M alnutrition 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

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**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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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. 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.

The metabolic disturbances consequent to liver disease, such as increased energy expenditure, insulin resistance, and low respiratory quotient (indicating reduced glucose and increased lipid oxygenation), 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. The estimated prevalence of hypermetabolism varies considerably, with the largest study of 473 cirrhotic patients reporting 34%. A smaller study of 50 cirrhotic patients found only 2 hypermetabolic patients, whereas a more recent study of 268 patients found 15%. 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. 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. Sepsis is common in liver disease and is likely to increase energy expenditure further. The use of \( \beta \)-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. It should be noted that significant differences have been shown between resting energy expenditure values measured by indirect calorimetry and such estimations.

Polyunsaturated fatty acid (PUFA) deficiency is common in cirrhosis, especially alcoholic cirrhosis, because PUFA synthesis from essential fatty acid precursors occurs in the liver. PUFA deficiency has been found in plasma lipids, erythrocytes, platelets, and adipocytes. Parenchymal cells are most likely deficient, although no data exist. The consequences of PUFA deficiency are unclear, and supplementation is controversial. 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. 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. Intriguingly, in alcohol-fed rats, a PUFA-enriched diet led to more severe liver injury than a diet enriched in saturated fatty acids. 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. 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. The risks of Wernicke’s encephalopathy and Korsakoff’s dementia are well described in alcoholic patients deficient in thiamine. Thiamine deficiency has also been shown in hepatitis C–related cirrhosis, 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. 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. Zinc deficiency in patients with chronic alcoholism is attributed to decreased intake and absorption and diuretic-induced increased urinary excretion. Supplementation with zinc has been shown to improve
glucose disposal in cirrhotic patients, and deficiency may contribute to the impaired glucose tolerance and diabetes commonly observed. Zinc deficiency is considered to precipitate hepatic encephalopathy; however, trials of supplementation have shown conflicting results. Zinc is also used in alcoholic patients for treatment of night blindness not responsive to vitamin A. Magnesium deficiency occurs in alcoholic liver disease, and muscle magnesium is an independent predictor of muscle strength. This is probably related to the reduced content of sodium-potassium pumps in skeletal muscle that accompanies magnesium deficiency. However, supplementation did not restore muscle magnesium or improve muscle function in patients with alcoholic liver disease. Interestingly, patients treated with spironolactone had higher contents of sodium-potassium pumps; the underlying mechanism is unclear and the subject of ongoing investigation.

Studies have shown that serum levels of 25-hydroxyvitamin D are low in patients with liver disease and fall with disease progression. The likely causes include reduced exposure to UV light, dietary insufficiency, and malabsorption. A high prevalence of osteoporosis is reported in both cholestatic and noncholestatic cirrhosis. Treatment with corticosteroids as part of immunosuppressive regimens for autoimmune hepatitis and following liver transplantation is a risk factor. Few randomized controlled trials have assessed the role of intervention in prevention of osteoporosis in chronic liver disease. However, it is reasonable to recommend correction of vitamin D insufficiency with vitamin D3 and calcium in conditions where osteoporosis is likely. In addition, hormone replacement therapy increases bone mineral density in primary biliary cirrhosis and should always be considered for postmenopausal women. All patients with chronic liver disease should undergo a dual-energy x-ray absorptiometry (DEXA) scan to assess bone mineral density. Treatment with bisphosphonates is recommended in those with osteoporosis, as for noncirrhotic patients. Oral alendronate (not risedronate) may cause esophageal ulceration and should be avoided in view of the risk of precipitating variceal hemorrhage; cyclical etidronate appears safe.

Diagnosis and Assessment

It is not difficult to diagnose malnutrition in a cachectic patient with advanced liver disease, but in earlier stages of the disease diagnosis is more challenging. In addition, the cachexia of liver disease may develop insidiously and be masked by edema. Early diagnosis is important to allow appropriate intervention, because malnutrition is predictive of complications of liver disease and mortality. There is no gold standard for clinical assessment. Body weight can be misleading in patients with ascites and peripheral edema, although one study has validated body mass index in cirrhotic patients with cut-off values of 22 kg/m² in nonascitic patients, 23 kg/m² for patients with mild ascites, and 25 kg/m² for patients with tense ascites. The creatinine height index can be unreliable owing to frequent disturbances in renal function in patients with liver disease.

