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 2014;4:141–150)

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 includes reduced nutrient intake due to anorexia and dietary restrictions, altered nutrient

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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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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

