein energy metabolism but should also aim to correct specific nutrient deficiencies. One of the most common complication of liver cirrhosis is osteoporosis thus requirement of calcium and vitamin D. Vitamin D is also known as the sunshine vitamin and is now recognised not only for its importance in bone health of humans but also for other health benefits including reducing the risk or progression of chronic liver diseases [20]. A 1,25 (OH)2D3, the active form of vitamin D has anti-proliferative and anti-fibrotic effect on hepatic stellate cells. Hepatic stellate cells are the major source of fibrillar and non-fibrillar matrix proteins in the process of liver fibrosis. Therefore, vitamin D deficiency is very common in these patients [20]. In case of Non-Alcoholic Fatty Liver Disease (NAFLD) the morbidity is rising worldwide, and epidemiological data showed that NAFLD morbidity is significantly higher in the vitamin D deficiency population than that in normal populations. Similarly, NAFLD patients tend to have a lower vitamin D level [21-23].

### Sodium

Sodium is essential for the regulation of blood volume, blood pressure, osmotic equilibrium and blood pH. It is another nutritional element that may contribute to malnutrition in some patients. Sodium restriction is often the first diet intervention received by a liver patient due to its effects on water retention and subsequently on the development of oedema, ascites. Ascitic fluid accumulates in the presence of excess sodium and therefore initially one should restrict dietary sodium intake. The 24-hours urinary sodium excretion indicates the amount of sodium in the diet necessary to ensure a negative sodium balance and thus a gradual diminution of fluid retention. Dietary sodium is usually restricted to 22 mmol/day, but occasionally in resistant cases, it may be necessary to reduce it to as low as 10 mmol/day [24]. When the liver disease progresses, the compensatory mechanism fails to cause a fall in arterial pressure. Consequently, the stimulation of baroreceptors leads to an increase in the renin-angiotensin system, circulating catecholamine's (vasopressin), and ultimately, sodium and water retention in the kidneys. According to Best Practice and Research Clinical Endocrinology and Metabolism as renal sodium and fluid excretion decreases, fluid backs up in the interstitial tissue, causing oedema and ascites [25]. The presence of ascites also increases the risk of other major complications such as renal failure, hepatic hydrothorax or variceal bleeding [26], all of these complications justify the need for sodium restriction. Diuretics are used to increase urinary sodium excretion and fluid removal. If diuretic does not give to the patients, it will lead to increase in ammonia in the blood and will cause Hepatic Encephalopathy (HE), and results in increase of Peripheral Benzodiazepines Receptor (PBR), subsequently Reactive Oxygen Species (ROS) which is also increased, followed by mitochondrial dysfunction, resulting in abnormalities in the brain astrocyte which then can lead to HE. Therefore, the management of HE is intended to lower ammonia levels by limiting protein intake. However, this restriction would lead to malnutrition [27].

Blood glucose is delivered to the liver through the portal vein; hyperinsulinemia in patients with liver cirrhosis may be secondary to either hepatic parenchymal cell damage or to portal-systemic shunting [28,29]. The rate at which insulin is degraded in the liver is reduced in patients with liver cirrhosis [29,30]. Moreover, despite peripheral hyperinsulinemia, insulin levels in the portal and hepatic veins are decreased in cirrhotic patients with portal systemic shunting [28]. Branched Chain Amino Acids (BCAA) such as valine, leucine, and isoleucine have a branched side chains instead of an aromatic group in aromatic amino acids, such as phenylalanine, histidine, and tryptophan. BCAAs help protein synthesis and turnover in the peripheral muscles with subsequent generation of energy. This leads to reduced BCAA levels in patients with cirrhosis [31].

### Zinc

Zinc is the second most prevalent trace element in the body and required for normal cell growth, development, differentiation, and it also involves DNA synthesis, RNA transcription, regulation of gene expression through metal-binding transcription factors and metal response elements in the promoter regions of the regulated genes. In liver disease, especially in Alcoholic Liver Disease (ALD), has been associated with hypozincemia and zinc deficiency for more than half a century [32]. Zinc also plays an important role in the regulation of protein and nitrogen metabolism as well as in antioxidant defence. Reduced zinc content is common in cirrhotic patients, but zinc deficiency cannot be effectively diagnosed based upon serum concentrations, since zinc is bound to albumin, which is also decreased in these patients.

