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Cirrhosis, Hepatic Encephalopathy, and Liver Transplantation - Special Focus on Nutrition

Review Article

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Abstract

Malnutrition and sarcopenia are common in patients with chronic liver disease (CLD) and are associated with increased risk of decompensation progressing to hepatic encephalopathy (HE), and poorer outcomes after liver transplantation (LT). Prevalence of malnutrition in cirrhosis ranges from 65-90% and is seen in 20% and >80% of patients with compensated and decompensated cirrhosis, respectively. Malnutrition and CLD increase healthcare burden by increasing incidence and severity of complications with associated poor survival. Specific issues that merit consideration in the assessment of nutritional status and management of malnutrition in the Indian context are reviewed here. Assessing and treating malnutrition are essential in the management of patients with CLD. Several screening tools to identify patients at risk and/or to confirm the presence and severity of malnutrition have been validated in cirrhotic patients. Complete nutritional care design with timely nutritional modification by a dietician is advisable. Most nutritional intervention studies and guidelines in cirrhosis/CLD recommend 30-35 kcal/kg dry body weight/day and protein intake of 1.2-1.5 g of proteins/kg/day. Adoption of a breakfast containing proteins and a late evening snack to shorten the period of nocturnal fasting are recommended in cirrhotic patients to achieve improvement in metabolic profile. Supplementation with branched chain amino acids (BCAAs) is known to improve abnormal glucose tolerance and serum albumin concentration in patients with CLD. Late evening snacks with BCAAs can be useful in improving protein metabolism and lipolysis in cirrhotic patients. Several clinical trials have suggested that BCAA supplementation improves nutritional status, reduces complications/arrests disease progression, and improves prognosis of cirrhotic patients regardless of patient age or disease stage.

Keywords: Malnutrition; Cirrhosis; Chronic liver disease; Hepatic encephalopathy, Liver transplantation; Nutrition; Branched chain amino acids

Nutrition in Cirrhosis and End Stage Liver Disease

Prevalence of malnutrition cirrhosis

Malnutrition is highly prevalent yet often neglected in patients with chronic liver disease (CLD) and is found in 65-90% of patients with advanced liver disease and in almost all candidates undergoing liver transplantation (LT). Malnutrition has been reported in 20% of patients with compensated cirrhosis and up to 80% of patients with decompensated liver disease [1].

Mechanism of malnutrition in CLD

Cirrhosis is a state of accelerated starvation with decrease in protein synthesis and increase in gluconeogenesis from amino acids, demanding proteolysis, with resultant sarcopenia. This sarcopenia is further aggravated by reduced dietary intake due to a variety of factors including dysgeusia, anorexia of chronic disease, inappropriate dietary protein restriction, salt restricted food that is not tasty, portal hypertension, impaired gut motility, decreased nutrient absorption and protein losing enteropathy, hospitalization with periods of fasting for diagnostic and therapeutic procedures, encephalopathy and gastrointestinal bleeding (Figure 1) [1,2].

Clinical outcomes related to malnutrition in CLD

Malnutrition and sarcopenia are well recognized as predictors

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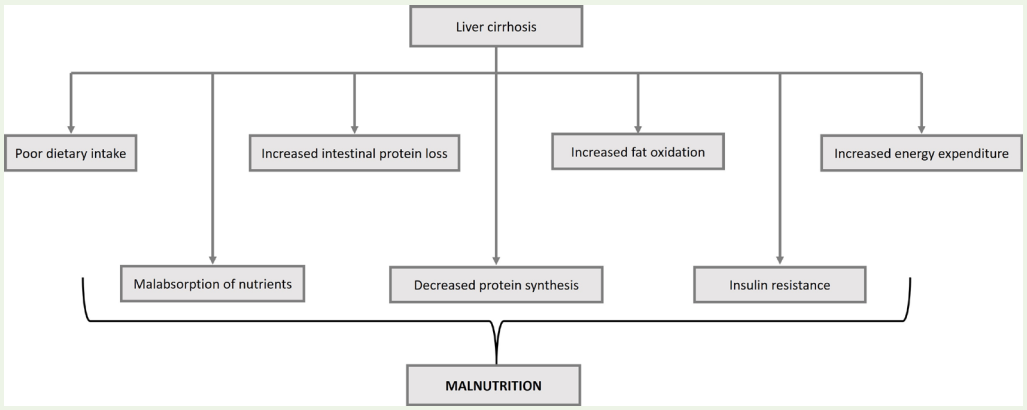

Figure 1: Factors leading to malnutrition in CLDs.

of morbidity and mortality in patients with advanced liver disease. Compared with the global population, a high prevalence of malnutrition and sarcopenia in cirrhosis has been reported in India varying between 47% and 84% [3]. Prevalence of sarcopenia in Indians is higher (61%) because of factors like lower muscle mass, high carbohydrate and low protein diet and lack of physical activity [4].

