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Invited Review

Nutrition in Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is a neuropsychiatric condition of unknown cause that leads to mental status changes and abnormal neuromuscular function in patients with acute and chronic liver failure.1-3 HE is an incompletely understood phenomenon and serves as a prognostic indicator in acute liver injury.4,5 Patients with HE develop cerebral edema and intracranial hypertension leading to brain herniation.4,5 Mortality rates of about 30% have been reported due to acute liver injury.4 Hepatocellular failure, portosystemic shunting, and exogenous factors such as sepsis and variceal bleeding along with the other common precipitants that contribute to the development of HE are listed in Table 1.

Several hypotheses attempt to explain the etiopathophysiology of HE. Metabolic products from the intestine are normally metabolized in the liver. However, in people with significant liver disease, impaired hepatic detoxification leads to systemic accumulation of by-products of gut metabolism, specifically ammonia.3,4,6-8 Portosystemic shunting causes blood to bypass the liver, and ammonia detoxification is reduced. Ammonia accumulates in the blood and crosses the blood–brain barrier; ammonia converts to glutamine, which enters the astrocytes, causing astrocyte swelling and metabolic encephalopathy.3,4,6-8 Ammonia-related astrocyte swelling is mediated by oxidative/nitrosative stress, the mitochondrial permeability transition, mitogen-activated protein kinases, and nuclear factor-κB.9 An increase in aromatic amines (the precursors for false neurotransmitters) and an increase in benzodiazepine receptor expression enhancing the inhibitory γ-aminobutyric acid–benzodiazepine neurotransmitter system alter neuronal excitation and inhibition, further contributing to the pathogenesis of HE.8

Table 1. Causes of Hepatic Encephalopathy

| Increased nitrogen load | Gastrointestinal bleeding, excess dietary protein, azotemia, constipation |
| Electrolyte imbalance | Hyponatremia, hypokalemia, metabolic alkalosis, metabolic acidosis, hypoxia, hypovolemia |
| Drugs | Narcotics, sedatives |
| Miscellaneous | Infection, surgery, acute on chronic liver disease, decompensated chronic liver disease, transjugular intrahepatic portosystemic shunt, zinc deficiency, hepatic or portal vein thrombosis |

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Minimal Hepatic Encephalopathy

Minimal hepatic encephalopathy (MHE), a preclinical stage of the spectrum, is HE in its mildest form and presents in about 30%-84% patients with liver cirrhosis. Patients with MHE have mild cognitive and psychomotor deficits with no recognizable clinical symptoms. MHE is difficult to diagnose and is usually diagnosed by neuropsychological and/or neurophysiological testing in patients who otherwise appear normal on neurological examination. MHE is a poor prognostic factor predicting the development of overt HE and significantly impairing health-related quality of life. The pathogenesis of MHE is considered similar to that of HE, with ammonia playing a key role.

Protein–Calorie Malnutrition in Liver Disease

A relationship between diet and HE has been hypothesized since 1883. Chronic liver disease with marked fibrosis and cirrhosis hampers the central role played by the liver in the metabolism of carbohydrate, fat, and protein, thereby altering nutrition status and amino acid metabolism in those with cirrhosis. In the early 1950s, it was reported that bouts of overt HE in patients with cirrhosis were controlled with low protein intake. This largely uncontrolled observation led to restriction of dietary oral protein intake in cirrhotic patients with or without HE and was an accepted standard of care for many decades to follow.

Multiple recent studies have shown the importance of maintaining positive nitrogen balance via increased protein and calorie intake in cirrhotic patients. Negative nitrogen balance due to protein restriction leads to protein–calorie malnutrition (PCM). PCM is prevalent in all stages of liver disease, undermining the capacity for liver regeneration and functional restoration. Anorexia, early satiety, ascites, altered mental status, and frequent hospitalizations lead to decreased protein intake and contribute to PCM.

Overzealous dietary restrictions, frequent paracentesis, diuresis, and lactulose therapy are iatrogenic causes often worsening the situation. Advanced liver disease accompanied by bile stasis, bacterial overgrowth, and pancreatic insufficiency causes major malabsorption of fat-soluble vitamins and nutrients.