Clinical Manifestations of Zinc Deficiency include Skin lesions, Depressed mental function, encephalopathy, Impaired night vision; altered vitamin A metabolism, Anorexia (with possible alterations in taste and smell acuity), Hypogonadism, Depressed wound healing and Altered immune function [33]. The effects of zinc deficiency are particularly obvious on the skin, as manifested by an erythematous rash or scaly plaques. Many common dermatological conditions (e.g., dandruff, acne, diaper rash) have been associated with zinc deficiency or effectively treated with zinc [32]. Patients with ALD and other forms of liver disease are predisposed to develop the skin lesions of zinc deficiency because of marginal underlying total body zinc stores. Alcoholic Liver Disease (ALD) is the major cause of morbidity and mortality nowadays. It has been estimated that 15%-30% of heavy drinkers develop advanced ALD. Alcoholic cirrhosis accounts for more than 40% of all deaths from cirrhosis and for 30% of all hepatocellular carcinomas [33,34]. Zinc deficiency is well documented in both humans with alcoholic cirrhosis and in animal models of ALD [34]. In a representative human study by Godde HF et al., the serum zinc concentration in alcoholic patients was 7.52 µmol/L [35], which was significantly lower than 12.69 µmol/L in control subjects. Vallee and associates [32] have demonstrated low serum zinc levels in the patients with cirrhosis of liver, which was overcome by the increased oral Zinc intake. One study shows that zinc deficiency associated with chronic alcoholism more often than with chronic liver disease [36]. Plasma Zinc levels have a significant diurnal variation but they remain low in patients with cirrhosis of liver,

as well as for those with malabsorption [37]. Fasting levels were 71 and 76 µg/100 mL and post meal levels 60 and 64 µg/100 mL in cirrhotic and malabsorptive subjects, respectively compared with fasting level 97 µg/100 mL and post meal level of 81 µg/100 mL in control subjects. There are a close co-relation of plasma zinc and plasma albumin levels, suggesting that low zinc level is associated with albumin deficiency in the cirrhotic [37]. Urinary zinc excretion appears to be increased in the cirrhosis but not in the patients with malabsorption [37].

Zinc and Viral Liver Disease, Hepatitis C Virus (HCV) is a globally predominant pathogen and a leading cause of death and morbidity. Persistent HCV infection is associated with the development of liver cirrhosis, hepatocellular cancer, liver failure, death and is estimated to affect 1-3% of the population in most countries globally [38]. The current standard of care for chronic HCV infection is based on the Direct-acting antivirals are inhibitors of the NS3/4A protease, the NS5A protein, and the NS5B polymerase. Similar to ALD, the serum levels of zinc are often decreased in HCV patients and serum levels also tend to negatively correlate with hepatic reserve and not only decreased in many patients with Hepatitis C, but there are functional correlations with the reduced serum zinc levels [39,40]. There are many therapeutic reasons why zinc may be beneficial in the treatment of Hepatitis C, including: 1) antioxidant function; 2) regulation of the imbalance between TH1 and TH2 cells; 3) zinc enhancement of antiviral effects of interferon; 4) inhibitory effects of zinc in the HCV replicon system; and 5) hepatoprotective effects of metallothionein [41-44]. Similar to HCV cirrhosis, the serum zinc levels are significantly decreased in patients with acute Hepatitis B infection and are frequently depressed with HBV cirrhosis [45,46]. Importantly, zinc therapy has shown some promising antifibrotic effects in chronic HCV. Multiple forms of zinc are available, with some of the most widely used including zinc sulfate, zinc gluconate, zinc acetate, zinc picolinate, and others. To the best of authors knowledge, zinc acetate is the only zinc supplement requiring a prescription, and extensive information on these supplements, including tablet dosing, is available on the Internet. The minimum Zn requirements with satisfactory growth, health, and well-being vary with the type of diet consumed and the existence of stress imposed by trauma, parasitic infestations, and infections. In general, the recommended daily dietary Zn requirement is estimated at 15 mg/day [47,48], and the tolerable upper intake level of Zn recommended is 25 mg/day [49].

