RESEARCH ARTICLE

MALNUTRITION IN LIVER CIRRHOSIS

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Abstract

Malnutrition is a common complication of liver disease and it adversely affects patient outcome. Aetiologic factors include hypermetabolism, malabsorption, altered nutrient metabolism and anorexia. Use of traditional nutritional assessment tools, such as anthropometry along with subjective global assessment scale and biometric measures, should be done to evaluate cirrhotic patients for malnutrition. Improvements in nutritional status can improve outcomes of patients with advanced liver disease.

Introduction:

Cirrhosis is a pathologic entity defined as diffuse hepatic fibrosis with the replacement of the normal liver architecture by nodules. In addition to fibrosis, the complications of cirrhosis include, but are not limited to, portal hypertension, ascites, hepatorenal syndrome, and hepatic encephalopathy. Cirrhosis may be classified broadly as compensated or decompensated. The development of complications like variceal hemorrhage, ascites, encephalopathy, jaundice, or hepatocellular carcinoma characterizes decompensated cirrhosis. The liver is an important regulator of metabolism, storage, synthesis, and absorption of nutrients. Accordingly, the severity of malnutrition increases with decreases in liver function.¹ Patients with chronic diseases frequently become malnourished; they have an inability to meet macronutrient and micronutrient requirements through oral intake.² Inadequate intake and/or associated malabsorption alters body composition and diminishes biological functions.² Malnutrition is common in patients with advanced liver disease; the prevalence is reported to be around 50%–90% among cirrhotic patients.¹ Malnutrition is diagnosed in about one-third of Child Pugh A patients and 50–90% of Child Pugh B/C patients.³,⁶ The prevalence of malnutrition among patients with even early-stage cirrhosis is concerning, given that nutrition status is associated with mortality and complications.⁷,⁸ In a large nationwide analysis of hospitalized patients with cirrhosis and portal hypertension, patients with protein calorie malnutrition had greater incidences of complications such as ascites (65%, compared with 48% without malnutrition) and hepatorenal syndrome (5% vs. 3% without malnutrition).⁷ Malnourished patients also had longer hospital stays and a two fold increase in in-hospital mortality, compared with well-nourished patients.⁷ Among a cohort of patients that were primarily Child–Pugh class A, those that were malnourished had a one year mortality rate of about 20%, whereas none of the patients that received sufficient amounts of nutrients died within the one year period.⁹ Complications such as infections, hepatic encephalopathy, ascites, and hepatorenal syndrome also increased with malnutrition; about 65% of malnourished patients develop complications compared with 11% among those who are well-nourished patients.⁹ Moreover, malnutrition is an independent predictor of death.³,⁴,⁹ Sarcopenia has also been proven to be an important negative prognostic indicator in patients with cirrhosis.¹⁰,¹¹ After liver transplantation,
Malnutrition has been associated with higher rates of infectious complications, longer stays in the intensive care unit, and higher mortality.\textsuperscript{12,13}

**Aetiology of Malnutrition**

The pathophysiological mechanisms and the clinical conditions that drive cirrhotic patients to an ill-balanced metabolic state are multiple and they intertwine (Figure 1). Inadequate offer of nutrients, the hypermetabolic state in cirrhosis, the diminished synthetic capacity of the liver and the impaired absorption of nutrients are the main reasons that disrupt the metabolic balance in End Stage Liver Disease (ESLD). Complications of cirrhosis such as ascites and hepatic encephalopathy also contribute.\textsuperscript{14}

**Hypermetabolism**

Resting energy expenditure (REE) is the amount of energy an individual uses to perform vital organ functions, free of activity and digestion.\textsuperscript{1} Whereas most cirrhotic patients have a REE that is similar to predicted values, 15\%–30\% of patients are hypermetabolic, i.e. REE >120\% compared with the predicted value.\textsuperscript{5} The causes of hypermetabolism are unclear; a study of 268 patients did not associate hypermetabolism with sex, aetiology, severity of disease, protein depletion, presence of ascites, or tumors.\textsuperscript{5} This finding is inconsistent with results from older studies that reported that energy expenditure is increased among patients with ascites or hepatocellular carcinoma.\textsuperscript{15,16} The increase in REE among patients with cirrhosis might result from infections or immune compromise. Plasma concentrations of catecholamines are increased in cirrhotic patients, indicating activation of the sympathetic nervous system.\textsuperscript{17} Sympathetic overactivity could induce systemic responses such as tachycardia and increases in cardiac output and blood glucose levels,\textsuperscript{18} which could all increase energy expenditure.\textsuperscript{1} Proposed causes for the increased levels of catecholamine include gastrointestinal bacterial translocation, an inflammatory phenotype of chronic liver failure, or central neural dysregulation of the circulation.\textsuperscript{1}