PCM is considered a negative prognostic factor altering immunity and is associated with life-threatening complications such as refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and variceal hemorrhage. PCM serves as a prognostic variable in the treatment for ascites and, in advanced liver disease, correlates well with short- and long-term mortality, clinical severity of liver disease, biochemical hepatic dysfunction, and liver graft and patient survival post-transplantation.

Protein Intake and HE Controversy

Controversy about protein intake in patients with HE continues despite multiple studies showing the benefit of adequate protein intake. The objective of nutrition support, especially protein intake in patients with HE, is to provide adequate nutrients to ensure the availability of specific substrates not only for protein and energy synthesis but also for normal hepatocyte survival and function. In patients with liver disease, loss of hepatic regulation of protein metabolism plays a significant role in mortality.

Skeletal muscle is the second largest site of ammonia metabolism, and alterations in muscle mass due to PCM have significant adverse implications for nitrogen metabolism in hepatic encephalopathy. Protein restriction in HE increases muscle catabolism and release of amino acids, leading to increases in serum ammonia levels and worsening HE. Enteral nutrition therapy in stable patients with cirrhosis has not shown to precipitate HE, worsen ascites, or cause hyponatremia. Instead, nutrition therapy improves the measures of visceral proteins and laboratory tests.

Nutrition (Protein) Requirements and Liver Disease

The Food and Nutrition Board of the Institute of Medicine released Dietary Reference Intakes for macronutrients (energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids) in 2005. Values of macronutrients are given as recommended dietary allowance (RDA). RDA is defined as an estimate of the minimum daily average dietary intake level that meets the nutrient requirements of nearly all (97%-98%) healthy individuals. The RDA for protein is estimated as the minimum amount of protein intake necessary to avoid a progressive loss of lean body mass as reflected by nitrogen balance. Resting energy expenditure is not significantly altered in compensated liver disease; however, hypermetabolism is noted in patients with acute episode of hepatitis or advanced stages of liver failure. The European Society for Parenteral and Enteral Nutrition (ESPEN) Consensus Group recommends a daily protein intake of 1-1.5 g/kg of body weight to prevent PCM in patients with liver disease.
In patients with PCM, a detailed dietary history to assess appetite, caloric intake, and percentage change in the body weight is critical. A physical examination may reveal glossitis, cheilitis, anemia, or temporal muscle wasting. Triceps skinfold measurement done with a Lange skinfold caliper midway between the acromion and the tip of the olecranon can be used to estimate body fat reserves. Midarm muscle circumference (MAMC) indicates muscle mass. Laboratory studies including serum albumin, prealbumin, transferrin, retinol-binding protein, and lymphocyte count help confirm the presence of malnutrition. The creatinine–height index is a ratio of measured 24-hour urinary creatinine excretion compared with the expected excretion of a gender- and height-matched normal adult (control) expressed as a percentage. Although rarely used, this is another useful parameter for PCM assessment in subjects with normal renal function.

Techniques to measure lean body mass, fat stores, and cellular immunity are additional parameters of nutrition assessment; however, they are rarely used in clinical practice in patients with chronic liver disease. In addition, conventional physical and laboratory parameters are frequently altered by the insidiously progressing liver cirrhosis, hampering the synthetic function of the liver. The in vivo neutron activation analysis is the gold standard for measurement of protein depletion and was used by Peng et al to comprehensively study body composition, metabolic activity, functional status, and dietary intake in a large, heterogeneous group of patients with liver cirrhosis. ESPEN emphasizes using a nutrition screening tool with a high degree of predictive validity. ESPEN suggests that screening tools should include quantitative information on body mass index (BMI) or MAMC, recent weight loss, and recent dietary intake and, for hospitalized patients, an evaluation of severity of disease as an index of nutrition requirements.

### Nutrition Assessment and Determination of PCM

Nutrition assessment of adults with end-stage liver disease (ESLD) is not only difficult but also controversial. Nitrogen balance has limitations because it reflects metabolic adaptation rather than true nutrition requirements in liver disease. Even though studies assessing nutrition status and requirements have been mostly performed on hospitalized patients (who are, in general, sicker than outpatients with cirrhosis), Carvalha and Parise found that 75.3% of the patients studied had some degree of PCM independent of the disease cause; malnutrition was moderate or severe in 38.3% of the patients. This strongly supports the need to assess PCM in hospitalized and out-patient cirrhotic patients.

