

## Malnutrition and Sarcopenia in Advanced Liver Disease

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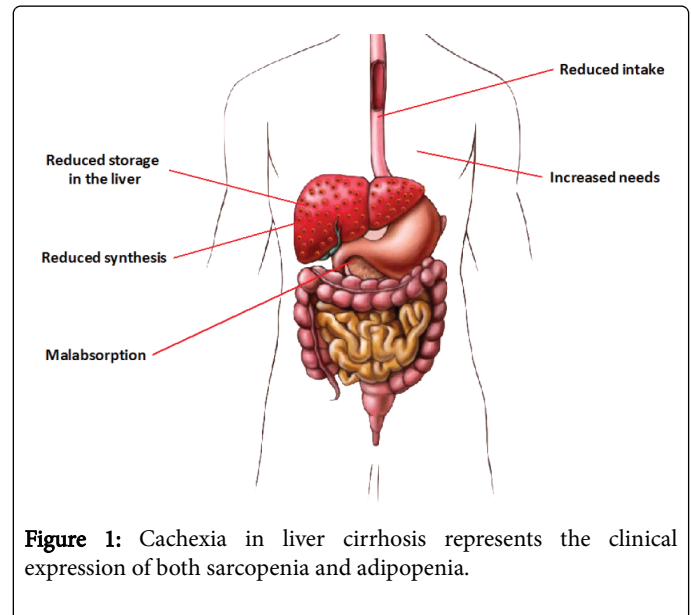
### Abstract

Sarcopenia as a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength that can lead to adverse outcomes, such as physical disability, poor quality of life, and death. The prevalence of malnutrition in chronic liver disease may range from 20% to 90%. Potentially all patients with cirrhosis are malnourished to some degree due to changes in nutrient ingestion, absorption, and utilization. Sarcopenia is common in liver transplant candidates and recipients and was associated with worse outcomes, including reduced survival. But it is of note that over - weigh or obesity does not exclude sarcopenia even in liver transplanted patients. The diagnosis of sarcopenia requires documentation of both low muscle mass and function. If possible, multidisciplinary, early intervention and aggressive treatment of nutrient deficiencies can prevent the physical downward trend that affects many patients with an advanced liver disease. Referral for transplant evaluation in appropriate patients should occur before the emergence of the clinical evidence of malnutrition. The degree of malnutrition allows the physicians to counsel the patient and family regarding the prognosis before and after transplantation. Frequent meals and nocturnal oral supplements represent a good nutritional strategy for cirrhotics, in order to decrease gluconeogenesis and protein catabolism.

**Keywords:** Sarcopenia; Malnutrition; Liver disease; Prevalence; Etiology; Diagnosis; Assessment; Post-transplantation; Management

### Introduction

During the 19th and the early 20th centuries, cirrhosis in alcoholics was named nutritional cirrhosis, and the clinical approach was to provide the patients with high-quality protein calories as well as to encourage the maintenance of alcohol abstinence [1]. Indeed, nutritional deficiencies are probably not the cause of cirrhosis in humans, but they do contribute to liver dysfunction. However, cirrhosis may accelerate the development of malnutrition [2]. Individuals with protein energy malnutrition typically suffer from a loss of skeletal muscle bulk and muscle weakness. This clinical syndrome is defined as sarcopenia [3]. Many factors may affect changes in skeletal muscles, such as prolonged inactivity, inflammation, age-related factors, anorexia, and unbalanced nutrition. The multifactorial character of the condition raises difficulties in practice to distinguish the underlying causative mechanisms. Sarcopenia at a clinical level includes both muscle loss and dysfunction, resulting in the expression of contractile muscle impairment, metabolic, endocrine abnormalities, and immune-inflammatory response dysfunction [4]. Aging-related-Sarcopenia is defined as primary sarcopenia while liver cirrhosis is a source of secondary sarcopenia [5]. However, it is of note that sarcopenia is not synonymous to cachexia, but there is a concrete overlay between these disorders (Figure 1) [5].



The original classification of surgical risk due to cirrhosis, by C.G. Child, in 1964, included nutrition as a variable to consider [6]. However, the subsequent modifications removed the factor mentioned above because of its subjective nature. In the same direction, the end stage of liver disease (MELD) score also does not take nutritional status into account [7]. Recent studies have demonstrated that sarcopenia is an independent predictor of reduced survival in cirrhotics with or without HCC [8,9]. Also, not infrequently, patients who are referred for liver transplant evaluation, due to significant muscle waste and weakness, do not meet liver allocation criteria to qualify for transplant

prioritization since the liver dysfunction itself is not severe. This fact can result in frustration for the patient, family, and sometimes referring physician, mostly created by the fact that there is an expected high mortality on the waiting list for this subset of patients deriving from hospitalizations or prolonged inability to intake food.

