Nutrition in End-Stage Liver Disease: Principles and Practice

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Malnutrition is commonly seen in both alcoholic and nonalcoholic liver disease[1–3] and has been shown to adversely affect outcome (see Figure 1).[4,5] By definition, it occurs when diet does not provide adequate calories and protein to maintain nutritional status or the body is unable to fully absorb or utilize food eaten secondary to liver disease. Despite the obvious relevance, clinical research in this field is surprisingly limited and malnutrition is frequently underdiagnosed in clinical practice.[6]

The prevalence of malnutrition in cirrhosis is as high as 65%–90%.[1–3] Evidence concerning the impact of etiology (of cirrhosis) on malnutrition is conflicting. Some studies have shown no difference in prevalence and severity of malnutrition in patients with viral- and alcohol-related cirrhosis who were abstinent.[2,7,8] Others have shown that alcoholic cirrhosis was associated with a poorer nutritional state compared with virus-associated cirrhosis.[9] Active alcoholism is a major cause of malnutrition per se and could contribute to the earlier development observed.[10] Protein depletion and reduced muscle function are common in cirrhosis, particularly in men and patients with alcoholic liver disease.[11] The reason for the male preponderance is unknown and is not related to hypermetabolism or reduced energy and protein intake.[11] The reduced levels of testosterone observed in male patients with cirrhosis[12] may contribute to decreased protein anabolism, but this requires further investigation. The largest studies on prevalence and severity have been the Veterans Affairs Cooperative Studies in 1984 and 1993, which focused on alcoholic hepatitis.[13,14] These and other studies showed that the severity of malnutrition correlated with that of the liver disease and the development of serious complications such as hepatic encephalopathy, ascites, hepatorenal syndrome, post-transplantation outcome, and mortality.[15–18] Also, short-term survival is reduced in parallel with severity of malnutrition.[19] The majority of patients in these pivotal studies had advanced liver disease; however, more sophisticated methods of analysis (neutron activation analysis or intracellular/extracellular body water) have shown that significant losses of body cell mass may occur in Child A cirrhosis.[20]

In this review, we examine the mechanisms underlying malnutrition in chronic liver disease, the assessment methods available, and the role of nutritional therapy (advice, supplementation, enteral or parenteral) in the various stages of chronic liver disease. Acute liver failure and transplantation and the emerging data on probiotics are considered separately.

Mechanisms of Malnutrition in Cirrhosis

A variety of mechanisms are considered to contribute to malnutrition in cirrhosis: poor dietary intake, malabsorption, increased intestinal protein losses, low protein synthesis, disturbances in substrate utilization, and hypermetabolism. Many of these are not fully understood.

In advanced liver disease, patients often have poor dietary intake. Recommended diets may be unpalatable because of the sodium restriction needed for control of ascites and peripheral edema. A distortion or decrease in taste sensation (dysgeusia) associated with zinc or magnesium deficiency is well described and may contribute.[21] Nausea and early satiety are well recognized, secondary to gastroparesis, tense ascites, small bowel dysmotility, and bacterial overgrowth.[22,23] When admitted to the hospital, malnutrition is paradoxically further worsened as patients are often starved, for instance, for endoscopy. In addition, as glucose storage is reduced in alcohol-induced cirrhosis,[24] gluconeogenesis is active and can cause muscle mass breakdown to provide amino acids for glucose

Abbreviations used in this paper: BCAA, branched-chain amino acid; DEXA, dual-energy x-ray absorptiometry; PUFA, polyunsaturated fatty acid; SAMe, S-adenosylmethionine.

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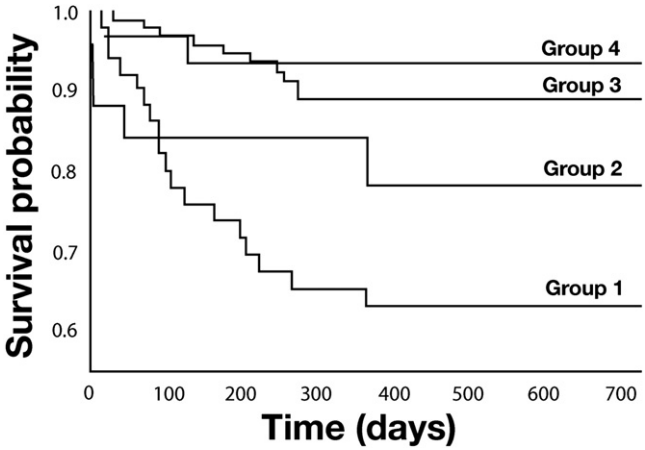