Parameters proposed by Blackburn et al were used by Mendenhall et al to devise a PCM score and classify PCM into marasmic-like or kwashiorkor-like nutrition disease in a VA cooperative study evaluating nutrition interventions in subjects with alcoholic hepatitis. The score values classified PCM as no malnutrition (PCM ≥100%), mild malnutrition (80%-99.9%), moderate malnutrition (60%-79.9%), and severe malnutrition (<60%) according to the recommendations of Blackburn et al. The PCM score correlated well with mortality, clinical severity of liver disease, and biochemical liver dysfunction. Improving PCM score via hospitalization improved 6-month and 1-year survival rates, underlining the importance and prognostic significance of nutrition in chronic liver disease.

### Hepatic Encephalopathy Precipitating Factors

During the past decade, many studies have supported the role of nutrition therapy in HE. The most important aspect of HE management is promptly recognizing and treating precipitating factors rather than assuming a deterioration of hepatocellular function. These common reversible factors are listed in Table 1 and include constipation, infection, electrolyte imbalance, gastrointestinal bleeding, increased protein intake, and medications. Thus, identifying and correcting the reversible precipitating factors can be beneficial in treating most episodes of HE.
Nutrition Support in Liver Disease

Metabolic derangements due to a decompensated liver lead to modification in substrate utilization and early recruitment of alternative fuels in the form of protein and adipose tissue. Glucose production occurs at the expense of muscle and adipose tissue using alanine and glycerol from muscle and adipose tissue, further worsening PCM and HE. Cirrhotic patients burn 70% of non-protein calories from fat compared with 40% in normal adults.

Even though carbohydrate continues to be the mainstay of caloric intake in cirrhotic patients, these individuals often have insulin resistance leading to decreased peripheral glucose utilization, decreased hepatic glucose production, and decreased hepatic glycogen reserves. Excess calorie intake in the form of carbohydrate should be avoided because of its tendency to promote hepatic lipogenesis, contribute to liver dysfunction, and possibly increase carbon dioxide production leading to increased work of breathing.

Patients with advanced liver disease should eat a diet that provides adequate calories, proteins, vitamins, and minerals. The diet should include total calories providing at least 1.2 times the estimated resting energy expenditure, generally at least 30 kcal/kg of body weight. The ESPEN guidelines recommend that 30%-35% of calories be consumed as fat and the remaining 50%-55% as carbohydrate. The protein intake should be at least 1 g/kg/d, and in patients with low spontaneous intake (<50 g protein per day), nutrition supplementation is indicated. In cirrhotic patients without ascites, actual body weight should be used to calculate basal metabolic rate using a formula such as that proposed by Harris and Benedict. In patients with ascites, the ideal weight according to body height can be used.

Oral intake should be encouraged in all patients. If patients are unable to maintain adequate oral intake, a nasoenteral tube should be inserted for enteral feeding. Parenteral nutrition is a less desirable option than enteral nutrition and should be reserved for patients in whom enteral feeding cannot be achieved. However, there is some evidence to suggest that parenteral feeding might be superior to enteral feeding in patients with portosystemic shunting. Enteral feeding could potentially worsen hyperammonemia in patients with portosystemic shunting because amino acid metabolism in the small intestinal mucosa can be a relevant source of portal ammonia that is not suppressed by antibiotics or lactulose.

Provision of 4-6 small meals daily with a nighttime snack may improve HE by avoiding protein loading and distributing protein equally. A late-evening meal has been shown to have a positive effect on nitrogen balance in patients with cirrhosis when compared with an equicaloric diet without a late-evening meal. Provision of nutrient-dense nighttime feeding in patients with cirrhosis after 9 p.m. and before 7 a.m. was shown to improve body protein accretion equivalent to about 2 kg of lean tissue sustained over 12 months. Vegetable protein, milk, and milk products have been shown to be well tolerated in alcoholic liver disease (ALD). They can be provided without restriction to improve nitrogen balance, even in patients with advanced encephalopathy.

Parenteral nutrition (PN) should be considered for patients with nonfunctional GI tracts and unprotected airways with advanced HE when swallow and cough reflexes are compromised. There are no systematic comparisons between enteral and parenteral nutrition in patients with cirrhosis and encephalopathy.

