Reprint of: Nutrition in the Management of Cirrhosis and its Neurological Complications☆

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Malnutrition is a common feature of chronic liver diseases that is often associated with a poor prognosis including worsening of clinical outcome, neuropsychiatric complications as well as outcome following liver transplantation. Nutritional assessment in patients with cirrhosis is challenging owing to confounding factors related to liver failure. The objectives of nutritional intervention in cirrhotic patients are the support of liver regeneration, the prevention or correction of specific nutritional deficiencies and the prevention and/or treatment of the complications of liver disease *per se* and of liver transplantation. Nutritional recommendations target the optimal supply of adequate substrates related to requirements linked to energy, protein, carbohydrates, lipids, vitamins and minerals. Some issues relating to malnutrition in chronic liver disease remain to be addressed including the development of an appropriate well-validated nutritional assessment tool, the identification of mechanistic targets or therapy for sarcopenia, the development of nutritional recommendations for obese cirrhotic patients and liver-transplant recipients and the elucidation of the roles of vitamin A hepatotoxicity, as well as the impact of deficiencies in riboflavin and zinc on clinical outcomes. Early identification and treatment of malnutrition in chronic liver disease has the potential to lead to better disease outcome as well as prevention of the complications of chronic liver disease and improved transplant outcomes. (J Clin Exp Hepatol 2015;5:S131–S140)

Malnutrition is common in end-stage liver disease (cirrhosis) and is often associated with a poor prognosis.[1,2] Malnutrition occurs in all forms of cirrhosis[3] as shown by studies of nutritional status in cirrhosis of differing etiology and of varying degrees of liver insufficiency.[4,5] The prevalence of malnutrition in cirrhosis ranges from 65 to 100% depending upon the methods used for nutritional assessment and the severity of liver disease.[6–9]

Nutritional intervention in cirrhotic patients should aim to support hepatic regeneration, prevent or correct malnutrition and prevent and/or treat the complications associated with cirrhosis. There is a general consensus of opinion that nutritional intervention in patients with cirrhosis improves survival, surgical outcome, liver function, and attenuates complications. Hence, the recognition and treatment of malnutrition is an important issue in the clinical management of these patients.

The aim of the present review is to highlight the implications of malnutrition in patients with cirrhosis on disease outcome, on management of the central nervous system (CNS) complications of cirrhosis and on outcomes following liver transplantation. Nutritional recommendations are also formulated and some areas for future research needs are identified.

Selection of published articles included and cited in the review was based upon PubMed searches using appropriate keywords and their combinations, on articles cited in recently published reviews on the topic of nutrition in cirrhosis and on published abstracts on the topic presented at international meetings of EASL and AASLD.

MALNUTRITION IN LIVER DISEASE

The functional integrity of the liver is essential for the supply and inter-organ trafficking of essential nutrients (proteins, fat and carbohydrates) and the liver plays a crucial role in their metabolism. Many factors disrupt this metabolic balance in the cirrhotic liver. Such factors include increased protein catabolism, decreased hepatic and skeletal muscle glycogen synthesis and increased lipolysis. The pathogenesis of malnutrition in chronic liver disease is multifactorial and

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Abbreviations: AAAs: aromatic amino acids; BCAAs: branched-chain amino acids; BMI: body mass index; CNS: central nervous system; CONUT: controlling nutritional status; HE: hepatic encephalopathy; ISHEN: International Society for Hepatic Encephalopathy and Nitrogen metabolism; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; PNI: prognostic nutritional index
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includes reduced nutrient intake due to anorexia and dietary restrictions, altered nutrient biosynthesis, impaired intestinal absorption, increased protein loss, disturbances in substrate utilization, abnormalities of carbohydrate, lipid and protein metabolism and increased levels of pro-inflammatory cytokines resulting in a hypermetabolic state.[10]

Sarcopenia or loss of muscle mass is a common complication of cirrhosis and adversely affects survival, quality of life, outcome after liver transplantation, and responses to stress including infection and surgery.[9] Sarcopenia contributes to the aggravation of other complications of cirrhosis including encephalopathy, ascites, and portal hypertension.[11–14] In addition, other complications such as infection have the potential to exacerbate skeletal muscle proteolysis and impaired protein synthesis in cirrhosis.