It should be noted that over nutrition is increasingly affecting humans worldwide [10], and, thus, being overweight / obesity is frequently observed in patients with advanced liver disease. For example, it is calculated that 72.4% of patients with compensated hepatitis C virus (HCV) - related cirrhosis have an excess caloric intake [11], and 61% of them could have a body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup> [12]. Both chronic HCV infections and being overweight / obesity can cause insulin resistance, which raises the risk of liver fibrosis progression and HCC occurrence in HCV-related cirrhotics [13,14]. However, overweight or obesity does not exclude sarcopenia. Sarcopenic obesity and sarcopenia with normal or increased BMI are already recognized in various clinical conditions, including breast cancer patients with adjuvant chemotherapy, rheumatoid arthritis, and in most patients with COPD or chronic kidney disease [4]. However, not infrequently, it also characterizes patients with a liver disease [15].

In the subset of patients suffering from malnutrition and muscle wasting, it is difficult and sometimes futile to reverse the process. Moreover, the challenge in cirrhotic patients, in general, is to achieve the goal of malnutrition prevention and possibly the minimization of the iatrogenic reasons of proper nutrition.

### Prevalence of malnutrition in patients with advanced liver disease

The prevalence of malnutrition in chronic liver disease may range from 20% to 90% depending on the methods used for the nutritional assessment and the severity of liver disease [16]. Protein-energy malnutrition (PEM) is frequently faced in patients with cirrhosis of nearly every etiology [17]. In a study of a total of 300 patients who attended the outpatient clinics of a reference center for liver diseases, more than 75% of those with advanced liver disease showed some degree of protein-calorie malnutrition and almost 40% presented with moderate or severe malnutrition. In the same study, while only 21% of Child A patients showed moderate or severe protein-calorie malnutrition, this was observed in approximately 52% of Child B and 58% of Child C patients [18]. This figure rises sharply as liver insufficiency progresses, which results in significant nutritional deficiencies for the majority of patients with Child C cirrhosis [19]. Data from a large multicenter study has further established that the prevalence of malnutrition is considerably higher in patients with a more severe liver impairment, > 50% in Child C but 20% - 25% in Child A-B patients [20].

The prevalence of malnutrition among patients with early-stage cirrhosis is of particular clinical importance because that nutritional status is associated with mortality and complications [16]. In a large nationwide analysis of hospitalized patients with cirrhosis and portal hypertension, patients with protein-calorie malnutrition had a greater incidence of complications such as ascites (65%, compared to 48% without malnutrition) and hepatorenal syndrome (5% vs. 3%). Malnourished patients also had longer hospital stays and had a two-fold increase in in-hospital mortality, compared with well - nourished patients [21]. Furthermore, among a cohort of patients that were primarily Child - Pugh class A (88%), those malnourished had a

poorer clinical outcome with the one - year mortality rate of about 20% because of major complications while none of the patients that received adequate amounts of nutrients died within the same period. Infections, hepatic encephalopathy, ascites, and hepatorenal syndrome are complications that also increased with malnutrition. In the same study, 65% of malnourished patients developed complications, compared with 11% of well - nourished patients [22]. Malnutrition is associated with higher rates of infectious complications, longer stays in the intensive care unit, and a higher mortality after liver transplantation. Additionally, patients with more severe malnutrition have longer postoperative hospital stays [16].

One of the fastest mounting causes of compensated and decompensated liver disease nowadays is nonalcoholic related steatohepatitis. These patients are often obese and suffer from type 2 diabetes and hyperlipidemia. Patients with nonalcoholic steatohepatitis or alcoholic liver disease have 25% prevalence of malnutrition, whereas 75% of those with other forms of liver disease are malnourished [23]. These data underlines the concept that patients may be malnourished while still maintaining body mass. This seemingly paradoxical finding may be because their body fat was retained while muscle atrophy was occurring. Many transplant centers defer patients from transplant listing until BMI is less than 35 because of comorbidities associated as diabetes [24]. The United Network for Organ Sharing provided data has shown that, in the past decade, the obesity-associated liver disease has become an increasing indication for transplantation. At the same time, the prevalence of obese patients on the waiting list has been reported to be 20%. The problem is even greater in countries in developing transition, and it is estimated that both under-nutrition and obesity may coexist [25].

### Etiology of malnutrition and specific nutritional issues

Patients with advanced liver disease have a reduced oral intake (Figure 2). As in other chronic illnesses, anorexia, together with nausea and vomiting, makes a significant contribution to malnutrition and may occur due to recurrent infections, the coexistence of other underlying diseases or due to a clinical expression of depression.