**Malabsorption**

There are multiple mechanisms that can lead to malabsorption of nutrients, particularly of fat, in cirrhotic patients. One complication that affects nutrient absorption in patients with cirrhosis is porto-systemic shunting. As cirrhosis progresses, porto-systemic shunting causes nutrients to bypass the liver, without metabolic processing.\textsuperscript{14} In addition,
many patients with cirrhosis that is secondary to alcohol abuse have chronic pancreatitis, which contributes to malabsorption; an analysis of autopsy results found that 18% of cirrhotic patients also had chronic pancreatitis.\textsuperscript{19} Another factor that leads to fat malabsorption in patients with cirrhosis is intraluminal bile acid deficiency, which results from the decreased capacity for bile production and porto-systemic shunting; intraluminal bile acid deficiency impairs formation of micelles and absorption of long chain fatty acids through the usual lymphatic route.\textsuperscript{20} Portal absorption of long chain fatty acids might also occur in patients with cirrhosis; a portal route for fat absorption has pathophysiological implications as it could result in excess hepatic storage of fat, which can reduce liver function and systemic availability of fat for organic functions.\textsuperscript{1}

\textit{Altered Macronutrient Metabolism}

Cirrhotics have increased levels of gluconeogenesis and protein catabolism and decreased levels of glycogenolysis, compared with healthy individuals.\textsuperscript{1} The altered rates of metabolism reflect a significant depletion in protein and fat reserves, reported in about 50% of cirrhotic patients.\textsuperscript{15,25} A number of factors contribute to the increased rates of gluconeogenesis in these patients.

Firstly, cirrhosis reduces the ability of hepatocytes to store, synthesize, and break down glycogen. These defects promote gluconeogenesis from fats and protein as alternate fuel sources. Following a short overnight fast, the rate of fat and protein catabolism in patients with cirrhosis is similar to that of healthy subjects who underwent two to three days of starvation.\textsuperscript{21}

Cirrhosis and insulin resistance are related; patients with cirrhosis have high postprandial levels of glucose and about three-fold higher serum levels of insulin after fasting than those of healthy individuals.\textsuperscript{22} Insulin resistance decreases peripheral glucose utilization and contributes to decreased hepatic glucose production and hepatic glycogen reserves.\textsuperscript{23} Increased serum levels of glucagon, which result from impaired degradation by the liver, increases the rate of gluconeogenesis.

Lastly, infection can increase rates of protein catabolism. The production of cytokines and other infection mediators activate proteolysis and increase oxidation of branched chain aromatic acids (BCAAs). This can promote the breakdown of muscle cells for substrates, if dietary protein intake is insufficient. In patients with cirrhosis, the utilization of oxidative fuels is associated with an increased rate of lipid oxidation, particularly in the fasting state.\textsuperscript{1}

\textit{Anorexia}

As in other chronic illnesses, anorexia makes a significant contribution to malnutrition. Anorexia can be caused by physical symptoms of discomfort such as nausea, bloating, fatigue, and vomiting. Patients with ascites often experience early satiety resulting from the mechanical effects of ascitic fluid, which compresses the stomach.\textsuperscript{24} Additionally, loss of appetite can be related to the up-regulation of inflammation and appetite mediators.\textsuperscript{25} Increased levels of Tumor necrosis factor might affect appetite and metabolism by acting on the central nervous system, altering the release and function of neurotransmitters.\textsuperscript{1} Cirrhotic patients have a two-fold increase in fasting levels of leptin (appetite suppressant) compared with healthy individuals which also might contribute to anorexia in these patients. Although some cirrhotic patients have been observed to have abnormal fasting levels of ghrelin (appetite stimulant), the relationship between ghrelin and anorexia is unclear; some studies have reported increases and others reported decreases.\textsuperscript{1} Aside from hormonal influences and physical discomfort, disinterest in food can result from dietary restrictions and taste alterations. Dietary limitations, such as sodium restriction for ascites management and limitation of protein intake for severe hepatic encephalopathy can reduce food variety; many patients do not accept the allowable foods. Although taste alterations have been commonly attributed to micronutrient deficiencies, researchers have questioned whether they are a consequence of cirrhosis itself.\textsuperscript{1} Alcohol related anorexia also plays its part in chronic alcohol users. Poor and irregular feeding is common among patients with alcoholic cirrhosis. In a study it was seen that before hospital admission, 53% of alcoholic patients reported anorexia, 40% reported irregular feeding, and 36% ate only one meal per day.\textsuperscript{26}