Over-nutrition in the form of obesity is now occurring more frequently in patients with liver disease. Obesity (defined as body mass index (BMI) $\geq$ 30) poses specific and important issues regarding the nutritional management of patients with liver disease, and is a potential etiologic factor for the progression to advanced liver disease.[9] Non-alcoholic fatty liver disease (NAFLD) may also lead to altered nutrient intake associated with obesity. NAFLD is a spectrum ranging from the relatively-benign steatosis to non-alcoholic steato-hepatitis (NASH), with progression to cirrhosis. The prevalence of NAFLD will likely increase secondary to the rising prevalence of obesity, a new reality that will require the design of both adapted and specific nutritional assessments as well as appropriate interventions.

Recently, a group of clinicians and scientists was appointed by the *International Society for Hepatic Encephalopathy and Nitrogen metabolism* (ISHEN) to develop a consensus document on the nutritional management of patients with cirrhosis and hepatic encephalopathy (HE) upon which best practice guidelines would be based.[15] The resulting consensus document emphasizes the need for nutritional assessment and lists requirements for supply of energy, protein, fiber and micronutrients. The following sections discuss in more detail these changes in relation to chronic liver disease.

ENERGY AND PROTEIN

Alterations of energy metabolism in chronic liver disease result in amino acid oxidation leading to protein deficiency, which occurs in all forms of cirrhosis. In addition, underlying pathophysiologic factors may cause loss of protein stores. Resting energy expenditure has been shown to be increased in cirrhotic patients[16] and alterations in energy metabolism related to survival in these patients[17] may even precede malnutrition in some cases.[18]

VITAMINS

In general, vitamin deficiencies in liver disease are related to disorders of hepatic function and diminished reserves and, with increasing severity of the disease, to inadequate dietary intake and/or malabsorption. Fat soluble vitamin deficiencies are common manifestations of malnutrition and liver disease.[19,20] A retrospective study reported that the majority of liver disease patients being considered for liver transplantation present with vitamin A and D deficiencies.[19]

Vitamin A

Vitamin A (retinol) is implicated in ocular retinoid metabolism, tissue repair and immunity, and is principally stored in hepatic stellate cells. As quiescent stellate cells become activated, they lose their vitamin A stores and are then capable of producing collagen and subsequent fibrosis. Vitamin A deficiency has been reported in patients with hepatitis C-related chronic liver disease[21,22] and is associated with non-response to antiviral therapy.[22] Vitamin A deficiency is also present in approximately 50% of patients with alcoholic cirrhosis[21,23] and patients with chronic alcoholism have been shown to have very low concentrations of hepatic vitamin A at all stages of their disease.[24] The presence of HE, a complex neuropsychiatric complication associated with liver disease, is associated with reduced serum retinol levels.[21] Serum retinol levels below $\leq$0.78 μmol/L are associated with liver-related death.[21] Because high doses of vitamin A are potentially hepatotoxic, care must be taken to avoid excessive supplementation.

Vitamin D

Vitamin D undergoes hepatic 25-hydroxylation, rendering the liver critical to the metabolic activation of this vitamin. Chronic liver disease commonly results in vitamin D deficiency.[25–28] In particular, a large proportion of patients with alcoholic liver disease have compromised vitamin D status.[29] Vitamin D deficiency has also been linked to poor outcomes in patients with hepatitis C. Recently, it was demonstrated that extremely low serum levels of vitamin D are associated with increased mortality in patients with chronic liver disease[30] and the authors speculated that an impaired immune function due to vitamin D deficiency could explain this observation. Low vitamin D levels are also associated with poor survival, and with the degree of liver dysfunction and severity of the disease as assessed according to the Child-Pugh system.[26,29,31] It was postulated that a key mechanism responsible for the low serum 25-hydroxy-vitamin D levels in patients with end-stage liver disease may relate to decreased hepatic production of vitamin D binding protein.[20]