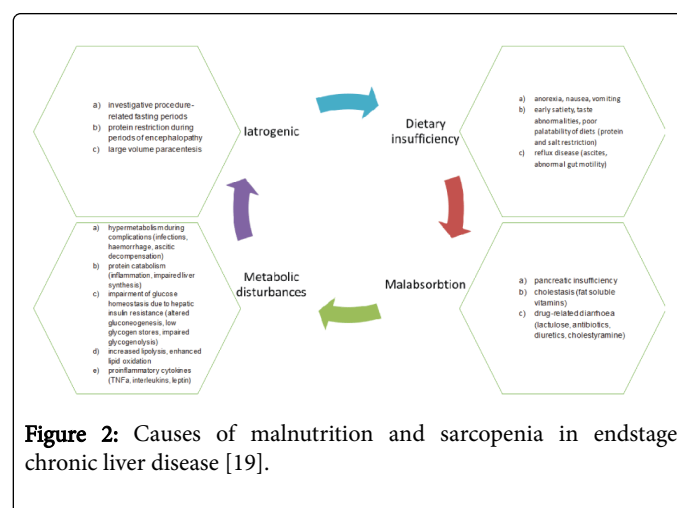


Figure 2: Causes of malnutrition and sarcopenia in endstage chronic liver disease [19].

Vitamin A and zinc deficiency may be the cause of an altered sense of taste observed in a proportion of patients with advanced liver disease, also partly due to neurotoxins or an abnormal excretion of sulfur metabolites [26,27]. Additionally, loss of appetite can be related to the up-regulation of inflammatory and appetite mediators [16].

Tumor necrosis factor- $\alpha$  could affect appetite and metabolism by affecting the central nervous system, modifying the release and function of neurotransmitters [28]. Increased leptin concentration in serum in patients with advanced liver disease could express with early satiety [29]. Cirrhotic patients had a 2-fold increase in fasting levels of leptin compared with healthy individuals, and this might contribute to anorexia in these patients [16]. Moreover, some cirrhotic patients have been observed to have abnormal fasting levels of ghrelin, a hormone mainly produced by the stomach which stimulates the appetite. Changes in ghrelin levels might be related to the state of anorexia [30,31].

Furthermore, recommended diets may be unpalatable due to dietary restriction of salt, fluids, protein, and sugar (in diabetics). Also, the patient may have early satiety resulting from the mechanical effects of ascitic fluid, conditions for gastroesophageal reflux, and abnormal gut motility [19]. The cirrhotic patient may experience fatigue of muscles used for chewing or a decreased ability to remain upright for a sufficient of time. These factors may exist to varying degrees in the same cirrhotic patient [26].

Among patients with alcoholic cirrhosis, the poor and irregular feeding is common. About 53% of alcoholic patients reported anorexia, 40% said intermittent feeding, and 36% ate only one meal per day. The socioeconomic status of patients with an alcoholic liver disease can also affect the overall oral nutrients intake, causing the majority of them to develop nutrient deficiencies, including low serum levels of B12, B6, folate and macronutrient scarcities [16].

Malabsorption is another important mechanism leading to malnutrition and sarcopenia. Multiple mechanisms can result in malabsorption of nutrients in cirrhotic patients (Figure 2). Because of portal hypertension and shunting of nutrient rich blood from the gut to the systemic circulation, there is a decrease in the first pass uptake of glucose and amino acids by the liver [32,33]. As cirrhosis advances, portosystemic shunting triggers nutrients to bypass the liver, without undergoing the metabolic process. There may also be a decrease in lipoprotein synthesis, affecting lipid transport and metabolism. Peripheral serum levels of nutrients are high, and there is mishmash between hepatic uptake and pancreatic hormone secretions. An analysis of autopsy results found that 18% of cirrhotic patients also had chronic pancreatitis. Furthermore, the decreased capacity for bile production and portosystemic shunting leads to fat malabsorption due to intraluminal bile acid deficiency that impairs the formation of micelles and absorption of long-chain fatty acids through the lymphatic route. The portal path for the fat absorption also has pathophysiologic implications as it might result in an excess hepatic storage of fat, which can shrink the liver function and the general disposal of fat for biological functions. Fat malabsorption also results in the deficiency of fat-soluble vitamins. The potential alternative mechanism associated with malabsorption in patients with advanced liver disease is bacterial overgrowth resulting from impaired small bowel motility. The same trend occurs after the administration of medications which lead to malabsorption, such as neomycin, which is commonly used in the management of hepatic encephalopathy [16,29].