\textit{Micronutrient deficiency}

Patients with advanced liver disease have an increased risk of micronutrient deficiencies that arise from anorexia, diuretic use and fat malabsorption. Because patients with ascites have restricted oral intake and are treated with diuretics, they commonly acquire zinc and magnesium deficiency.\textsuperscript{1} Zinc deficiency impairs wound healing, immune reaction, protein metabolism and alters appetite and taste.\textsuperscript{27} Although rates of deficiencies in water-soluble vitamins vary among studies, vitamin A and vitamin D deficiencies are most commonly reported.\textsuperscript{1} More than 90% of patients
with cirrhosis have some level of vitamin D deficiency and 29% have severe vitamin D deficiency (< 17.5 nmol/L).²⁸

**Sarcopenia in Cirrhosis**

Since skeletal muscles play a central role in protein metabolism and storage, one may define clinical adult protein malnutrition as skeletal muscle loss.²⁹ On the other hand, adipose tissue is the largest repository of calories, and therefore, adult energy malnutrition may be considered as a reduction in whole body fat mass. Loss of muscle mass also has been called ‘sarcopenia’ and loss of fat has been referred to as ‘adipopenia’. However, it is generally accepted that malnutrition in cirrhosis comprises reduced muscle mass, strength and function (sarcopenia), as well as loss of subcutaneous and visceral fat mass (adipopenia).²⁹ Sarcopenia was originally described as loss of muscle mass related to aging, and that seen in cirrhosis would be termed as secondary sarcopenia.²⁹ The term hepatic cachexia has been used to define a proportionate loss of both muscle and adipose tissue mass. Recent epidemic of obesity and fatty liver-related cirrhosis has brought to attention a unique entity of ‘sarcopenic obesity’ which is a disproportionate loss of skeletal muscle mass with preserved or increased visceral or subcutaneous adipose tissue mass. Thus, malnutrition in cirrhosis is an all encompassing term and includes sarcopenia, adipopenia, cachexia, precachexia, obesity, sarcopenic obesity, and micronutrient deficiencies.³⁰ Cirrhotic patients with sarcopenia have reduced survival, experience increased rates of infection and have worse outcomes following liver transplantation. The prevalence of sarcopenia was found to be 30% in patients without encephalopathy, 49% with minimal change encephalopathy and 56% with overt encephalopathy.³¹ This may reflect a causative relationship between these two common sequelae of cirrhosis.³² The aetiology of sarcopenia (Figure 2) is more complex than simple protein and calorie malnutrition. Cirrhosis also results in depleted glycogen stores and metabolic alterations that cause excessive protein catabolism, increased activation of the ubiquitin–proteasome pathway and inappropriate muscle autophagy. Satellite cell (required for muscle growth and repair) differentiation and proliferation is also reduced due to a combination of elevated myostatin levels (negative regulator of satellite cell differentiation and proliferation), reduced IGF-1 and hypogonadism.³³ Although BCAAs are utilised for energy production in cirrhosis, the main cause for reduced BCCA levels is their uptake by muscle to assist in ammonia detoxification via glutamine synthase.³⁴ Thus in sarcopenic cirrhotic patients, both reduced circulating BCAA levels and reduced muscle mass may contribute to impaired ammonia clearance.³³
Nutritional assessment
Nutritional status is recognized as a predictor of morbidity and mortality in patients with advanced liver disease. Assessment of nutrition is challenging in cirrhotics, due to the complications of altered rates of protein metabolism and presence of ascites and edema. Some laboratory tests are used as part of the nutritional assessment in cirrhosis, including the prothrombin time or International Normalized Ratio (INR), albumin, prealbumin, creatinine height index, and indirect evaluation of the immune function, like the delayed-type hypersensitivity reactions. Nevertheless, as cirrhosis confounds these common parameters of nutritional status, their utility in these patients is limited. For example, patients with cirrhosis may have significant impairment in their hepatic synthetic function that results in low serum albumin, prealbumin, transferrin levels, and prolonged INR, which may lead to an overestimation of the prevalence of malnutrition. Also, the creatinine height index is an inaccurate measure of malnutrition in cirrhosis as creatinine levels could be low due to muscle wasting, or alternatively could be high as in renal impairment, which is common in these patients. Lastly, T cell anergy is a tolerance mechanism in which the lymphocytes are inactivated following an antigen encounter, and this phenomenon is frequently present in cirrhotic patients which makes delayed-type hypersensitivity an inaccurate measurement of malnutrition. The methods which are universally used to evaluate the nutritional status and to detect the presence of malnutrition are subjective global assessment (SGA) and anthropometric parameters.