Vitamin E

Vitamin E deficiency has been well documented in alcoholic liver disease.[32] However the beneficial effects of vitamin E supplementation in liver disease are dependent

upon the nature of the disorder. For example, vitamin E supplementation in ambulatory patients with decompensated alcoholic cirrhosis was not beneficial at 1-year follow-up[33] and, in a study of patients with mild-to-moderate alcoholic hepatitis, vitamin E supplementation had no beneficial effects on tests of liver function or mortality at 3-month follow-up when compared with placebo.[34] On the other hand, since oxidative stress has been proposed as an important mediator of hepatic injury in NASH,[35–37] vitamin E supplements were evaluated in a double-blind placebo-controlled trial in adults with histologically confirmed NASH.[38] The study demonstrated that vitamin E supplementation resulted in significant improvement in pathologic features of NASH including improvement in liver enzymes, as well as decreases in markers of steatosis and inflammation on liver biopsy.

Vitamin B_1

Thiamine (vitamin B_1) in the form of its diphosphate ester, is an enzyme cofactor involved in glucose and amino acid metabolism and is also, as its triphosphate ester, a component of neuronal membranes. Thiamine deficiency is common in many forms of cirrhosis particularly alcoholic liver disease where it is caused by inadequate dietary intake, decreased hepatic storage, and impairment of intestinal thiamine absorption by ethanol.[39] Wernicke's encephalopathy is a seriously under-diagnosed metabolic encephalopathy with severe neurological symptoms and region-selective neuronal cell death caused by thiamine deficiency is often encountered in chronic alcoholism.[40,41] A neuropathologic study examining brain tissue from patients with autopsy-proven cirrhosis revealed evidence of both acute and chronic hemorrhagic lesions in thalamus and mammillary bodies that are typical of Wernicke's encephalopathy as well as mild-to-severe cerebellar degeneration in cirrhotic patients, suggesting a role of chronic liver disease *per se* on brain thiamine status, a finding that has been attributed to a loss of liver thiamine stores.[42] Unsuspected and irreversible thalamic and cerebellar lesions due to thiamine deficiency could explain the incomplete resolution of neuropsychiatric symptoms following the use of treatment strategies or liver transplantation in patients with end-stage liver failure.

Vitamin B_2

Vitamin B_2 is a cofactor implicated in energy metabolism and also in antioxidant responses. Riboflavin (vitamin B_2) deficiency has been described in patients with either alcoholic or non-alcoholic cirrhosis[43] and has been explained by inadequate intake, increased utilization, deficient absorption and storage, or abnormal metabolism of the vitamin.[44] However, a clear link between riboflavin deficiency and malnutrition in chronic liver disease has not, so far, been definitively established.

Vitamins B_6, B_9 and B_{12}

Deficiencies in pyridoxine (vitamin B_6), folate (vitamin B_9) and cobalamin (vitamin B_{12}) may develop rapidly in chronic liver disease due to diminished hepatic storage. It was reported that alcoholic liver disease patients had low pyridoxine levels with elevated cystathionine and decreased alpha-aminobutyrate/cystathionine ratios, consistent with decreased activity of pyridoxine-dependent cystathionase.[45] Cobalamin is an enzyme cofactor for metabolism of homocysteine to methionine and the metabolism of homocysteine is affected by alcohol abuse. In a recent study, the levels of vitamin B_{12} correlated negatively with homocysteine and positively with the markers of alcohol-related liver injury.[46] Another study showed that plasma levels of vitamin B_{12} in patients with decompensated chronic liver disease were high, whereas plasma folate levels were low.[47] However, whether or not the above changes in vitamin status are of significance for the nutritional management of chronic liver disease or its complications awaits further studies.