Sarcopenia is associated with a high rate of infection and long duration of hospital stay, recurrent HE, poor quality of life, increased treatment-related mortality, increased healthcare cost and tumor recurrence with poor survival in patients with hepatocellular carcinoma (HCC) [5-10]. Sarcopenia also contributes to the model for end-stage liver disease (MELD) score by 10 add-on points [11]. Optimizing nutritional status in this patient population is therefore of critical importance [12].

Nutritional assessment in patients with CLD

Literature documents wide variety of diagnostic tools and different cut off values/ criteria giving wide range of malnutrition prevalence in different studies. Commonly used are subjective global assessment (SGA), mid arm muscle circumference (MAMC), triceps skinfold thickness (TSF), and handgrip strength (HGS), and less commonly, imaging devices (bioelectrical impedance analysis, computedtomography [CT], and magnetic resonance imaging [MRI]) [13].

Although nutritional assessments for cirrhotic patients are challenges faced in clinical current practice, regular nutritional assessment should be done as soon as the patient is diagnosed for cirrhosis and thereafter, it should be done yearly if it is a compensated cirrhosis and monthly - every 3 months - every 6 months in case of decompensated cirrhosis.

Frailty test are quicker and easier methods to perform in routine clinical practice in Indian clinics. Often body mass index (BMI) and mid-arm circumference/skin fold thickness are used as tools though they are less reliable especially in presence of ascites.

In clinical setups, if possible, best way to assess for sarcopenia is non-contrast CT at L3 and Dexa scan.

There is a need for development of an easy and efficient tool for nutritional assessment of patients with CLD in routine clinical practice.

Nutritional management principles in CLD

As per European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, hemodynamically stable cirrhosis patients with sedentary lifestyle require 30-35 kcal/kg dry body weight/day [14]. The protein intake should be 1.2 g of proteins/kg/day in the absence of malnutrition or 1.5 g/kg/day in the presence of malnutrition [2]. Fat being a dense energy food, it provides more calories than proteins. As cirrhotic patients need energy, fats do help on to achieve patients' nutritional goals.

Meal pattern during the day (multiple, small, frequent 4-6 hourly meals) should prevent prolonged periods of fasting: early morning breakfast [high protein content] and late evening snacks [energy-dense e.g. comprising of complex polysaccharide (50 g)] have both been found to be beneficial and can avoid an early onset, gluconeogenic starvation like state [3]. Nocturnal branched chain amino acids (BCAAs) administration as a late evening snack (LES) has reported to improve serum albumin level and glucose tolerance in cirrhosis patients (Table 1) [15,16]. Fluid restriction to less than 1.2-1.5 liters is advised in cirrhotic patients having dilutional

Table 1: Recommended nutrition in chronic liver disease.

Clinical condition	Non-protein energy (kcal/kg per day)	Protein or amino acid (g/kg per day)
Inadequate intake/ malnutrition	35-40	1.5
Compensated cirrhosis	25-35	1.0-1.2
Encephalopathy	25-35	➢ Encephalopathy I-II: Transiently 0.5, then 1.0-1.5 if protein intolerant: vegetable protein or BCAA supplement ➢ Encephalopathy III-IV: 0.5-1.2 BCAA-enriched solution

BCAA: Branched chain amino acids

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hyponatremia [3]. Physical exercise being an anabolic stimulus is also very helpful in regaining the loss of muscle mass [1].

Correction of sarcopenia by nutritional therapy reflects in improvement of deranged parameters and clinical outcomes. For patients with sarcopenic obesity, hypocaloric and high protein diet i.e. approximately 800 kcal/day, but 1.2 to 1.5 g proteins/day should be given to the patients. Goal should be to reduce the weight by 5% to 10% [3].