The European Society of Clinical Nutrition and Metabolism (ESPEN) guideline recommends the use of the SGA, anthropometry analysis, or the handgrip strength test to identify patients with cirrhosis who are at risk of malnutrition. SGA is a bedside assessment tool used to collect information on dietary intake, weight change, and gastrointestinal symptoms; it includes an examination for subcutaneous fat loss, muscle wasting, edema, and ascites. However, this technique consistently underestimates the prevalence of malnutrition in this population when compared with assessments made using objective measures and it does not accurately predict outcome. Royal Free Hospital Global Assessment (RFH-GA) (Figure 3) incorporates both subjective and objective variables. In this schema, measurements of body mass index, calculated using estimated dry body weight, and mid-arm muscle circumference are utilized, together with details of dietary intake, in a semi-structured algorithmic construct.

Traditional anthropometric measures such as weight, mid-arm circumference (MAC), and triceps skin-fold thickness (TSF) are non-invasive bed-side methods for determination of nutritional status of cirrhotic patients but suffer from high inter-observer variability. Diagnosis of malnutrition is established on values of MAC and/or TSF below the 5th percentile in patients aged 18–74 years, or the 10th percentile in patients aged over 74 years. In a study, the use of body mass index (BMI) proved to be a reliable parameter for the detection of malnutrition by using different BMI cut-off values depending on the presence and severity of ascites. In particular, patients with a BMI below 22 Kg/m² with no ascites, 23 Kg/m² with mild ascites and 25 Kg/m² with tense ascites were considered malnourished.
In liver cirrhosis patients, reactance and resistance (impedance) readouts from Body Impedance Analysis (BIA) can be used to calculate phase angle or body cell mass as a measure of cell mass and cell function for the nutritional assessment.\(^3\) Most of our body water is stored in our muscle. Therefore, if a person is more muscular there is a high chance that the person will also have more body water. The basic principle of BIA is that electrical conduction is faster through water (because of lower resistance) and slower through fat tissue due to the resistance imposed by fat deposits, thus estimating the percentages of total body water (TBW), fat, and fat-free tissues. In BIA analysis, an estimate of the phase angle can be obtained, which is based on changes in resistance and reactance as alternating current passes through tissues causing a phase shift, and is an indicator of the distribution of water between the intra- and extracellular spaces.\(^4\) In Cirrhosis, low phase angle is associated with increased mortality as in many other disease entities.\(^3\)

Hand-grip dynamometry provides a functional assessment of muscle strength and in patients with cirrhosis, is a sensitive and specific marker for depletion of body cell mass\(^5\) and is positive correlated with total body protein stores.\(^5\) The prevalence of malnutrition assessed using hand-grip strength is consistently higher than that obtained with other bed-side techniques.\(^5,8,41\) Subjects are classified as malnourished if their grip strength is less than two standard deviations (SD) from the mean of the age and sex groups.\(^8\) Cut-off points suggested for reduced muscle strength are < 20 kgf for women and < 30 kgf for men.\(^29\)

The handgrip test has been compared with the SGA in patients with cirrhosis and was found to be a superior predictor of clinical complications such as uncontrolled ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome.\(^8\) ESPEN 2019 guidelines suggested that handgrip strength could be a valuable tool to measure efficacy of nutritional intervention.\(^40\) Reduced muscle function can also be designated by reduced gait speed; practical diagnostic cut-offs for gait speed is considered to be: < 0.8 m/s or < 1.0 m/s.\(^28\)