Malnutrition might also contribute to the increased energy expenditure observed in these patients. Resting energy expenditure (REE) represents the extent of power that an individual uses to perform vital organ functions, free of activity and digestion [16,29]. The resting energy expenditure in cirrhotic patients may be high, low, or normal depending on their medical condition, the presence of inflammation, and the degree of malnutrition. In advanced liver

disease, the respiratory quotient ranges from 0.6 to 0.7 finding of hypermetabolism [26,27]. Indeed, most cirrhotic patients have an REE that is similar to the predicted normal values, but 15% - 34% of patients are hypermetabolic [34-36]. Hypermetabolism defined as REE > 120%, compared with the predicted value [26,27]. The causes of hypermetabolism are unclear. Infection, a frequent complication of advanced liver disease, could stimulate a hypermetabolism state. Older studies had reported that energy expenditure increased among patients with ascites or hepatocellular carcinoma [29]. Also, hypermetabolism may be influenced by extrahepatic factors, such as portal hypertension and portosystemic shunting [35]. This fact is further supported by the proof that hypermetabolism exists in patients with presinusoidal or extrahepatic portal obstruction [37] and in patients who have received liver transplants [38,39]. However, the results of a recent study including 268 clinically stable patients highlighted that hypermetabolism is not associated with the age, sex, etiology, severity of liver disease, protein depletion, presence of ascites, or tumors [34]. Hypermetabolic patients tended to weigh less [34] and to suffer more frequently from malnutrition [35]. Also, hypermetabolic patients have a higher mortality than do normometabolic patients with advanced liver disease [38]. Furthermore, it seems that there is significant variability in REE among patients with cirrhosis. Up to 30% of cirrhotic patients are hypometabolic [29], but a successful management of portal hypertension with TIPS placement results in a decrease in the hypermetabolic state [40].

There is indirect evidence that an intensified sympathetic nervous system activity was observed in 25% of cirrhotics as the consequence of disturbances in liver circulation and could result in a hyperdynamic status [35]. In cirrhotic patients, plasma concentrations of catecholamines were found increased, which could induce systemic responses (tachycardia, increases in cardiac output and blood glucose levels), all of which could increase energy expenditure. Some of the proposed causes for the increased levels of catecholamine include bacterial translocation in the gastrointestinal tract, an inflammatory sequence of events detected by chronic liver failure, or central neural dysregulation of the circulation [16].

The advanced liver disease also related to an altered pattern of energy consumption with the increased use of lipids. In fact, there is a more rapid transition from the consumption of carbohydrates to the use of fat stores resembling the metabolic pattern that is seen in starvation. There is a shift in the metabolism in cirrhotic patients from carbohydrate to fat metabolism after an overnight fast (12 h to 14 h) while in normal controls, it takes 2 to 3 days to shift the metabolism to fat utilization. Indeed, studies have shown that after an overnight fast, 58% to 75% of the energy utilized by patients with cirrhosis originated from fat oxidation, while healthy people used only 35% and 55% from carbohydrates [29,33].

Cirrhotic patients have increased levels of gluconeogenesis and protein catabolism and decreased levels of glycogenolysis, compared with healthy individuals [41,42]. The change in the rate of metabolism reflects a significant depletion of protein and fat reserves, reported in about 50% of cirrhotic patients [16].

Protein handling and utilization significantly changed in patients with cirrhosis, even in those with normal liver function. There is an increased protein oxidation as amino acids are broken down for energy by the liver. There is accelerated protein breakdown as essential protein needs to be altered but protein resynthesis is inefficient. Further, more glucose metabolism is also changed because the liver does not appropriately degrade insulin. These patients develop

hyperinsulinemia, insulin resistance, and consequent glucose intolerance, leading to shifting to fat as fuel. More specifically, patients with chronic liver disease have increased rates of gluconeogenesis, and some factors contribute to this phenomenon: 1) Cirrhosis reduces the ability of hepatocytes to store, synthesize, and break down glycogen. 2) Cirrhosis and insulin resistance. These patients have 3-fold higher serum levels of insulin after fasting and high postprandial levels of glucose. 3) Infection can increase the rates of protein catabolism [16].

Lipid metabolism, however, is also affected because of both the release of triglycerides from the adipocytes and the decrease in apolipoprotein synthesis and lipoprotein conjugation in the hepatocytes. Arachidonic acid may be scarce, and the cholesterol-phospholipid ratio in cell membranes may be increased, resulting in changes in membrane fluidity.