Figure 1. Malnutrition is predictive of survival in patients with liver cirrhosis. Survival rates in patients with midarm muscle circumferences below the 5th (group 1), 10th (group 2), and 75th (group 3) percentiles and above the 75th percentile (group 4). $P < .001$ at 6, 12, and 24 months between patients with severe and moderate malnutrition (groups 1 and 2, respectively) and those with normal and overnourished nutrition (groups 3 and 4, respectively). Patients with transplants were screened at the time of transplantation. Reprinted with permission from Alberino et al.[5]

formation.[25] Patients need frequent meals to protect muscle mass, which are not always provided. However, even when inpatients receive specific attention to nutrition, as in the Veterans Affairs Cooperative Studies, only 67% were found to consume the recommended 2500-kcal diet.[13,14] In severe cholestasis, intraluminal bile salts are reduced with consequent malabsorption of fat and fat-soluble vitamins. This can be further worsened by neomycin, which may blunt intestinal villi, and the use of cholestyramine for pruritus, which may induce bile salt deficiency.[26]

The metabolic disturbances consequent to liver disease, such as increased energy expenditure,[27,28] insulin resistance,[29] and low respiratory quotient (indicating reduced glucose and increased lipid oxygenation),[30] may contribute to malnutrition even in the early stages. Hypermetabolic patients tend to weigh less, are more frequently malnourished, and have a higher mortality than normometabolic patients.[31] The estimated prevalence of hypermetabolism varies considerably, with the largest study of 473 cirrhotic patients reporting 34%.[32] A smaller study of 50 cirrhotic patients found only 2 hypermetabolic patients,[33] whereas a more recent study of 268 patients found 15%.[11] The cause of hypermetabolism is unclear, with one group finding no association with sex, etiology, severity of disease, protein depletion, and presence of ascites or tumor.[11] Indirect evidence suggests that 25% of hypermetabolism in cirrhosis may be explained by increased sympathetic nervous system activity, possibly as part of the commonly observed hyperdynamic circulation.[34] Sepsis is common in liver disease and is likely to increase energy expenditure further. The use of β-blockade for variceal bleeding prophylaxis, which will reduce metabolic rate, is likely to be a confounding variable. Measurement of energy expenditure by indirect calorimetry is not straightforward or frequently available, and estimates such as the Harris–Benedict equation are commonly applied.[35] It should be noted that significant differences have been shown between resting energy expenditure values measured by indirect calorimetry and such estimations.[36]

Polyunsaturated fatty acid (PUFA) deficiency is common in cirrhosis, especially alcoholic cirrhosis, because PUFA synthesis from essential fatty acid precursors occurs in the liver.[37] PUFA deficiency has been found in plasma lipids, erythrocytes, platelets, and adipocytes.[37] Parenchymal cells are most likely deficient, although no data exist. The consequences of PUFA deficiency are unclear, and supplementation is controversial.[38] PUFA contributes to the fluidity of cell membranes and the release of an array of secondary messengers (including eicosanoids), and PUFA deficiency is an independent predictive factor of mortality in alcoholic cirrhosis.[37] However, attempts to reverse deficiency have been disappointing; for example, parenteral nutrition containing Intralipid (a soybean oil, linoleic acid–based lipid emulsion; Fresenius Kabi, Uppsala, Sweden) failed to improve long-chain PUFA deficiency in 9 malnourished alcoholic patients.[39] Intriguingly, in alcohol-fed rats, a PUFA-enriched diet led to more severe liver injury than a diet enriched in saturated fatty acids.[40] Also, PUFA deficiency has been shown to reverse alcohol-related mitochondrial dysfunction in rodents via an increase in phospholipid arachidonic over linoleic ratio, which raises cytochrome oxidase activity.[41] Thus, PUFA deficiency may be an adaptive phenomenon to counteract the decline in adenosine triphosphate synthesis flux.

Micronutrient Deficiencies in Cirrhosis

Deficiencies in water-soluble vitamins (vitamin B complex and C) are common in alcoholic cirrhosis in particular but also occur in nonalcoholic liver disease.[42] The risks of Wernicke's encephalopathy and Korsakoff's dementia are well described in alcoholic patients deficient in thiamine.[43] Thiamine deficiency has also been shown in hepatitis C–related cirrhosis,[44] and administration of thiamine to all cirrhotic patients has been recommended. Fat-soluble vitamin deficiencies occur more commonly in the cholestatic liver syndromes. Vitamin A (retinol) deficiency has been described in cirrhosis and is considered a risk factor for development of cancer, including hepatocellular carcinoma.[45] Vitamin E, an antioxidant, is reduced in cholestasis and alcoholic liver disease. Low levels of trace elements such as selenium and zinc have been described.[46] Zinc deficiency in patients with chronic alcoholism is attributed to decreased intake and absorption and diuretic-induced increased urinary excretion.[47] Supplementation with zinc has been shown to improve