MINERALS AND TRACE ELEMENTS

Zinc

Zinc is an essential trace element required for normal cell growth, development and differentiation and zinc deficiency is common in many types of chronic liver disease.[48] Zinc supplementation reportedly reverses clinical signs of zinc deficiency in patients with liver disease[49] and a recent randomized, double-blind, placebo-controlled clinical trial demonstrated that low dose zinc supplementation prevents deterioration of clinical status of cirrhosis.[50] Furthermore, zinc supplementation produced metabolic effects and trended toward improvements in liver function, HE and overall nutritional status.[50] However, a previous double-blind clinical trial showed only a marginal effect of zinc supplementation on HE.[51]

Magnesium

Magnesium deficiency is common in chronic liver disease.[52] It has been demonstrated that alcohol impairs magnesium transport and homeostasis in brain, skeletal muscle, heart and liver.[53] Magnesium deficiency is also associated with peripheral insulin resistance, which is common in alcoholic liver disease[54] and, in a randomized clinical trial, magnesium treatment was reported to improve hepatic enzyme levels.[55]

Selenium

Selenium is incorporated into the active sites of multiple seleno-proteins with established antioxidant functions[56,57] and several studies have shown that chronic liver disease is associated with decreases in serum, whole blood, and hepatic selenium content[58–60] where selenium status

correlated with severity of liver disease being most profoundly decreased in patients with decompensated cirrhosis. It was recently shown that selenium deficiency was also related to the severity of hepatic fibrosis in patients with hepatitis C-related chronic liver disease being one of the factors contributing to insulin resistance in these patients.[61]

Manganese

Total body manganese stores are increased in patients with liver disease,[62,63] which may lead to selective manganese accumulation in several areas of the brain.[64–66] Manganese deposition in basal ganglia structures of the brain has been proposed as the cause of T1-weighted magnetic resonance signal hyperintensities[65] and cirrhosis-related Parkinsonism.[67] Recent reports describe dysfunction of the nigrostriatal dopaminergic neuronal pathway related to manganese toxicity in patients with end-stage liver disease.[68,69]

Iron and Copper

Iron overload and excessive alcohol consumption might act in synergy to promote hepatic fibrogenesis. It was demonstrated that transferrin-iron saturation is associated with an increased incidence of cirrhosis, particularly in the presence of alcohol misuse.[70] Also, untreated iron overload can lead to liver cirrhosis.[71] Copper and copper-associated protein accumulation may be observed in chronic biliary obstructive processes and cirrhosis.[72]

NUTRITION AND DISEASE OUTCOME

Protein-calorie malnutrition is more common in patients with cirrhosis compared to the general population, and is associated with higher in-hospital mortality rates.[73] The severity of liver disease generally correlates with the severity of malnutrition, and protein-calorie malnutrition correlates with worsening clinical outcome.[7] In addition, the degree of malnutrition correlates with the development of serious complications such as ascites, and hepatorenal syndrome[7,12] as well as with a greater risk of post-operative complications and mortality rates in patients with cirrhosis.[74,75]

Even at early stages of the disease, impaired nutritional status is associated with poor clinical outcome. Child-Pugh A patients have a higher 1 year-rate of major complications (refractory ascites, HE, variceal bleeding or hepatorenal syndrome) and/or death.[76] In addition to clinical outcome, a range of physiological functions are also affected by a poor nutritional status in cirrhotic patients. For example, knee and ankle muscle strength and handgrip strength are decreased in these patients.[76–78] Furthermore, malnutrition in cirrhotic patients is related to impaired immunocompetence.[44,79,80] Infections and sepsis are also associated with liver cirrhosis and malnutrition.[81,82]

NUTRITION AND THE CENTRAL NERVOUS SYSTEM COMPLICATIONS OF CIRRHOSIS

Malnutrition is implicated in disorders of neuropsychiatric function in cirrhotic patients who are prone to developing HE and it has been demonstrated that low energy intake and poor nutritional status may facilitate the development of this complication.[83] For example, a recent prospective study demonstrated that cirrhotic patients with muscle depletion are at higher risk of HE and that the amelioration of nutritional status is an effective goal to decrease the prevalence of cognitive impairment in these patients.[84]

As mentioned above, cirrhosis is often associated with thiamine (vitamin B_1) deficiency leading to increased prevalence of Wernicke's encephalopathy, a finding that has been attributed to loss of liver stores of thiamine.[85] In addition, cirrhosis is characterized by an imbalance in plasma levels of aromatic amino acids (AAAs) and branched-chain amino acids (BCAAs) and it has been suggested that altered plasma and brain BCAA/AAA ratios are implicated in the pathogenesis of HE in cirrhosis.[86,87]