Alternate Sources of Proteins for Liver Disease

Branched-Chain Amino Acids

Branched-chain amino acids (BCAAs) are essential amino acids and include leucine, isoleucine, and valine. Because of alterations in amino acid metabolism, patients with ESLD on page 3 have high levels of serum aromatic amino acids (phenylalanine, tryptophan, and tyrosine) and low levels of BCAAs. Normalization of BCAA levels promotes protein synthesis and reduces plasma ammonia concentrations, thereby permitting an increased nitrogen intake and facilitating protein anabolism in severely protein-intolerant cirrhotic patients. BCAAs are also thought to compete with aromatic amino acids in amino acid transport across the blood–brain barrier and ultimately in the synthesis of false neurotransmitters. Human and animal experimental studies have elucidated other beneficial effects of BCAAs. Human growth factor (HGF), a pleiotropic substance with mitogenic activity involved in hepatic regenerative process, is secreted by hepatic stellate cells. Specifically leucine, are potent stimulators of HGF production and hepatic regeneration; they improve biochemical profiles, fulfill nutrient requirements, and improve Child-Pugh-Turcotte scores. BCAA supplementation is effective in downregulating protein metabolism in cirrhosis, improving nitrogen balance; however, it does not seem to decrease mortality.

Two long-term randomized studies reported increased event-free survival rates and quality of life (an essential marker of outcome that is measured quantitatively by the Short Form 36 questionnaire) in cirrhotic patients with BCAA supplementation. More recently, Horst et al reported a randomized study wherein 37 hospitalized, protein-intolerant, cirrhotic patients had positive nitrogen balance without experiencing HE when fed a BCAA-enriched solution compared with an equivalent amount.
of dietary protein. Despite the beneficial effects, the BCAA-enriched formulations are unpalatable and costly compared with non–BCAA-enriched formulations; the special formulas also fail to consistently improve HE scores, thus limiting their use.49

BCAAs have been evaluated for hepatocellular cancer prevention. In a cirrhotic patient cohort, prevalence of obesity was comparable to an age- and gender-matched general population. Obesity, hyperinsulinemia, and diabetes with other risk factors including male gender, low serum albumin concentration, and high serum α-fetoprotein concentration are considered significant risks for developing hepatocellular cancer.28,57 BCAA supplementation significantly decreased the development of hepatocellular cancer in type C cirrhotic patients with BMI >25 kg/m². In contrast, BCAA supplementation showed no inhibitory effect on the incidence of liver cancer in lean cirrhotic patients with BMI <25 kg/m², supporting the use of BCAA-enriched solutions in obese cirrhotic patients.57 A definite statement on such a cancer-preventive effect by nutrition intervention with BCAA requires further investigation.

Even though the clinical usefulness of BCAA-enriched formulations in patients with advanced liver disease has been debated in multiple studies,37,49,50,53,54,58-69 the discussion seems to have settled in favor of BCAA use in cirrhosis. ESPEN upgraded its recommendation for BCAA supplementation in decompensated liver cirrhosis in the latest revision of its guidelines in 2006.

**Vegetable and Casein Protein**

With low levels of methionine, aromatic amino acids, and ammoniagenic amino acids, vegetable protein is presumably better tolerated than animal proteins in patients with advanced liver disease and cirrhosis.38,45-47 In a randomized, crossover comparison study, Bianchi et al19 proved vegetable protein to improve nitrogen balance, increase average daytime integrated blood glucose, and improve clinical grading of HE. Vegetable protein with an abundance of dietary fiber can increase nitrogen incorporation and elimination in gut by decreasing the intestinal transit time and increasing the intraluminal pH and fecal ammonia excretion.15,38,45-47 Patients eating increased amounts of vegetable proteins have increased plasma arginine and citrulline concentrations, which may facilitate ammonia removal via the Krebs-Henseleit cycle.15

In patients with HE, dairy (casein) proteins may be better tolerated than are proteins from mixed sources. Gheorghe et al15 reported improvement of HE using a modified high-calorie, high-protein diet. Vegetable- and milk-derived protein was initiated to ensure that an adequate energy requirement of 30 kcal/kg/d and protein requirement of 1.2 protein g/kg/d were met. This high-calorie, high-protein diet improved mental status in about 80% of the study population. Yogurt has several constituents, including lactose and milk protein, in addition to the bacterial content, that could be instrumental in improving MHE. Plauth et al reported a randomized trial demonstrating that probiotic yogurt supplementation over 60 days can reverse MHE in patient with nonalcoholic cirrhosis with good adherence.59