Protein catabolism is a hallmark of critical illness. One can assess protein requirement by measuring the nitrogen balance, intake excretion, in which intake represents nutritional nitrogen and excretion, the sum of measured urinary nitrogen plus an estimate of cutaneous and gastrointestinal losses. Achievement of a positive nitrogen balance is widely considered to be the primary goal of nutritional support, and several studies of nutrition in liver disease have reported clinical improvements associated with increases in nitrogen balance. Indeed, improved nitrogen balance calculations of improvement over time in response to nutrition is the single nutritional variable most consistently associated with improved outcome during critical illness. However, nitrogen balance is rarely measured outside clinical trials and is not routine practice at the authors’ hospital.

The 2 common bedside assessments, plasma protein concentration and anthropometry, both have significant drawbacks. Plasma protein concentration correlates better with the severity of liver disease than with malnutrition. Anthropometric techniques such as midarm muscle circumference assess body composition. Fat-free mass (lean body weight; water, protein, and mineral) and fat mass are measured, and these techniques are referred to as 2-compartment systems. Anthropometric techniques may be affected by edema and have been shown in one study to classify up to 20%–30% of healthy controls as undernourished. However, several other studies have shown that anthropometric measurements and handgrip strength correlate well with more sophisticated assessments such as DEXA in cirrhotic patients. Indeed, midarm muscle circumference was shown to be an independent predictor of mortality in advanced cirrhosis. In an Italian multicenter study of more than 1000 patients, survival was related to midarm muscle circumference for Child A and B but not C. Midarm muscle circumference has also been shown to be independently associated with survival and improve prognostic accuracy when combined with the Child score. The measurement of phase angle by bioimpedance analysis as an indicator of body cell mass has been shown to be of prognostic significance in cirrhosis; however, most, but not all, investigators deem it unreliable in patients with ascites. Subjective global assessment uses clinical information obtained during history taking and examination to determine nutritional status without objective measurements and can determine outcome in patients with cirrhosis. However, when compared with nutritional prognostic index and handgrip strength, handgrip strength was the only method that predicted a poorer clinical outcome.
guidelines state that bedside methods such as subjective global assessment, anthropometry, or handgrip strength are adequate for identification of undernutrition and that composite scores do not add value. For quantitative analysis, the determination of phase angle or body cell mass using bioimpedance analysis is recommended rather than anthropometry, despite limitations with ascites. The authors’ current practice is to use subjective global assessment or handgrip strength.

Although anthropometrical methods are useful for initial assessment, they are of much less value for monitoring treatment effects because of their high coefficient of variation and interobserver variability. Thus, more sophisticated methods are often used in research studies, such as DEXA and in vivo neutron activation analysis. The limitations of 2-compartment assessment methods that distinguish fat mass from fat-free mass have been recently highlighted. This study compared a 4-component model (data obtained from densitometry, deuterium dilution, and DEXA) with reference and bedside 2-component techniques, such as anthropometry, DEXA, and bioimpedance analysis. Significant differences were found between 2-compartment and 4-compartment techniques, and the authors concluded that assumptions relating to the density and hydration fraction of fat-free mass were violated in cirrhosis and thus standard 2-component techniques are inaccurate. They advocate multicomponent models for research or when precise data are required. In a separate study, they described a new method for assessing nutritional status in cirrhosis using midarm muscle circumference, dietary intake, and a subjective override. This method was found to be reproducible, valid against a 4-component model, and a significant predictor of survival (see Figure 2).