MALNUTRITION AND OUTCOME FOLLOWING LIVER TRANSPLANTATION

The presence of malnutrition in patients awaiting liver transplantation, the only curative treatment for end-stage liver disease, is well recognized[88,89] and cirrhotic patients on the waiting list for liver transplantation often present with a spectrum of malnutrition disorders ranging from under-nutrition to obesity. The negative impact of malnutrition on liver transplantation had initially been reported in early retrospective studies[90] and both preoperative hypermetabolism and body cell mass depletion was shown to be of prognostic value for transplantation outcome.[17] However, while the presence of a poor nutritional status may generally be considered to be one of the predictive factors for increased morbidity and mortality rates after liver transplantation, hard evidence for this supposition continues to elude us. For example, while some studies found that malnutrition in transplant patients resulted in increases in operative blood loss, length of stay in the intensive care unit, mortality and total hospital costs,[91–93] these observations were not confirmed by others.[78,94,95]

Malnutrition is known to lead to glycogen depletion, and this has been suggested to result in increased plasma lactate: pyruvate ratios during the an hepatic phase and to favor the development of a post-operative systemic inflammatory response syndrome and multi-organ failure in these patients.[96] In a prospective study, Merli et al[97] presented data suggesting that malnutrition should be taken into account as a factor that increases both costs and post-transplant complications. Moreover, they demonstrated

that malnutrition was the only independent risk factor for the length of stay in the intensive care unit and the total number of days of hospitalization in these patients. Others reported that pre-transplant nutritional status has a serious impact on the incidence of post-transplant sepsis.[98] In view of the rather discrepant findings from studies of the effects of malnutrition on post-transplant outcome, further assessments are required in order to make specific recommendations for nutritional management in cirrhotic patients awaiting transplantation.

In the post-transplant period, nutritional therapy has been shown to improve balance and decrease the incidence of viral infections with a trend to shortening length of stay in the intensive care unit and consequent lowering of costs.[99,100]

There has been a dramatic increase in the prevalence of obesity in liver-transplant recipients. Obesity increases early morbidity and mortality at the time of transplantation[101,102] and patients with a BMI greater than 35, when compared with patients with a BMI below 30, manifest higher intra-operative blood loss, more frequent multi-organ failure, and higher risk of infections. Results of other studies suggest that obese patients have higher post-transplant complications, longer hospital stays and higher hospital costs.[101–106] Obesity may also exaggerate the negative impact of risk factors such as donor graft cold ischemia time.[107] Patients with diabetes or coronary artery disease, both commonly associated with obesity, are approximately 40% more likely to die within 5 years of liver transplantation compared to non-diabetics or to patients without coronary artery disease.[108,109] Metabolic syndrome, a disorder in which obesity, insulin resistance, high blood pressure and dyslipidemia coexist, is highly prevalent in liver transplant patients[110] and is predicted by alcoholic etiology of cirrhosis, excessive weight prior to transplantation, as well as reduced intakes of calcium, potassium, fiber and folate.[110] Finally, in line with these observations, despite excellent graft function, many long-term liver transplant survivors manifest a sarcopenic obesity-phenotype characterized by increased body fat but low muscle mass.[111]

The impact of nutritional status on neurological complications following liver transplantation has recently been reviewed.[10] Neurological complications post-liver transplantation are legion and include diffuse encephalopathy, seizures, intracranial hemorrhage and stroke, post-operative metabolic encephalopathy, fatal progressive neurological deterioration, peripheral nerve damage, central pontine myelinolysis, cerebral abscess, ataxia, non-encephalopathic psychosis and confabulation.[112–114] The incidence of these complications is generally reported to be in the 25–75% range.[112,115–121] As mentioned above, some of these "complications" may be attributable to unrecognized pre-existing neural deficits related to malnutrition.