Nutritional intervention with BCAA in CLD

Deficiency of the essential BCAAs valine, leucine, and isoleucine is involved in the development of liver diseases. Administration of BCAAs in patients with CLD stimulates hepatic protein synthesis and subsequently results in an improvement in their nutritional status, thus resulting in a better quality of life. A decrease in the BCAA: aromatic amino acid [AAA] ratio due to alterations in amino acid metabolism in patients with liver disease may be responsible for some of the complications associated with liver disease, such as HE. Normalization of this ratio via BCAA supplementation has the potential to prevent these complications. BCAAs may be the preferred nutrients for cirrhotic patients due to their higher energy efficiency than glucose or fatty acids. A late evening snack containing BCAAs improves protein metabolism and lipolysis in patients with cirrhosis and thereby can improve respiratory quotient (RQ), nutritional state, and glucose intolerance [17].

Mechanism of action of BCAAs in CLD

BCAAs are involved in various biological actions, and their supplementation is a promising therapeutic option for patients with CLD [15].

In liver cirrhosis, BCAAs induce mitochondrial biogenesis and inhibit reactive oxygen species (ROS) production; stimulate albumin and glycogen synthesis; inhibit hepatocyte apoptosis, promote liver regeneration, and stimulate Hepatocyte growth factor (HGF) production; and improve insulin resistance. In patients with HCC, BCAAs inhibit proliferation of HCC cells and hepatocarcinogenesis.

Several clinical trials have suggested that BCAA supplementation improves the prognosis of cirrhotic patients, regardless of patient age or disease stage. In patients with advanced cirrhosis, they prevented progressive hepatic failure and improved surrogate markers with improved perceived health status. In patients with advanced cirrhosis, they are effective in improving nutritional status and may also improve abnormal glucose tolerance in addition to improving serum albumin concentration [15].

Across India, 111 experts in gastroenterology and hepatology participated in 10 virtual, focused-group meetings. Evidence-based discussions were conducted about nutritional assessment and management principles in patients suffering from CLDs. Expert opinions were formulated and finalized after collating the discussion from all meetings and developed into a consensus document.

Expert Opinion on Nutritional Recommendations for Liver Cirrhosis

Eggs are a good source of proteins, with egg yolk providing 2.5 grams of proteins. Protein restriction is to be avoided; however, in patients with renal dysfunction up to 1 g/kg is advised. Lemon and black salt may be used to improve palatability for patients restricted to low salt diet. Fat intake can be increased by incorporating ghee in the meals.

Dietary source of BCAAs include chicken, salmon, turkey, tuna, milk and milk products. To meet their protein requirements, 12-15 grams of BCAA per day can be given to patients.

It is important to restrict sodium intake and not fluids in patients with ascites. Screening of micronutrients and appropriate supplementation with vitamin A, D, magnesium, and zinc is equally important.

Physical exercise is also very helpful in regaining the lost muscle mass. Weight bearing/training exercises and simple resistance exercises can help in regaining the muscle mass e.g., running stationary cycle at home and upper limb weight training exercises with 1-1.5 kg dumbbells.

Nutrition in Hepatic Encephalopathy

HE is a frequent and serious complication of cirrhosis that is associated with poor prognosis and quality of life [15]. HE is associated with prolonged hospitalizations, repeated re-admissions, and high rates of mortality, irrespective of the severity of the underlying liver disease [18]. Overt and clinically evident forms of HE occur in 30%–45% of patients with cirrhosis and 10%-50% of patients who undergo transjugular intrahepatic portosystemic shunt (TIPS) placement [18,19]. Estimates of the prevalence of minimal HE (mHE) in patients with cirrhosis range from 20% to 80%, often asymptomatic. Patients with a previous episode of overt HE have a 42% risk of recurrence at 1 year, and those with recurrent overt HE have a 46% risk of another episode within 6 months, despite receiving standard care [18]. Large bleed, spontaneous peritonitis, and infection are common reasons for recurrence of HE episodes.

Pathophysiology of HE

Pathogenesis of HE is multifactorial. Elevated blood ammonia is one of the main pathogenic factors for the development of HE. However, monitoring of serum (arterial) ammonia has no linear correlation to HE status and prognosis and is possible only in hospitalized patients as a simple and quick method, but it is not yet available for outpatient clinics. Other factors include systemic and neuroinflammation, oxidative stress and cellular senescence and blood-brain barrier (BBB) permeability/altered integrity with altered neurotransmission causing deleterious effects [18].