**Figure 2.** Scheme for determining nutritional status in patients with cirrhosis. Patients are categorized in relation to their body mass index (BMI), midarm muscle circumference (MAMC), and dietary intake into one of 3 categories: adequately nourished, moderately malnourished (or suspected to be), and severely malnourished. A subjective override based on factors such as profound weight loss or recent significant improvements in appetite and dietary intake can be used to modify the classification by one category only. Reprinted with permission from Morgan et al.78

**Table 1.** Standard Approach

<table>
<thead>
<tr>
<th>Step</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Assess nutritional status&lt;br&gt;Body mass index ± subjective global assessment or handgrip strength</td>
</tr>
<tr>
<td>2.</td>
<td>Teach&lt;br&gt;Frequent meals (4–7/day with 1 late evening snack)&lt;br&gt;Low-sodium diet (2 g or 88 mmol/day) if ascites or edema</td>
</tr>
<tr>
<td>3.</td>
<td>If moderate-severe malnourishment&lt;br&gt;Encourage oral intake&lt;br&gt;Add oral nutritional supplement&lt;br&gt;Prospective calorie count every 2–3 days&lt;br&gt;Provide multivitamins and correct specific deficiencies (eg, vitamin D, zinc)&lt;br&gt;Fluid restriction only when hyponatremia present (sodium level &lt;120 mmol/L)&lt;br&gt;Consider patients for indirect calorimetric studies&lt;br&gt;Consider DEXA scan for bone mineral density and treatment if osteoporotic</td>
</tr>
<tr>
<td>4.</td>
<td>If intake &lt;35–40 kcal · kg⁻¹ · day⁻¹ and protein &lt;1.2–1.5 g · kg⁻¹ · day⁻¹&lt;br&gt;Start enteral nutrition to provide above requirements</td>
</tr>
<tr>
<td>5.</td>
<td>If hepatic encephalopathy or protein intolerant&lt;br&gt;Maximize encephalopathy treatment (lactulose, rifaximin, and so on)&lt;br&gt;Consider BCAAs</td>
</tr>
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</table>

**Treatment**

Patients with cirrhosis should have a full assessment of nutritional status at presentation (see previous text and Table 1). An intake of 35–40 kcal · kg⁻¹ · day⁻¹ (dry body weight) and 1.2–1.5 g · kg⁻¹ · day⁻¹ of protein is desirable. Conventional diet therapy combined with supplementation is the mainstay of long-term nutritional support in the majority. The first report showing the benefit of a nutritious diet in alcoholic cirrhosis was published as long ago as 1948, and several studies since have shown that a modified eating pattern with 4–7 small meals, including at least one late evening carbohydrate-rich snack, improves nitrogen economy and partially reverses the abnormal substrate oxidation of cirrhotic patients.

Restriction of sodium, the main extracellular compartment electrolyte, is crucial to minimize the diuretic dose.
necessary to control ascites, peripheral edema, and hepatic hydrothorax. A 2-g (88 mmol/L) sodium-restricted diet is recommended rather than the previous 0.5 g, which is very unpalatable.

In severely malnourished patients with cirrhosis, feeding approximately 40 kcal · kg⁻¹ · day⁻¹ orally over 1 month increases body fat mass, irrespective of the degree of liver damage. When counseling is insufficient to maintain an intake of 35–40 kcal · kg⁻¹ · day⁻¹ and 1.2–1.5 g · kg⁻¹ · day⁻¹ protein, as documented by calorie count, chemically defined nutritional oral supplements should be added. A controlled trial with a daily supplement of 1000 kcal and 34 g protein for 1 year in alcoholic cirrhosis showed a reduction in hospitalization due to fewer infective episodes and a trend to improved survival. Additionally, 3 months of treatment with a daily supplement containing 500 kcal, 32 g protein, 11 g fat, and 70 g carbohydrate improved nutritional and biological parameters in malnourished cirrhotic patients.

If nutritional supplementation is insufficient to maintain desired intake, then artificial nutrition should be commenced, either via a nasogastric feeding tube (enterally) or intravenously (parenterally). A nasoenteric (nasoduodenal or nasojugal) feeding tube is considered a better option; however, insertion requires an endoscopic procedure, and thus nasogastric tubes are used more commonly. Although mostly used for inpatients because of practical considerations, both forms of artificial nutrition may be tolerated at home, with appropriate support.

