

# Diet and nutrition therapy in pre-liver transplant patients

**Neha Bakshi, Kalyani Singh**

*Lady Irwin College, Department of Foods and Nutrition, University of Delhi, New Delhi 110001, India.*

## ABSTRACT

Malnutrition is universally prevalent among pre-liver transplantation patients. Malnutrition among cirrhotic patients had been associated to increased morbidity and mortality rates. Also, severely malnourished patients before the transplant surgery have a higher rate of complications and a decreased overall survival rate after liver transplantation. In light of the high incidence of malnutrition and associated complications, it is essential to initiate treatment as early as it is assessed. This review addresses the aetiologies of malnutrition and appropriate treatment strategies to correct it in pre-liver transplant phase. Treatment should focus on maintaining nutrient intake and correcting various nutritional deficiencies. The dietician plays an integral role as part of the transplant team by providing appropriate nutrition therapy for solving various nutrition problems.

**Key words:** End stage liver disease; liver transplantation; pre-liver transplant

## Corresponding Author:

Ms. Neha Bakshi, Lady Irwin College, Department of Foods and Nutrition, University of Delhi, Sikandra Road, Mandi House, New Delhi 110001, India. E-mail: nehabakshi.9@gmail.com

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## INTRODUCTION

Liver transplantation (LT) revolutionized the management of liver disease. LT is the only option for those with end stage liver disease (ESLD).<sup>[1]</sup> According to Institute of Health Metrics and Evaluation of Global Burden of Disease, deaths from cirrhosis in all age groups is ranked 12th globally and 19th in South Asia in 1990 and was ranked 12th globally and 11th in South Asia in the year 2010. Hence, an increasing death from cirrhosis is seen in South Asia over a period of time.<sup>[2]</sup>

## METABOLIC CHANGES IN ESLD

Various metabolic changes that occur in ESLD patients are presented in Table 1<sup>[3-7]</sup> which affect the nutrition state of pre-LT recipients. These factors are inadequate dietary intake, increased intestinal protein losses, malabsorption, low protein synthesis, hypermetabolism and disturbed substrate utilization.<sup>[8,9]</sup>

## CONSEQUENCES OF PREOPERATIVE MALNUTRITION ON LIVER TRANSPLANTATION OUTCOME


Survival in cirrhosis decreases according to the severity of malnutrition.<sup>[10,11]</sup> Preoperative hypermetabolism and body cell mass depletion was proven to be better predictors of the outcome of LT than the traditional Child-Pugh score.<sup>[12]</sup> Undernutrition may induce an exaggerated cytokine response favouring postoperative systemic inflammatory response syndrome and multi-organ failure in these patients.<sup>[13]</sup> Zinc deficiency is a precipitating factor for hepatic encephalopathy.<sup>[14]</sup> Deficiencies of water-soluble vitamins (B and C) and fat soluble vitamins (A, E, D, and K) may occur in patients with cirrhosis which increases the susceptibility of cell membranes to lipid peroxidation.<sup>[8]</sup> Low retinol levels leads to an increased risk of developing hepatocellular carcinoma.<sup>[15]</sup>

Hence, careful nutritional assessment of candidates for LT is very important because the nutritional status of these patients may ultimately influence morbidity and mortality. Unfortunately, no gold standard exists to determine the extent of malnutrition in this population.<sup>[16]</sup> An suitable nutritional

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**Table 1: Metabolic changes in ESLD for liver transplant candidates<sup>[5-7]</sup>**

Metabolic changes	Abnormalities
Glucose metabolism	Insulin resistance; depleted hepatic glycogen stores; fat is utilized as the main substrate for energy, increased gluconeogenesis, lipid oxidation and protein catabolism
Protein metabolism	Increased protein catabolism; amino acid metabolism alterations; imbalance of BCAA and aromatic amino acids
Lipid metabolism	Polyunsaturated fatty acids deficiency; deficiency of essential fatty acid and long-chain polyunsaturated fatty acids

ESLD: end stage liver disease; BCAA: branched-chain amino acids

**Table 2: Formula for REE<sup>[18,19]</sup>**

Gender	Formula
For males	REE (kcal) = $66 + 13.7 \times W$ (kg) + $5 \times H$ (cm) - $6.8 \times A$ (years)
For females	REE (kcal) = $655 + 9.6 \times W$ (kg) + $(1.7 \times H$ (cm) - $4.7 \times A$ (years)

REE: resting energy expenditure

assessment can include combination of nutrition tools like anthropometry, body composition analysis, subjective global assessment, and hand grip strength to formulate a composite score for assessment of malnutrition.<sup>[17]</sup>

## NUTRITION TREATMENT FOR PRE-LIVER TRANSPLANT PATIENTS

The goals of nutritional therapy are to improve protein energy malnutrition and correct nutrient deficiencies. This can be accomplished by meeting nutrient requirements.