ASSESSMENT OF NUTRITIONAL STATUS

Accurate nutritional assessment remains a challenge in patients with cirrhosis since many of the traditionally-employed parameters of nutritional status vary with severity of liver disease and there are no methods currently considered to represent a gold standard. Commonly used methods including subjective global assessment (based on physical symptoms of malnutrition and a knowledge of nutritional history), anthropometrics and bio-impedance analysis are all influenced by liver disease *per se*.[122,123] Moreover, in a recent prospective study, a range of methods including subjective global assessment, anthropometry, handgrip dynamometry and associated biochemical tests were found to result in a wide variability of results and lack of a clear consensus.[124]

In one potentially interesting new development, Morgan et al[125] validated a method whereby BMI and mid-arm muscle circumference were combined with details of dietary intake in a semi-structured algorithm construct to provide a sensitive and reproducible instrument for nutritional assessment in patients with chronic liver diseases. Use of this method has, however, not gained wide acceptance at this moment in time.

In another recent study, parameters such as the prognostic nutritional index (PNI) and controlling nutritional status (CONUT) were tested as nutritional assessment tools in patients with chronic liver disease.[126] These are simple assessment constructs of only two or three biochemical examinations of (blood albumin, total lymphocyte count, and total cholesterol) that were shown to be associated with both the severity of chronic liver disease and anthropometric values leading the authors to propose that they represent simple effective tools for nutritional assessment in patients with chronic liver disease. However, the use of albumin, a visceral protein synthesized by the liver, in these equations is questionable since visceral proteins appear to correlate better with the severity of underlying liver disease rather than with malnutrition status.[127] It has also been demonstrated that blood iron levels are significantly decreased in chronic liver disease patients suffering from malnutrition but is not altered in well-nourished chronic liver disease patients,[128] a finding that could afford complementary information on nutritional status in these patients. At the present time, given the lack of a single indicator of malnutrition in liver disease, the subjective global assessment in conjunction with a combination of other tests is generally employed.[129–131] Given the wide consensus that nutritional status should be routinely assessed in all patients with chronic liver disease in order to recognize malnutrition and prevent nutritional depletion, the development of a simple, well-validated and reproducible tool for the assessment of nutritional status in these patients is long overdue.

NUTRITIONAL RECOMMENDATIONS

General Nutritional Recommendations in Cirrhosis

Nutritional recommendations for cirrhotic patients in general focus on suppression of hepatotoxic agents and the provision of optimal macronutrient supply in terms of energy, protein, carbohydrates and lipids together with micronutrients such as vitamins and minerals.[15,132] Energy, macro- and micronutrient supplies should be based on the results of individual nutritional assessments and adjusted for weight maintenance and/or repletion. General recommendations are summarized in Table 1.

Nutritional Recommendations for HE in Cirrhosis

Nutritional recommendations for cirrhotic patients with HE should follow ISHEN practice consensus recently published by Amodio et al.[15] These recommendations, including specific pattern of dietary intake,[133,134] which should also be based on individual nutritional assessment, are summarized in Table 2.

Nutritional Recommendations Related to Liver Transplantation in Cirrhosis

The interval between listing and transplantation provides a therapeutic window to establish nutritional management before the surgical procedure. The main goals of pre-transplant nutritional management are prevention of further energy and nutrient depletion and correction of macro- and micronutrient deficiencies. Nutrient supply should include adequate calories, proteins, vitamins, minerals and trace elements. Determining the extent of nutritional supplementation requires calculation of the individual patient's energy needs.

Table 1 General Recommendations for Cirrhotic Patients.

Nutriment	Recommendation
Energy	30–50 kcal/kg body weight Sufficient to restore/maintain nutritional status and enhance liver regeneration (adjust for obese patients)
Protein	1.0–1.8 g/kg body weight depending on the severity of malnutrition (adjust if renal disease present)
Carbohydrates	45–75% of caloric intake or 4–6 meals rich in carbohydrates per day
Lipids	20–30% of caloric intake (adjust if steatorrhea present)
Vitamins	B group vitamin supplements Particular attention to lipid-soluble vitamins Correct specific deficiencies
Minerals	Zinc, magnesium and selenium supplements Correct specific deficiencies

Preoperative malnutrition, surgical stress, post-interventional complications and post-operative protein catabolism suggest the need for early nutritional support following liver transplantation. Early post-transplant nutritional intervention improves a number of surrogates of nutritional status in liver-transplant patients. Pre-transplant nutritional assessment and nutritional intervention followed by post-surgical monitoring and follow-up after recovery are required. Additional well-designed and controlled studies are needed in order to elaborate precise nutritional recommendations for these patients.