Micronutrient deficiencies are common in patients with cirrhosis. Patients with ascites have restricted intake of animal protein, and they commonly acquire zinc and magnesium deficiency because of diuretics use [43]. Whereas many water-soluble vitamin deficiencies (folate, pyridoxine, vitamin C) are associated with alcoholic liver disease, patients with nonalcoholic cirrhosis may also be deficient in water soluble as well as fat-soluble vitamins. The disruption of enterohepatic circulation can lead to abnormal utilization of folate and B12. Thiamine has shown to decrease in patients with hepatitis C cirrhosis [44]. The serum levels of lipid soluble vitamins are frequently reduced in patients with cholestatic liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis. These levels should be routinely assessed in these patients. For example, in a study included 180 patients with PBC, the proportion of vitamin A, D, E or K deficiency was 33.5%, 13.2%, 1.9%, and 7.8%, respectively [16]. Also, up to 40% of patients with nonalcoholic liver diseases may have deficiencies in vitamin A [45]. Vitamin K may be deficient in cirrhotics given the repeat courses of antibiotics, and vitamin D levels are often low and correlated with the severity of the liver disease [16]. Osteoporosis is common in patients referred for liver transplant, irrespective of the etiology of the liver disease. Possible causes include the lack of outdoor activity, decreased intake, relative malabsorption, and decreased hydroxylation by the liver [46].

### Diagnosis and assessment

In earlier stages of chronic liver disease, diagnosis of malnutrition is sometimes challenging. Several factors complicate the evaluation of nutritional status in patients with cirrhosis, and several commonly used markers of malnutrition are not useful in the clinical setting [29]. Moreover, cachexia may develop insidiously in advanced liver disease and be masked by significant peripheral edema, as usually in the case of patients with the simultaneous presence of ascites. For the same reasons, body weight can be misleading in this group of patients. One study has evaluated body mass index (BMI) in cirrhotic patients, specifying that optimal cut-off values could be 22 kg/m<sup>2</sup> in patients with no ascites, 23 kg/m<sup>2</sup> for those with mild, and 25 kg/m<sup>2</sup> for patients with tense ascites, respectively. In the same study, peripheral edema or the removal of ascites did not affect the diagnostic performance of BMI, which seems to be a reliable parameter to grossly detect malnutrition in the clinical settings [47]. Also, many of the laboratory tests using typical markers of nutritional status, such as albumin and pre-albumin, are less reliable in patients with cirrhosis, owing to low levels of synthesis typically seen in patients with advanced liver disease rather than because of poor nutritional status [29]. On the other hand, plasma protein concentration, the more

standard bedside assessment tool for malnutrition, seems to correlate better with the severity of liver disease than with nutritional status [48], and its serum levels frequently fluctuate during periods of active inflammation [16]. Also, the creatinine height index can be unreliable due to frequent disturbances in renal function in patients with advanced liver disease [49]. In conclusion, low albumin and creatinine levels in serum, only in well-compensated cirrhosis, express the presence of cachexia, but in patients with decompensated liver cirrhosis, these parameters are difficult to assess due to sodium and water retention, the reduced synthetic capacity of the liver, and the decreased creatinine levels in serum.

All the clinical points mentioned above implies that other parameters must be used in an effort to evaluate these critically ill patients, and the diagnosis of sarcopenia requires the documentation of both low muscle mass and function. Several approaches to the measurement of muscle mass have studied (Table 1). The most commonly used being a cross-sectional analysis of muscle areas, such as the psoas muscle area or the skeletal muscle index, calculated from radiographic images at a uniform vertebral level (such as L3 or L4 spine) [8,50].

Also, several techniques that attempt to quantify the measure of body composition indirectly have also used. Bioelectrical impedance analysis (BIA) is a simple, non-invasive, inexpensive, and quick method to estimate body cell mass that incorporates analysis of total body water as well as muscle and fat mass [3,51]. It has also been used in patients with cirrhosis, even facilitating the identification of patients at high mortality in liver transplantation. However, the validity of BIA in patients with ascites has been questioned because of erroneous method estimates of body fluid compartments, especially in patients with marked extracellular volume expansion, as in many patients with cirrhosis [52].