A whole protein formula providing 35–40 kcal · kg⁻¹ · day⁻¹ energy and 1.2–1.5 g · kg⁻¹ · day⁻¹ protein is recommended for enteral feeding. Standard preparations contain approximately 100 kcal energy, 4 g protein, and 3.5 mmol of sodium and potassium per 100 mL. Concentrated high energy (1.5 kcal/mL) and protein formulas are available in many countries and may be preferable in patients with hyponatremia and ascites to regulate fluid balance. This may also improve treatment adherence because less volume needs to be consumed. For patients who develop steatorrhea, it is important to limit long-chain fatty acids and increase short-chain and medium-chain fatty acids in the formula. Pancreatic enzymes should be supplemented, especially in patients with alcohol-related cirrhosis in whom pancreatic insufficiency is common. As these enzymes are inactivated by gastric acid, proton pump inhibitors are necessary. Four randomized trials concerning total enteral nutrition in cirrhosis have been reported. Three showed an increased dietary intake over conventional oral diet, and 2 showed improvements in liver function. One showed lower hospital mortality compared with conventional diet. The fourth was performed in well-nourished patients admitted with variceal bleeding and failed to show benefit in nutritional status or disease-related morbidity and mortality. However, most of these patients were able to eat 2000 kcal/day from day 4. In hospitalized patients with an inadequate dietary intake, enteral nutrition should be commenced as soon as possible, ideally within 24–48 hours of admission. This is illustrated by a prospective study in 396 patients showing that a decrease in dietary intake was an independent predictor of hospital mortality and corresponded with a deterioration of liver function.

Two important considerations during nasogastric feeding are hepatic encephalopathy and variceal bleeding. Hepatic encephalopathy must be treated aggressively with lactulose or rifaximin and attention given to possible precipitating causes (e.g., electrolyte status, hypoxemia, sedative use, and presence of sepsis or variceal bleed). Traditionally, a restricted protein diet has been considered a mainstay of treatment; however, cirrhotic patients exhibit increased protein requirements to achieve balanced nitrogen metabolism, and normal protein diets have been given safely to patients with hepatic encephalopathy. Thus, restriction is rarely required but, if necessary, usually for no more than 48 hours. It should be noted that the recommended protein supplementation is based on “dry” body weight and may need alteration in edematous patients. Importantly, the risk of aspiration pneumonia in patients with advanced hepatic encephalopathy during tube feeding must be weighed against the potential complications of parenteral nutrition (see below). The European Society for Parenteral and Enteral Nutrition guidelines support insertion of fine-bore nasogastric tubes in patients with esophageal varices. This has been addressed in only one study, in which 22 patients with esophageal varices after bleeding and endoscopic treatment were randomized to either nasogastric feeding or no oral diet for 3 days. Recurrent bleeding occurred in 3 patients from the nasogastric tube group but none of the controls. In light of these findings, it has been suggested that the guidelines should state that tube feeding is dangerous in patients with esophageal varices that have bled before and that in patients without former bleeding, there is a tendency for an adverse effect. The European Society for Clinical Nutrition and Metabolism authors responded that endoscopic therapies in this study were unbalanced between the 2 groups, which might have influenced outcome, with a higher proportion of injection sclerotherapy in the feeding group as opposed to a greater number of band ligations in controls. They also referred to a small series of tube-fed cirrhotic patients in which fine-bore tubes did not provoke variceal hemorrhage and a trial of low/normal protein diets via fine-bore tube in hepatic encephalopathy in which gastrointestinal bleeding occurred in only one of 30 patients. They concluded “if patients are unable to maintain adequate oral intake, tube feeding is recommended (even when esophageal varices are present).” They acknowledged that there is concern in the immediate days following a bleed. In-
deed, our current practice is to wait at least 24 hours following endoscopic therapy for a bleed and then insert a nasogastric tube and commence feeding.

Total parenteral nutrition (containing Intralipid, amino acids, dextrose, electrolytes, vitamins, and minerals) in severe alcoholic hepatitis has shown benefit in liver function but not (short-term) survival. One study in patients with transjugular intrahepatic portosystemic shunts concluded that small intestinal metabolism contributes to postfeeding (enteral) hyperammonemia, which may worsen hepatic encephalopathy, and that, in such cases, parenteral nutrition may be superior to enteral nutrition. Further supportive evidence comes from a meta-analysis of studies performed in the 1980s using parenteral nutrition in hepatic coma. This showed probable improved survival, but the studies were very heterogeneous and so firm conclusions are difficult to draw. However, the risks of mechanical complications (eg, pneumothorax) and catheter-related sepsis are high in malnourished cirrhotic patients; it is essential that parenteral nutrition is administered via a dedicated line to reduce the incidence of sepsis. Also, the osmotic strength of parenteral mixtures requires the infusion of large amounts of fluid that may be excessive for patients with ascites. Thus, enteral feeding is the preferred mode of artificial nutrition in liver disease, and the parenteral route is reserved for intensive care patients with multi-organ failure and subsequent paralytic ileus that prevents successful enteral feeding. It should be mentioned that a randomized trial comparing the two in liver disease has never been performed.