FUTURE RESEARCH

Several issues relating to the impact of malnutrition and outcomes in chronic liver disease remain to be addressed. Firstly, a well-designed, validated, accurate, simple and reproducible tool for nutritional assessment is needed. Secondly, there has been little focus on the prevalence, impact, consequences, and mechanistic targets or therapy for sarcopenia in cirrhosis. Studies for the identification of signaling pathways responsible for regulation of muscle mass in cirrhosis, including sarcopenic obesity, are required. Another important issue relates to nutritional recommendations for obese cirrhotic patients. In addition, the impact of vitamin A hepatotoxicity as well as vitamin E, riboflavin and zinc deficiencies on the progression of cirrhosis and its complications require further investigation. Finally, the important issue of nutritional recommendations in liver-transplant patients remain to be comprehensively formulated. Figure 1 summarizes important issues relating to nutrition and chronic liver disease.

Table 2 Nutritional Recommendations for Cirrhotic Patients with HE.

Nutrient	Recommendation
Energy	Optimal daily energy intake; 30–40 kcal/kg body weight Small meals evenly distributed throughout the day and late snack[a] of complex carbohydrates; (adjust for obese patients)
Protein	Optimal daily protein intake; 1.2–1.5 g/kg body weight Encourage diet rich in vegetables and dairy protein If patient intolerant to dietary protein, consider BCAA supplementation[b]
Fiber	25–45 g/daily
Vitamins and minerals	Multivitamin preparation in patients at increased risk of malnutrition; Correct specific deficiencies

[a]Late evening snacks allow cirrhotic patients to minimize gluconeogenesis, reduce protein utilization and favor a positive nitrogen balance.[127,128]

[b]BCAAs, which are not metabolized by the liver, provide an alternative source of proteins.

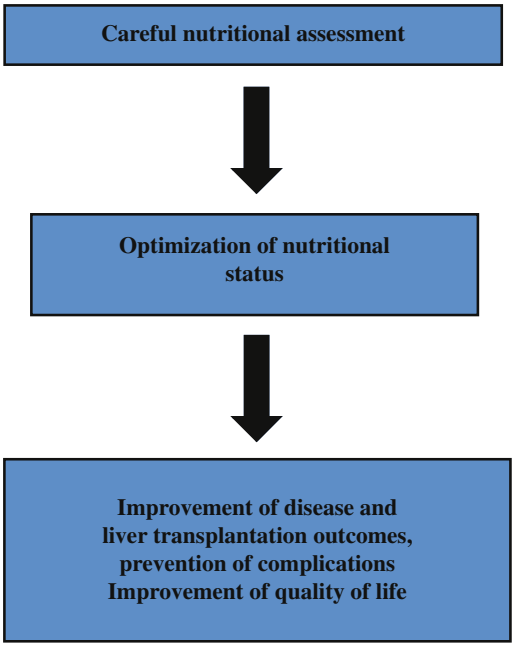

Figure 1 Impact of nutritional management on outcome in cirrhotic patients.

CONCLUSION

In summary, malnutrition is common in chronic liver diseases and may impact negatively on disease outcome, on the incidence and severity of complications and on outcome following liver transplantation. The pathogenesis of malnutrition in chronic liver disease is multifactorial. Malnutrition in liver transplanted patients is one of the predictive factors for increased morbidity and mortality. The incidence of complications of liver disease *per se* and of liver transplantation increases with malnutrition and the impact of nutritional intervention on outcomes in cirrhotic patients may vary with the etiology and severity of the disease. Nutritional status in cirrhotic patients should be precisely and accurately assessed in order to design a nutritional intervention adapted to the needs of the individual patient. Early identification and treatment of malnutrition has the potential to lead to better disease outcome, prevention of complications of the disease and improved post-transplant outcomes.

CONFLICTS OF INTEREST

All authors have none to declare.

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