Measure	Components	Abnormal Test Result Range	Considerations for Patients with Cirrhosis
Psoas muscle area / Skeletal muscle index	Cross-sectional imaging (CT or MRI) at specified level (e.g., L4)	Varies per study	Radiation exposure
Bioimpedance analysis	Estimates amount of fat vs lean body mass	< 90% of the standard skeletal muscle	Limited accuracy in patients with significant ascites
Dual X-ray absorptiometry	Estimates skeletal muscle mass	< 10th percentile based on age and gender	Radiation exposure
Hand strength grip	Hand strength from dominant hand	< 5th percentile based on age and gender	Limited in those with severe hepatic encephalopathy, interobserver variability
Anthropometry	1. Triceps skin-fold thickness	< 5th percentile	Interobserver variability
	2. Mid-arm muscle circumference	< 5th percentile	
	3. BMI	< 20 kg/m <sup>2</sup>	
	4. Weight loss	≥ 5% - 10%	

Subjective Global Assessment	Muscle wasting, fat loss, dietary intake, functional capacity	Severe muscle wasting and subcutaneous fat loss, inadequate dietary intake > 5 wk, minimal functional capacity	Interobserver variability
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**Table 1:** Evaluation of nutritional status - sarcopenia in patients with cirrhosis.

The evaluation of phase angles or body cell mass using BIA, despite some restraints in patients with ascites, reflect two methods superior to others such as anthropometry and 24 h creatinine excretion. The extent of phase angle by bioimpedance analysis could be used as an indicator of body cell mass and has been shown to be of prognostic significance in cirrhosis. However, most but not all investigators deem it unreliable in patients with ascites.

The assessment of phase angle or body cell mass, using bioimpedance analysis rather than anthropometry, is recommended for quantitative analysis despite its limitations with ascites [53]. Also, dual X-ray absorptiometry, which incorporates X-rays at two different energy levels to separate bone from soft tissue and evaluates the ratio of low to high energy attenuation to separate body fat from lean body mass, has been used. Although these imaging modalities lack a functional assessment of muscle strength, they have the advantages of being relatively easy to standardize and eliminating disease-specific confounders such as volume status and HE and, in many cases, can be performed in retrospective studies to establish preliminary associations with clinical outcomes. However, the radiation exposure when computed tomography is used, the lack of high-quality prospective data comparing these methods, the limited availability of bio-impedance and absorptiometry testing, and the lack of functional assessment remain significant limitations of these radiographic approaches [50]. The assessment of fat storage and skeletal muscle mass could be accomplished using anthropometric measurements, not without problems, that include triceps skin-fold thickness and midarm circumference, for example. Body composition may be affected by edema [54] and, furthermore, these measurements have been shown to classify 20% - 30% of healthy persons as undernourished [55]. Furthermore, other potential limitations of anthropometry include poor interobserver reproducibility and overestimation of these values because of the third spacing of fluid [17]. However, several studies have shown that anthropometric measurements and handgrip strength correlate well with more sophisticated assessments such as DEXA in cirrhotic patients [56,57]. Indeed, midarm muscle circumference was recognized as an independent predictor of mortality in advanced cirrhosis [22]. In an Italian multicenter study that included more than 1,000 patients, survival was associated with midarm muscle circumference for Child A and B patients, but the association was not verified for those patients with Child C [58]. Also, midarm muscle circumference has been shown to be independently associated with survival and improve its prognostic accuracy when combined with the Child score [59].

There are also several standardized approaches to the measurement of muscle function that are available and can be used in combination with radiographic procedures. Handgrip strength (HGS), most often measured with devices such as the Jamar dynamometer, is among the most widely used [56,60,61]. HGS is sensitive, although less specific, for the identification of patients with protein-calorie malnutrition in

cirrhosis. Also, tests that assess several muscle groups simultaneously or in series are also now validated in many groups, including the short physical performance battery (repeated chair stands, balance testing, and walking speed), gait speed, and the timed get-up-and-go test [3]. Although these physical tests offer a crucial functional assessment of the patient's muscle mass abilities, they may be subject to interobserver variability and are likely to be more heavily influenced by disease-specific complications, including edema and HE [50].

Finally, tools such as the Subjective Global Assessment (SGA) have been used as a bedside method to identify patients with malnutrition and muscle depletion in cirrhosis. Subjective global assessment (SGA) is a practical bedside method that uses clinical information, without objective measurements, to assess the undernourished [53]. SGA collects the information acquired during the evaluation of medical history and the physical examination. It is considered reliable as it calculates the recent body weight change, but it is not affected by fluid retention or the formation of ascites [62]. Features of the SGA include the presence of gastrointestinal symptoms and weight loss, dietary intake, and physical examination for fat, edema, and muscle wasting [63]. The SGA has been validated in patients with decompensated cirrhosis [64,65] and is probably the easiest to administer at the bedside. On this base, for assessing nutritional status in patients with cirrhosis, the Royal Free Global Assessment (RFH-SGA) scheme has been proposed. The parameters that are taken into account are body mass index (BMI), midarm muscle circumference (MAMC), and dietary intake, and it divides patients into three categories: adequately nourished and moderately or severely malnourished. It is reproducible, valid, and represents a significant predictor of survival [62]. Society for Clinical Nutrition and Metabolism guidelines favor bedside methods such as subjective global assessment, anthropometry and handgrip strength for the identification of undernutrition and the phase angle evaluation or body cell mass assessment using bioimpedance analysis for quantitative analysis [66].