Severe alcoholic hepatitis, defined by a Maddrey score >32, has a significant mortality rate. Although corticosteroids remain the mainstay of treatment, there have been several studies of nutritional support. A multicenter, randomized, controlled trial that compared 4 weeks of treatment with total enteral nutrition or corticosteroids showed no difference in mortality during treatment between the 2 groups. Deaths were found to occur earlier in the enteral nutrition group. However, 10 of the survivors treated with corticosteroids died in the first year of follow-up compared with 2 of 24 who received enteral nutrition. The majority of these deaths were due to sepsis. The investigators hypothesized that the increase in infection seen with prolonged immunosuppression could be reduced by improving gut barrier function and thus reducing bacterial translocation. They went on to examine the combination of enteral nutrition with corticosteroid treatment in a pilot study in 13 patients and found no deaths related to infection.

Finally, insertion of a percutaneous feeding gastrostomy may be indicated in patients with an esophageal/upper gastrointestinal stricture, but ascites, impairment of the coagulation system, and portosystemic collateral circulation due to portal hypertension are significant risk factors.

Value of Branched-Chain Amino Acids

Over the years, the use of the branched-chain amino acids (BCAAs) leucine, isoleucine, and valine has been the subject of continued interest. These are essential amino acids, meaning that they cannot be synthesized de novo, must be obtained from the diet, and are largely metabolized by muscle rather than liver. In cirrhosis, there is a likely reduced total body pool of BCAAs due to reduced lean muscle mass and defective use secondary to hyperinsulinemia. Conversely, amino acids metabolized by the liver are elevated in cirrhosis (eg, the circulating aromatic amino acids phenylalanine, tryptophan, and tyrosine). BCAAs compete with the serotonin precursor tryptophan for the same amino acid transporter in the blood-brain barrier, and the imbalance between the two in cirrhosis probably influences brain ammonia levels directly or indirectly. This is considered to be an important mechanism underlying the development of hepatic encephalopathy, and so supplementation with BCAAs may reduce brain uptake of tryptophan and improve encephalopathy. Additionally, both enteral and parenteral BCAA supplementation improved cerebral perfusion in cirrhotic patients, which again may improve encephalopathy; the underlying mechanism is unclear.

Oral BCAAs have been shown to benefit patients with hepatic encephalopathy; moreover, a large multicenter study showed that oral BCAAs given for 1 year improved the Child score, reduced hospital admissions, and prolonged event-free survival. A further large trial showed improved event-free survival and quality of life in Japanese patients treated with BCAAs for 2 years compared with controls. However, a Cochrane analysis based on 11 trials of oral supplementation and 556 patients found no convincing evidence of benefit. Although no toxicity was reported, many patients stop supplementation because of the taste and amount of water required. Importantly, no benefit of BCAA supplementation was observed in protein-tolerant patients.

Parenteral administration of BCAAs to patients with acute liver failure-related encephalopathy within intensive care units has been advocated because these patients have increased total amino acids but reduced BCAAs. However, there have been no controlled studies.

The timing of BCAA supplementation was addressed by one crossover study of 12 cirrhotic patients. Daytime administration improved nitrogen balance and Fischer’s ratio; however, both were further significantly improved with nocturnal administration. At 3 months, a significant increase in serum albumin level was observed in patients administered nocturnal BCAAs but not daytime BCAAs. It is possible that daytime BCAAs are used primarily as calories, whereas nocturnal
BCAAs may be preferentially used for protein synthesis. The use of BCAAs remains controversial, and they are not widely available in many centers due to their expense and unpalatability. The authors currently follow the European Society for Parenteral and Enteral Nutrition guidelines, which recommend that enteral feed enriched with BCAAs be reserved for patients who develop encephalopathy with enteral feeding despite appropriate treatment. This represents a very small proportion of patients.