Biochemical derangements in HE

Physiologically normal Fischer's ratio (i.e. BCAA/AAA ratio) is 3.0-3.5:1. This ratio is decreased in patients suffering from cirrhosis. BCAAs decrease as they are rapidly consumed to form glutamate from α ketoglutarate [α-KG] as a pivotal step in ammonia detoxification to glutamine (GLN) in muscles and brain [Figure 2] [20].

Accelerated consumption of α-KG may disturb the function of tricarboxylic acid (TCA). AAA increase is due to decreased ability of the diseased liver to metabolize these amino acids. Therefore,

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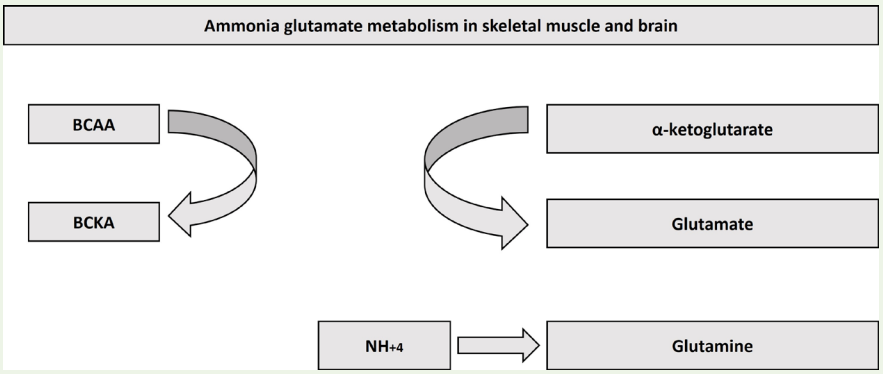

Figure 2: Biochemical derangements in hepatic encephalopathy.
AAA: Aromatic amino acid; BCCA: Branched chain amino acid; BCKA; Branched chain ketoacids.

decreased Fischer's ratio leads to augmented uptake of AAAs by the brain causing an imbalance in the synthesis of nor-epinephrine and serotonin and increased synthesis of false neurotransmitters e.g. octopamine, phenyl ethanolamine, and tyramine [18].

Impact of HE

HE manifests as a wide spectrum of neurological or psychiatric abnormalities, from subclinical alterations (*mild cognitive impairment detectable only by neurophysiological/neuropsychological assessment*) to marked disorientation, confusion and coma [18,21]. Neuroinflammation and neuronal cell death are features of HE and episodes of overt HE can lead to irreversibility.

Treatment of HE

Therapeutic approach aims to manage bouts of overt HE efficiently with respect to duration and its consequences and further preventing recurrence and hospital readmissions. Most of the therapies for HE targets ammonia.

Lactulose remains the first line of therapy in the management of HE patients. Rifaximin can be given if patients are refractory to lactulose monotherapy or to prevent episodes of HE recurrence [17]. Around 0.25 g of BCAA per kg body weight can be given orally in patients who are protein intolerant or in patients having recurrent HE episodes to prevent recurrences [14].

Nutritional treatment principles and evidence-based therapies for HE

Energy requirements in patients with cirrhosis per se and cirrhosis with HE are considered to be similar, with focus on prevention and/or delaying progression of the disease [1]. Type and amount of food for each HE patient is advised to be adjusted to maintain a total energy intake of at least 1.3 times the basal energy expenditure (BEE) (e.g., a protein intake of 1.2 to 1.5 g/kg including BCAAs increased according to degree of hepatic decompensation), in accordance with ESPEN guidelines [14].

In patients with HE, the protein intake should not be restricted but preferably be enriched by high biological value proteins (vegetable and dairy proteins preferred over animal proteins). BCAA can be used in case of protein intolerance as well [14]. Additionally, micronutrient and vitamin [both fat and water soluble] deficiency, if identified should be corrected.

Salt restriction should be avoided to avoid poor palatability /poor intake because strict salt restriction can be associated with higher incidence of hyponatremia and diuretic-induced renal impairment. Therefore, intake of 5-6 g/day of salt is advisable.