### Post organ liver transplantation sarcopenia

Sarcopenia is characteristic of liver transplant candidates and organ recipients and associated with worse outcomes, including reduced survival. The prevalence of sarcopenia, defined by cross-sectional imaging, increased from 62.3%, pre - transplant, to 86.8%, one - year post - transplant [67]. On the other hand, increased weight and body mass index are commonly observed after liver transplantation [68], with one series finding the median weight gain to be 5.1 kg and 9.5 kg at one and three years, respectively [69]. Most weight gain occurs within the first year after the liver transplant [70], and it seems that much of this weight gain expresses an increase in fat mass. Furthermore, in a group of patients with long-term survival after a liver transplantation, the assessments of body composition in many organ recipients were correlated to those seen with sarcopenic obesity. It is of note that sarcopenic obesity represents a condition that, when compared to obesity with normal muscle mass, is associated with a higher risk of metabolic syndrome and coronary artery disease [67]. Regarding the potential mechanisms of sarcopenia development after liver transplantation, it seems that immunosuppression contributes to both ongoing muscle loss and delayed regeneration. Calcineurin inhibitors (CNIs), the backbone of liver transplant immunosuppression regimens, have multiple effects on muscle. Intracellular calcineurin activation regulates genes involved in skeletal muscle maintenance, growth, and remodeling. Elevations in intracellular calcium levels could activate calcineurin, resulting in the clinical expression of a group of genes involved in the preservation,

growth, and regeneration of the skeletal muscles. Calcineurin stands as the dominant regulator of muscle remodeling, enhancing the differentiation of the skeletal muscles through upregulation of myogenin or MEF2A in parallel with the downregulation of the Id1 family and myostatin [71]. In animal models, the simultaneous administration of calcineurin inhibitors and growth factors was found to inhibit skeletal muscle hypertrophy. Moreover, the same was their effect during periods of intense muscle effort [67]. Additionally, activation of calcineurin in skeletal myocytes selectively up-regulates slow-fiber-specific gene promoters. Conversely, inhibition of calcineurin activity by the administration of cyclosporin A promotes slow-to-fast muscle fiber transformation [72]. Myostatin acts as a principal mediator between CNI use and sarcopenia. This role is carried out through reduced satellite cell activation that results in the inhibition of muscle growth and regeneration. In animal studies, CNI administration was found to increase myostatin expression, namely, a growth differentiation factor that impedes muscle growth. Small pilot data derived from transplant recipients at the clinical level established an increased skeletal muscle myostatin expression compared with controls [67]. Other agents that affect muscle and are used in the standard immunosuppression regimens after liver transplantation have also been related to sarcopenia. Rapamycin and possibly other mTOR inhibitors were found to block muscle hypertrophy [67]. Also, steroids have long been described to result in myopathy that is histologically characterized by type II muscle fiber atrophy [73]. In a patient case report, the anti-metabolite mycophenolate mofetil was found to be involved as the causative agent of induced myopathy that reversed with the withdrawal of the drug [74].

After liver transplantation, lifestyle may play a significant role in the persistence of sarcopenia. Many transplant recipients continue a sedentary way of life [67]. Even when enrolled in a study that assessed the benefit of exercise after transplant, less than half adhered. However, among those that did adhere to exercise recommendations, there was a trend toward improvements in exercise capacity and body composition, which was achieved with nutrition and exercise behavior modifications initiated early after OLT [75].

### Management of malnourished patients

Because most cirrhotic patients who require inpatient care are moderately to severely malnourished, a high level of awareness by the attending physician is needed to ensure nutritional repletion (Figure 3). Such patients should not go longer than 24 h to 48 h without adequate nutrition. The most common cause of failure to provide a patient with adequate nutrition is the need to keep patients from ingesting anything by mouth for tests and medical procedures. The second cause is a concern that enteral or oral feeding may disrupt therapeutic manipulations such as band ligation after variceal bleeding.