**Additional Nutritional Supplements**

Nutritional supplements containing S-adenosyl-methionine (SAMe), a coenzyme involved in methyl group transfers, are postulated to improve gut or systemic defenses to infection and injury. Experimental models have shown that SAMe protects against tumor necrosis factor hepatotoxicity. Patients with alcohol-induced liver disease have reduced SAMe levels that may predispose to mitochondrial glutathione depletion and dysfunction, and oral administration resulted in significantly decreased liver transplantation and liver mortality in patients with alcoholic liver disease compared with placebo. Supplementation also reduced pruritus and elevated serum bilirubin levels in gestational cholestasis. However, a Cochrane analysis concluded that there was no evidence supporting or refuting the use of SAMe and high-quality randomized trials were needed before they could be recommended. Another frequently taken supplement is polyenylphosphatidylcholine (lecithin), a mixture of glycolipids, triglycerides, and phospholipids and an essential component of the plasma membrane. Lecithin has been shown to prevent cirrhosis in alcohol-fed baboons, but in humans it did not improve clinical outcome in heavy drinkers.

**Liver Transplantation**

Several studies have examined the impact of preoperative malnutrition on outcome posttransplantation. A series of 100 patients 6 months posttransplantation found that muscle wasting was one of 6 variables associated with reduced survival. Other studies have shown that preoperative malnutrition impacts negatively on posttransplantation outcome. These include a prospective study of 150 patients who underwent transplantation for cirrhosis and who could be divided into high-risk and low-risk groups, with survival rates of 54% and 88%, respectively, based on preoperative nutrition and resting energy expenditure. Other studies have shown higher rates of complications and mortality in cirrhotic patients with malnutrition compared with those with adequate nutrition who undergo transplantation. More recently, however, this has been questioned. A prospective series of 53 patients from the Mayo Clinic who underwent transplantation failed to show an association between any preoperative nutritional parameters and survival or global resource utilization. In this series, the postoperative mortality was quite low after 1 year (7.5%), as was the frequency of preoperative malnutrition (9.4%), and patients were offered preoperative nutritional support. Thus, this study could be interpreted as showing either that adverse outcome after transplantation is associated with factors other than preoperative nutritional state, or that preoperative nutritional support can overcome the adverse effect of malnutrition on outcome. An older study used a prognostic nutritional index based on serum albumin and transferrin levels, triceps skinfold thickness, and delayed hypersensitivity responses to assess malnutrition and outcome posttransplantation. All patients were found to be malnourished pretransplantation, but there was no correlation between this index and mortality or morbidity posttransplantation. A further prospective series of 61 candidates for transplantation showed poor correlation between nutritional parameters...
and the Child score and Model of End-Stage Liver Disease score. Interestingly, a retrospective study in 121 patients examined risk factors for acute rejection and found that the only significant predictor on multivariate analysis of a reduction in acute cellular rejection was decreased midarm muscle circumference, that is, malnourished patients had a lower incidence of acute rejection.

To date, no controlled trial has shown that preoperative intervention improves clinically relevant outcomes. A study of 82 patients randomized to enteral supplementation (750 kcal, 20 g protein, and 34 g fat) and conventional diet or conventional diet alone showed an improvement in handgrip strength and midarm muscle circumference but not outcome. The difference in overall survival at 6 months posttransplantation almost reached significance, and a larger sample size might have shown benefit. Two studies have examined nutritional support following transplantation. Early postoperative enteral nutrition, within 12 hours, reduced the rate of viral infections and showed a trend toward a lower rate of bacterial infections. Postoperative parenteral nutrition compared with intravenous administration of fluid and electrolytes reduced the length of intensive care stay.

Obesity has a negative impact on outcome after nonliver surgery. However, the published reports on obesity in liver transplantation are inconclusive. Most recently, a case-control study from John Hopkins University Hospital examined 121 patients undergoing transplantation. Although postoperative complications, hospital stay, and cost were higher in severely obese patients (body mass index >32.3 kg/m² for women; >31.1 kg/m² for men) compared with nonobese patients, there was no difference in overall survival rates.