**Micronutrients**

Patients with advanced liver disease are at increased risk of micronutrient deficiency. Patients with alcoholic liver disease are at increased risk for thiamine, folate, and magnesium deficiencies.22 Thiamine supplementation is critical to prevent Wernicke's encephalopathy. Fat malabsorption due to undiagnosed pancreatic exocrine insufficiency and chronic cholestasis increases the risk for vitamin A, D, and E deficiencies.22

Animal protein restriction, diuretic use leading to urinary zinc losses, and increased needs lead to zinc deficiency in cirrhosis.22 Zinc deficiency is a near-constant finding in patients with advanced stages of liver disease. Distortion or decrease in taste sensation (dysgeusia) associated with zinc or magnesium deficiency is well described in the literature and may contribute to reduced intake and malnutrition.70

Zinc is essential for the function of >300 enzymes, including those of the urea cycle.22 The effects of zinc deficiency on the activity of hepatic ornithine carbamoyltransferase (OCT) and plasma ammonia were studied in rats by Rabbani et al.70 A study group received a zinc-deficient diet containing 2 ppm zinc and the control group received a diet containing 110 ppm zinc. The plasma ammonia levels in the study group became significantly higher than those of the controls and remained elevated throughout the study period. Blood urea nitrogen increased initially for 2 weeks in the deficient rats, but by the end of 4 weeks, the levels were lower than in the controls.71 The hepatic OCT activity in deficient animals was significantly lowered compared with the activity in the controls by the third week.71 Zinc should be supplemented empirically as there is reasonable evidence that supplementation is associated with improvement in amino acid metabolism and clinical grade of encephalopathy.22,71,72

**Medical Therapy of Hepatic Encephalopathy**

Most manifestations of HE are reversible with medical treatment with a focus to identify and remove precipitating factors and decrease ammonia accumulation.40,73,74 Lactulose, a nonabsorbable disaccharide, has been the mainstay of HE treatment in acute and chronic settings
despite insufficient high-quality evidence to support this treatment. Its use is limited by poor patient tolerance and compliance. The main side effects of nonabsorbable disaccharides include an excessively sweet taste, flatulence, abdominal cramping, and electrolyte imbalance, particularly hypernatremia, which can deteriorate the patient’s mental status.

Antibiotics are superior to lactulose in improving HE. Historically, neomycin or metronidazole has been used, but both carry the risk of serious adverse effects. Rifaximin is a nonabsorbed derivative of rifamycin with a broad spectrum of activity against aerobic and anaerobic gram-positive and gram-negative organisms. Clinical trials have compared rifaximin with lactulose or neomycin for the treatment of HE. Although no randomized, placebo-controlled studies have assessed the efficacy and long-term safety outcomes of rifaximin in the treatment of HE, rifaximin has demonstrated better efficacy and safety profiles compared with lactulose and neomycin. Future studies should assess HE outcomes with more consistent indexes and measurements and should compare the efficacy and safety of rifaximin with those of metronidazole.

**Use of Probiotics and Synbiotics**

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. 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. There is also evidence that synbiotic/probiotic supplementation improves hepatic function in MHE. The data suggest that in addition to lactulose and antibiotics, dietary intervention with probiotic yogurt can be an effective strategy for MHE therapy.

**Conclusion and Recommendations**

Although there is overwhelming evidence that the incidence of complications of liver disease increases with malnutrition, the impact of nutrition therapy on outcomes in patients with liver disease varies with the indication. The multifactorial
wasting condition that is so frequently encountered in patients with Child-Pugh-Turcotte class B and C cirrhosis can lead to PCM, predisposing to encephalopathy and other life-threatening complications of liver disease.

The initial and most important step for the clinician is to recognize the magnitude of the patient's malnutrition. An evaluation by trained personnel to review the individual's nutritional needs is necessary to design dietary regimens that supply sufficient energy and protein. Early identification and treatment of malnutrition can lead to good pre- and posttransplant outcomes.

Current guidelines indicate that MHE should be treated with medications without protein restriction. In patients with severe hepatic encephalopathy, treatment should be focused on medical management. Temporary protein restriction may be considered if hepatic encephalopathy is refractory to medical therapy (Figure 1).

References
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