The diet prescription, advocated in the literature, is a low salt diet (<2000 mg/day) with high protein (1.2 g/kg/day to 1.5 g/kg/day) and small, frequent feedings, as many as 6 per day [53]. It has been shown that patients are likely to archive a positive nitrogen balance when given a high-protein, juicy, bedtime snack [58]. In the most severely malnourished patients, up to 1.8 g/kg/day protein intake is associated with increased probability of positive nitrogen balance [26,53]. The daily energy recommendation, proposed by the American Society of Parenteral and Enteral Nutrition (ASPEN) and ESPEN guidelines, includes 25 to 40 kcal/kg per day [66,76]. The ASPEN guideline endorses the administration of 25 to 35 kcal/kg per day for patients

without encephalopathy and, in those with acute encephalopathy, 35 kcal/kg per day. The 2006 ESPEN guidelines, which focus on prevention and treatment of malnutrition, recommend a much higher energy intake for all patients with stable cirrhosis, ranging from 35 to 40 kcal/kg per day [66]. The ASPEN guideline also counsels 30 to 40 kcal/kg per day for stable, malnourished patients [66,76].

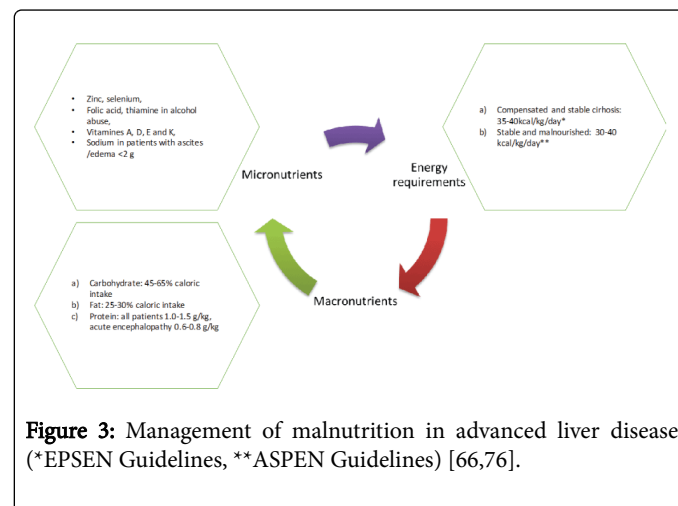


Figure 3: Management of malnutrition in advanced liver disease (\*EPSEN Guidelines, \*\*ASPEN Guidelines) [66,76].

Energy recommendations are tied to patients' dry weight or ideal body weight in the presence of ascites. If the patients cannot maintain an adequate intake of calories from food, the ESPEN guideline recommends the use of an oral supplement or overnight enteral feeds [66]. Carbohydrate restriction is not recommended for patients with cirrhosis despite the high prevalence of insulin resistance and diabetes in this population [66]. It has been suggested that carbohydrates account for 45% – 65% of caloric intake, based on the dietary reference intake [16].

For patients with cirrhosis, the general protein recommendation is 1.0 g/kg per day to 1.5 g/kg per day [66,76]. Because of increased gluconeogenesis in parallel with muscle catabolism and decreased absorption in cirrhotic patients, this quantity is much higher than the 0.8 g/kg per day recommended for healthy individuals. Until the cause of the encephalopathy is reversed, patients with acute encephalopathy can be retained on temporary protein constraint (0.6 g/kg per day - 0.8 g/kg per day), and then, the typical protein intake can be restarted [76]. Medium-chain triglycerides are not regularly needed except for patients with severe fat malabsorption and steatorrhea, which is the case of cirrhotics with severe and durable cholestasis. For patients with an advanced liver disease, diet supplementation with fat-soluble vitamins (A, D, E and K), zinc, and selenium is recommended. Deficiencies in these nutrients are frequently observed in patients with compensated liver disease [76,77]. In severe cases, it has been shown that patients tolerate tube placement and feeding much better if the health care providers discuss the importance of enteral nutrition in a positive and enthusiastic manner. Nausea would not be a contraindication to enteral feeding, particularly if the tube passes below the pylorus. Total parenteral nutrition should be prescribed only as a last resort in patients who have absolute contraindications to central feeding. Consequences of this approach include prolonged ileus, intestinal ischemia, severe malabsorption, and the high likelihood of aspiration of a tube and the risk of infection.

## Conclusion

The attending hepatologist should assume that all patients with cirrhosis are malnourished to some degree due to changes in nutrient ingestion, absorption, and utilization. Sarcopenia is common in liver transplant candidates / recipients and associated with worse outcomes, including reduced survival. It is of note that being overweight or obese does not exclude sarcopenia even in liver transplanted patients. The diagnosis of sarcopenia requires documentation of both low muscle mass and function. If possible, multidisciplinary, early intervention and aggressive treatment of nutrient deficiencies can prevent the physical downward trend that affects many patients with an advanced liver disease. Referral of appropriate patients for transplant evaluation should occur before the emergence of the clinical evidence of malnutrition. The evidence of malnutrition allows the physician to counsel the patient and family regarding the prognosis before and after transplantation.

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