Oral dietary intake is preferred in patients with early HE and in those who can tolerate recommended intake. In patients with advanced HE and in those who are not able to take orally, nasogastric tube feeding or parenteral nutrition should be considered. Critically ill patients with cirrhosis have higher nutritional requirements due to a net catabolic state and should be replenished as a priority [14,18].

Role and rationale of BCAAs in HE patients

BCAAs may not prevent HE but may prevent the progression of hepatic failure and may improve minimal HE and muscle mass [15]. BCAA therapy was found to improve the manifestation of overt HE in a systematic review, while it was found to have no effect on mortality, quality of life, or nutritional parameters [22]. BCAAs have been documented to promote muscle protein synthesis and improve muscle mass loss; however, additional multicenter clinical trials to determine the effect of BCAAs versus active interventions are needed [17,22].

Expert Opinion on Nutritional Recommendations for Bcaas In He

Protein restriction should only be done in an inpatient department (IPD) setting for patients suffering from recurrent and severe HE

Dairy protein can be better tolerated than protein from mixed sources and that vegetable protein is better tolerated than meat protein; as they have low levels of ammonia-genic amino acids.

BCAAs can be used as supplements for achieving the total protein requirements of HE patients. For patients who are protein intolerant or are having recurrent HE episodes, BCAA supplementation can help meet protein requirements or reduce the number of HE episodes. International Society of Hepatic Encephalopathy and Nitrogen

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Metabolism (ISHEN) guidelines recommend BCAA supplements occasionally for patients intolerant of dietary proteins.

Small meals or liquid nutritional supplements evenly distributed throughout the day and as late-night snacks should be offered. Parenteral BCAAs can be given in cases of HE.

Around 0.25 g BCAA per kg body weight can be given orally in patients who are protein intolerant or in patients having recurrent HE episodes. Experts opined that BCAAs function more like a drug than a supplement in such patients.

Nutrition in Patients Undergoing Liver Transplantation

Alcoholic liver disease, followed by non-alcoholic fatty liver disease (NAFLD), is the most common cause of liver transplantation in the Indian population. Pre-transplant malnutrition and sarcopenia are associated with increased risk of decompensation, infections and increased waitlist mortality, while post-transplant these complications predict poor outcomes with longer time to extubation after transplantation, increased post-operative infections, prolonged intensive care unit (ICU)stay and hospitalization, and decreased survival [23].

Principles of nutritional management in patients with liver disease and transplant candidates

Assessment of nutritional status of all patients being prepared for LT should undergo thorough nutritional evaluation.

Before Liver Transplantation

Pre-transplant nutritional improvement is very important and should aim to prevent further nutrient deficiency and muscle depletion and to correct vitamin and mineral deficiencies to improve the post-operative outcomes specifically to minimize risk of infection, reduced hospital ICU stay, and debility [23].

ESPN guidance recommends enteral nutrition (EN) with a gastric or jejunal small-bore feeding tube for patients incapable of ingestion and parenteral nutrition (PN) for patients with fulminant hepatic failure and those in coma, for patients who are moderately or severely malnourished and who cannot achieve adequate energy intake, either orally or via EN due to gastrointestinal dysfunction [14].

Carbohydrate intake should exclusively be provided by glucose infusion [2-3 g/kg body weight per day] without causing hyperglycemia. Dietary fat should not be restricted unless true fat malabsorption has been diagnosed. Whole-protein formulas or BCAA-enriched formulas are advisable in patients who develop HE during re-feeding. Protein intake should be at least 1 g/kg/day initially with progressive increment to up to 1.8-2.0 g/kg/day as tolerated. Recovery of all weight loss happens in the 1st post-transplant year, fat mass progressively increases, but muscle mass recovery is subtle and non-significant by the end of the first year [23].

Patients with ESLD are susceptible to vitamin and mineral deficiencies, which need to corrected appropriately. Probiotic supplements can alter gut microbiota, prevent bacterial translocation, decrease endotoxin levels, and restore neutrophil phagocytic capacity [23].

Nutritional Support after LT

After LT surgery, energy and protein requirements are increased for weeks. In the immediate phase after the surgery, protein catabolism is markedly increased, and patients should receive about 1.5-2.0 g/kg/day of proteins. Resuming EN within 12 h of LT has been shown to reduce postoperative infections and to produce better nitrogen retention, bile duct complications, length of ICU stay, and time on ventilator. Patients should be advanced from nutritional support to an oral diet using smaller and more frequent feedings as soon as tolerated after LT [23] (Table 2).