Immunonutrition, supplementation with nutrients that have been shown to beneficially influence immunologic or inflammatory parameters in clinical or laboratory studies (eg, glutamine), has shown positive results in other gastrointestinal surgery. A pilot study of 15 patients given an immunomodulatory diet containing arginine, n-3 fatty acids, and nucleotides (Impact; Novartis Consumer Health, Nyon, Switzerland) before and after transplantation showed an increase in total body protein and a trend to reduction in infections compared with historical controls receiving standard nutrition.

**Use of Probiotics and Synbiotics**

Although not directly related to nutrition and liver disease, the use of probiotics and synbiotics alongside nutritional supplements merits consideration in the treatment of the frequent septic episodes that accompany liver decompensation. Probiotics are living microorganisms, prebiotics are indigestible carbohydrates that stimulate the growth and activity of beneficial bacteria within the intestinal flora, and synbiotics are a combination of the two. There is increasing evidence that bacterial translocation of intestinal flora combined with failure of antibacterial defense mechanisms plays a key role in the development of sepsis. Probiotic or prebiotic treatment aims to augment the intestinal content of lactic acid–type bacteria at the expense of other species with more pathogenic potential and thus reduce the incidence of sepsis.

A randomized study compared postoperative infections in 95 liver transplant recipients treated with an early supply of standard enteral feed supplemented with either a synbiotic regimen including *Lactobacillus plantarum* and fermentable fiber, a heat-inactivated *Lactobacillus plantarum* and fiber, or selective intestinal decontamination. The patients who received the synbiotic regimen developed significantly fewer bacterial infections (13%) than those undergoing intestinal decontamination (48%). The mean duration of antibiotic therapy, hospital stay, and intensive care unit stay was also shorter in the synbiotic group but did not reach significance. The same group compared the postoperative use of a mixture of 4 prebiotics versus the same mixture plus a probiotic preparation containing lactic acid bacteria (synbiotic) in 66 patients. The incidence of postoperative bacterial infections was significantly reduced (48% given prebiotics compared with 3% given synbiotics), and the duration of antibiotic therapy was significantly shorter in the latter. There is also evidence that synbiotic/probiotic supplementation improves hepatic function. Synbiotic treatment improved the Child score in 55 cirrhotic patients with minimal hepatic encephalopathy, with significant improvements in bilirubin level, albumin level, and prothrombin time. Also, supplementation with the probiotic VSL#3 (lactobacillus and bifidobacterium bacteria: VSL Pharmaceuticals, Inc, Fort Lauderdale, FL) improved hepatic function and serum alanine transferase level in patients with alcohol-related and hepatitis C–related cirrhosis.

**Conclusions**

In summary, malnutrition is common in end-stage liver disease and adversely affects prognosis. Nutritional support improves outcome in patients unable to maintain an intake of 35–40 kcal · kg⁻¹ · day⁻¹ and 1.2–1.5 g · kg⁻¹ · day⁻¹ protein. Simple methods of assessment such as subjective global assessment, midarm muscle circumference, and calorie counting are useful, and standard enteral products may be used in the majority of patients.

However, considerable difficulties remain concerning the treatment modalities. Enteral nutrition is usually considered first line, but the parenteral route may be required if the patient is intolerant due to nausea and vomiting or develops increasing encephalopathy. However, there is a significant risk of catheter-related sepsis. The value of BCAAs remains uncertain despite a considerable number of studies, and a more palatable form
would help clarify their value. There is very little information concerning nutrition in acute liver failure and conflicting data regarding the effect of preoperative malnutrition and intervention on outcome in liver transplantation, although early postoperative nutrition seems to be of benefit. Symbiotics may provide additional benefits over dietary supplementation in reducing infective episodes, which impact malnutrition. Future research should be aimed at answering these questions. In particular, disease-specific nutritional therapy should be considered for acute liver failure, sepsis, transplantation, and encephalopathy. Further large-scale intervention studies are required before treatment guidelines can be based on a formal meta-analysis. The implementation of these crucial studies will be extremely difficult, and researchers will need to collaborate on a national or international scale.

References


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