Recent interest has focused on the use of imaging technique, such as cross-sectional CT/MR, for assessing core skeletal muscle mass. On Computed Tomography (CT) images at the level of third or fourth lumbar vertebra, skeletal muscle area can be measured and normalized for stature.\(^35\) The skeletal muscle area at third lumbar vertebra has been shown to be linearly correlated with whole body muscle mass.\(^42\) Third lumbar vertebra skeletal muscle index (L3 SMI) is established as the muscle area (in cm\(^2\)) contained in this axial plane divided by the square of the height of person (in m\(^2\)). The cut-offs for sarcopenia in cirrhotic patients are 42 cm\(^2/\)m\(^2\) and 50 cm\(^2/\)m\(^2\) for women and men, respectively.\(^35\) Loss of skeletal muscle mass on CT has been associated with increased mortality in cirrhotic patients,\(^10\) obese cirrhotic patients, patients wait listed for liver transplantation and in orthotopic liver transplant recipients.\(^39\) A French group\(^43\) has also showed that transverse psoas muscle thickness measured at the level of the umbilicus was inversely correlated with death on the wait list. However, although these assessments are objective and are not influenced by hepatic synthetic dysfunction or salt and water retention; they are costly, involve radiation and cannot easily be repeated to monitor progress.

Dual-energy X-ray absorptiometry (DEXA), In vivo neutron activation analysis, and Isotope dilution are other methods used to measure nutritional status.\(^36\) Though they provide relevant and accurate information, their widespread application has been limited by cost and technical complexity.\(^5\) DEXA is based on measurement of body composition according to a model dividing the body elements in bone, fat, lean and bone-free lean masses, which can be distinct according to the energy photons passing through the body.\(^44\) Through DEXA, the frequently used measure to assess functional muscle is appendicular lean mass (APLM) - an APLM index of < 4.61 kg/m\(^2\) in women and < 6.57 kg/m\(^2\) in men indicates sarcopenia.\(^45\) A study\(^46\) assessing body composition using DEXA showed significant changes in body fat and mass composition absorptiometry in patients with Child Pugh A to C cirrhosis. Specifically, a higher loss of body fat was seen in the early stages of cirrhosis followed by an accelerated loss of lean mass and function (sarcopenia) in the later stages of cirrhosis.

**Protein Supplementation in cirrhosis**

The restriction of dietary protein intake in patients with cirrhosis and hepatic encephalopathy became a common practice in the 1970’s and 1980’s, based on uncontrolled observations.\(^47\) Increased understanding of the pathophysiology of cirrhosis has shown that most patients do not have high level porto-systemic shunting, and that protein restriction in these patients has no impact on their encephalopathy and it may worsen their nutritional status.\(^48\) Studies have also revealed that protein requirements are increased in cirrhotic patients and that high protein diets are well tolerated.\(^49\) Cirrhotic patients have different tolerance of dietary protein as vegetable and dairy protein may be better tolerated than meat protein.\(^50\) A consensus statement from the International Society for Hepatic
Encephalopathy and Nitrogen Metabolism (ISHEN) also recommends that patients with recurrent or persistent hepatic encephalopathy should consume a diet low in animal protein and rich in vegetable protein. Nocturnal oral supplements have been found beneficial in reducing gluconeogenesis and protein catabolism during the overnight fasting period. A systematic review has shown that in patients with cirrhosis a late-evening snack: (i) reverses the aberrant substrate utilization pattern; (ii) has a more efficacious effect on substrate utilization and nitrogen retention than day time calorie supplementation alone; (iii) may improve Health related quality of life (HRQOL) and survival and; (iv) may reduce the frequency and severity of HE. The review further concluded that the optimal caloric content and formulation for the late evening snack cannot be determined on the basis of the published data; however, evidence suggested that it should contain at least 50 g of complex carbohydrate. The ESPEN guidelines for nutrition in liver disease recommend that patients with liver cirrhosis should have an energy intake of 30 – 35 kcal/kg ideal body weight per day and a protein intake of 1.2–1.5 g/kg ideal body weight per day. Oral BCAA supplements (0.25 g/kg/day) may facilitate provision of an adequate nitrogen intake in the occasional patient who is truly protein intolerant.

Malnutrition has been identified in up to 60% of cirrhotic patients and is increasingly being associated with poorer prognosis among this patient population. Nutritional assessment should be done routinely in patients with cirrhosis of liver by taking a good dietary history, with anthropometric data and muscle strength measurement to timely identify those who are approaching the state of malnutrition so that an adequate early nutritional intervention could be initiated to prevent the perils of widely prevalent malnutrition in these patients.

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