With dietitian consultation, patients are instructed to be on a calorie-sufficient diet comprised of low-fat content, with adequate amounts of lean protein foods to promote muscle gain and healthy body composition.

Table 2: Nutritional interventions before and after liver transplantation.

Before LT	After LT	Special consideration
Small frequent meals	Increase BEE for 4 weeks post -LT (starting to 10-15 kcal/kg/d on POD 3 to 25-35kcal/kg)	Special attention to avoid rejection
Caloric intake ≥1.2× BEE (30-35 Kcal/kg/d)	Increase proteins 1.5-2.0 g/kg/d	Prevent treat infections
Glucose 2-3 g/kg/d (monitor for risk of hyperglycemia)	Vitamin and mineral supplementation	Watch for ill effects of immunosuppressive therapy: e.g. corticosteroids (diabetes, glucose intolerance); calcineurin inhibitors (weight gain, increase BEE)
Proteins up to 1.5 g/kg/d including BCAAs	Reduce sodium 3.0 g/d	
Fats not restricted unless malabsorption	Minimize excessive weight gain to avoid hyperlipidemia, insulin resistance/hyperglycemia, arterial hypertension, and liver donor steatosis	
Possible fluid restriction for hyponatremia		
Enteral (tube) nutrition in severe nutritional risk patients		
Reduce sodium intake to 2-3 g/d		
Supplements: Vitamins and minerals, probiotics, prebiotics, symbiotics, immunonutrients like arginine, omega -3 fatty acids, lactoferrin		
Advise physical rehabilitation program		

BCAA: Branched chain amino acids; BEE: Basal energy expenditure; LT: Liver transplantation: POD: Post operative day.

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BCAA treatment in liver transplantation

There is a lack of substantial data for efficacy of BCAAs in pre and post transplantation patients. Absence of preoperative BCAA treatment was found to be an independent risk factor for postoperative severe infection and in-hospital death in subjects undergoing living-donor liver transplantation (LDLT).On the contrary, pre-treatment with BCAA before LDLT may reduce the incidence of post transplant bacteremia and sepsis. Data reports that early interventional oral BCAAs might prolong the liver transplant waiting period by preserving hepatic reserve in patients with cirrhosis [15]. A pre-LT BCAA-enriched formula has been reported to lower ammonia, thereby improving Fischer's ratio and albumin, prealbumin, total lymphocyte count, BCAAs/tyrosine ratio [BTR], glucose intolerance, liver regeneration, immune system function, maturation of dendritic cells and the ability of peripheral blood mononuclear cells and preventing postoperative sepsis. Oral BCAAs can be of importance to improve post-LT mortality by preserving the hepatic reserve of scheduled LT recipients [15,20].

Expert Opinion on Nutritional recommendations For Bcaas in Patients Undergoing Liver Transplantation

Frequent feeding with concentrated meals is advised. Focus on fortifying habitual nutritional intake e.g., changing the composition of chapati flour, adding seeds, nuts and millets to meals, kneading pulses and millets into the chapati flour, whey water (paneer water and curd water) and lentils, pulses, beans, soya, quinoa, or amaranth, are recommended.

Supplemental sip feeding, e.g., 2 × 200 mL drinks of a standard polymeric formula containing 300 kcal each,could be given in malnourished cirrhotic patients who are unable to reach their nutritional requirements.

Hypomagnesia and hypoglycemia are common metabolic disturbances seen in post-transplant patients, and these should be timely addressed.

Conclusion

Nutritional assessment and management of malnutrition are crucial in patients with CLD, and these can be improved by close cooperation between attending physicians, hepatologists, nursing staff, dieticians, and family members. ESPEN guidelines recommend energy intake of 30-35 kcal/kg/day and protein intake of 1.2-1.5 g/kg/day as standard advice. Frequent meals with late evening snacks are important to practice. Patients with CLD have been successfully treated clinically with BCAA supplements. Potential benefits of BCAAs include positive effects on ammonia detoxification with decreased ratio of BCAAs to AAAs, liver regeneration, albumin synthesis, immune and hepatic function, glucose metabolism, and thus improved outcome in CLD.

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