### Magnesium

Magnesium deficiency is often noted in the patients with portal cirrhosis [50]. Almost approximately one of all magnesium is present in bone; severe liver disease is associated with deficiency. Clinical features of deficiency are sign of increased neuromuscular excitability including hyperesthesia carpopedal spasm, muscular cramps, tetany and even convulsions. The exact reason for the deficiency in hepatic disease is not clear. It may be due to poor intake or increased excretion.

### Copper

Normal humans ingest approximately 2-5 mg of copper daily and absorb approximately 2-2.5 mg. Balance is maintained by excretion of an equal amount in the bile and faeces. In Wilson disease, there is defect of mechanism in copper excretion through the biliary system. Associated with this retention of copper is a deficiency in the liver's synthesis of serum copper binding protein, ceruloplasmin. Patients have serum ceruloplasmin level of less than 20 mg/100 mL. (normal 20-40 mg/100 mL). Urinary copper excretion, however, is greatly increased (normal: less than 50 µg/24 hr). Increased deposition of copper occurs due to decreased transport in liver, brain, kidney and other organs [51,52]. There is limited success in treating the disease by chelation with D-Penicillamine. The removal of the copper from tissue is slow but this can delay organ damage and, in some cases, reverse the course of disease [52]. Copper may be increased in the liver of biliary cirrhosis or chronic active hepatitis and co-relates in these diseases with the duration of cholestasis. Chronic active hepatitis may then be confused with Wilson disease [51,53].

### Iron

Some of the patients with chronic liver disease develop gastrointestinal lesions that bleed, such as haemorrhagic gastritis or oesophageal and gastric varices. Chronic blood loss leads to iron deficiency and resultant microcytic, hypochromic anaemia. It should not be forgotten that the most often patients with chronic alcoholism and cirrhosis have microcytic indices due to low folic acid and/or $B_{12}$. The cause of bleeding should be core acted and anaemia if chronic treated by oral or parenteral Iron replacement.

Classification of iron storage disorder in liver disease:

Idiopathic (familial haemochromatosis) [54],

- Latent or pre-cirrhotic stage.
- Cirrhosis stage.
- Cirrhosis of liver with secondary iron overload.
- Liver disease associated with certain anaemia's (thalassaemia, pyridoxine responsive anaemia's, hereditary spherocytosis).
- Liver disease associated with dietary iron load (as seen in South African black using iron cooking utensils).
- Liver disease associated with increased transfusion.
- Congenital transferrin deficiency.

Increased iron storage result in haemochromatosis. With increased iron deposition in parenchymal cells, fibrosis of liver occurs. Other organ of body such as pancreas, endocrine gland and heart are similarly affected. The increased iron in the body may be due to increased absorption. Transfusion is obvious reason for increased intake.

In most cases, it is related to increased intake often associated with alcoholism. South African blacks brew their alcoholic beverages and beers in their iron containing pots, resulting in a high intake of iron [55,56]. Other significant factor is that alcohol by itself can increase iron absorption [57] and low protein diet enhances iron overload [58]. Idiopathic familial haemochromatosis is rare autosomal recessive disorder [59]. Serum ferritin may be helpful in early identification of susceptible members of family [60]. This becomes increasingly important with the Scandinavian observation that iron-fortified foods have increased the occurrence of high serum iron levels [61]. Certainly, the patients susceptible to hemochromatosis should receive a low-iron diet.

## CONCLUSION

Protein calorie malnutrition frequently occurs in patients with cirrhosis and leads to a negative prognosis for the patient by increasing the risk of other disease complications. The development of PCM is multifactorial and although protein and sodium are not the only contributing factors to PCM, they have strong influences and it is important for healthcare providers to identify patients which is at the risk of PCM, and then provide them with the best and most appropriate nutrition intervention beneficial to patient according to their needs, clinical status, and disease stage. Larger clinical trials investigating the use of vegetable-casein protein mixtures for patients with cirrhosis are needed. It is advised to liver cirrhotic patients that they should not skip meals or eat large quantities at ones, no feasting and no fasting. More emphasis should be laid on protein rich food such as milk and its derivatives, white portion of egg and nuts. They should not be replaced by fruit juices and salads. Thus, the aforesaid study shows that the nutrition rich diet may proved to be a first line target and a promising therapy for liver cirrhotic patients.

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