### Energy requirement

When energy expenditure is related to lean body mass, patients with advanced liver disease have increased resting energy expenditure (REE).<sup>[18,19]</sup> Despite the usually offsetting errors of excess total body water in estimation of REE from the Harris-Benedict equation [Table 2],<sup>[18,19]</sup> it is still considered useful to measure the REE by way of indirect calorimetry in some patients with severe liver disease. Increased REE (hypermetabolic) was found over controls in patients with cirrhosis. But this is not a uniform finding since hypometabolism as well as normometabolism have been observed in patients with cirrhosis.<sup>[19-21]</sup> When related to predicted energy expenditure among stable cirrhotics, a subgroup of 15-20% may be considered as hypermetabolic, 25-30% as hypometabolic and the large majority as normometabolic.<sup>[21]</sup> Increased REE has also been observed during complications of liver disease, such as acute hepatic failure,<sup>[18]</sup> high volume ascites,<sup>[22]</sup> or presence of hepatocellular carcinoma.<sup>[23]</sup> Measurements of total energy expenditure in patients with cirrhosis indicate that the 24 h energy requirement of cirrhosis patients amounts to about 130% of the basal metabolic rate (BMR).<sup>[24]</sup> Diet-induced

**Table 3: Nutrition in chronic liver disease-recommendations 1997<sup>[45]</sup>**

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

BCAA: branched-chain amino acids

thermogenesis<sup>[25,26]</sup> and the energy cost of defined physical activity in stable cirrhosis patients<sup>[27,28]</sup> and it also shows no deviation from values obtained in healthy patients. The spontaneous physical activity level is also low in cirrhotics.<sup>[5,28]</sup>

In cirrhotics without ascites, the actual body weight should be used for the calculation of the BMR using Harris and Benedict formulae. In patients with ascites the ideal weight according to body height should be used. In general, non-protein energy provision of  $1.3 \times$  REE is sufficient.<sup>[29,30]</sup> For most patients, the daily caloric need equals  $(1.2-1.4) \times$  REE (25-30 kcal/kg body weight).

Administration of adequate calories is critical for the efficient use of protein sources, particularly when patients are protein restricted. Excess calories particularly from carbohydrate, should be avoided because it promotes hepatic lipogenesis, liver dysfunction and increased carbon dioxide production leading to increased work of breathing.<sup>[31]</sup>

For patients with 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.<sup>[32]</sup> The serum lipid variables appeared to be more useful indicators of functional liver improvement than the classic liver function tests.<sup>[33]</sup>

### Protein requirements

In clinical intervention trials proteins were given in amounts of 0.6-1.2 g/kg per day for patients with cirrhosis and severe encephalopathy<sup>[34]</sup> and 0.5-1.6 g/kg per day in patients with alcoholic hepatitis with or without low grade encephalopathy.<sup>[35]</sup> Patients with stable cirrhosis appear to have increased protein requirements of 1.2 g/kg per day to maintain nitrogen homeostasis as opposed to 0.8 g/kg per day in normal individuals.<sup>[36]</sup> The reasons for this phenomenon are not yet clear, but the increased protein requirement seems to be due to increased whole body protein degradation which may be due to low plasma levels of insulin-like

**Table 4: Nutrition recommendations for a liver transplant candidate**<sup>[58-63]</sup>

Nutrient	General recommendations
Calories	Energy needs vary with each individual; 30-35 kcal/kg dry weight for maintenance; 35-40 kcal/kg dry weight for malnourished patients; 25-35 kcal/kg dry weight for hepatic encephalopathy; 150-175% of predicted basal energy expenditure (calculated on dry weight)
Proteins	0.8-1.0 g/kg dry weight in compensated liver disease; 1.5-2.0 g/kg dry weight in decompensated liver disease; 0.6-1.0 g/kg dry weight for hepatic encephalopathy, BCAA-enriched formulas
Fats	25-40% of calories, moderate amounts of medium chain triglycerides oil when steatorrhea present
Carbohydrates	Restrict simple carbohydrate if glucose intolerance is present
Sodium Fluid	2-4 g/day depending upon level of fluid retention 1,000-1,500 mL/day if fluid retention or hyponatremia is present
Vitamins	Fat malabsorption leads to malabsorption of fat-soluble vitamins; vitamin A: liver unable to synthesize retinol-binding protein; vitamin D: decreased biliary excretion of 1,23-dihydroxycholecalciferol; vitamin E: cholestatic liver disease affect vitamin E because it is carried by lipoproteins; B vitamins: excess losses due to alcohol abuse
Minerals	Mineral bioavailability, tissue distribution, and toxicity can be affected by decreased liver production of their protein carriers; manganese and copper excretion in bile affected by an interruption in enterohepatic circulation; Serum potassium, magnesium, and phosphorus levels may decrease as a result of diuretic administration, refeeding syndrome, malabsorption, or alcoholism; 800-1,200 mg calcium/day

growth factor (IGF)-1.<sup>[19]</sup>

According to Morgan *et al.*<sup>[37]</sup> (2006) whole protein formula providing 35-40 kcal/kg per day energy and 1.2-1.5 g/kg per day protein is recommended for enteral feeding. Standard preparation contains approximately 100 kcal, 4 g protein, and 3.5 mmol of sodium and potassium per 100 mL. Concentrated high energy (1.5 kcal/mL) and protein formulas 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.

A study by Nielsen *et al.*<sup>[38]</sup> (1995) showed protein balance in a subgroup of patients did not change protein balance values.

Protein intake increased from 1.0 g/kg per day to 1.8 g/kg per day. With increasing protein intake, 84% of the increase in intake was retained. The rate of protein retention was not saturated at the intakes obtained in this study.

Protein requirement and protein utilization were investigated further by measuring protein synthesis and degradation. In 2 separate studies, patients with cirrhosis of the liver were refed on a balanced diet for an average of 2-4 weeks. Protein and energy intakes were doubled in both studies. Refeeding caused a statistically significant increase of about 30% in protein synthesis in both studies while protein degradation was only slightly affected. The increase in protein synthesis was associated with significant increases in plasma concentrations of total amino acids while insulin, growth hormone, IGF-1 and IGF-3 were not changed significantly. The results indicate that the efficient protein utilization is due to increased protein synthesis, rather than decreased protein degradation.<sup>[5]</sup>

### Value of branched-chain amino acids

Branched-chain amino acids (BCAAs) (leucine, isoleucine, valine) are essential amino acids. In cirrhosis, there is a likely reduced total body pool of BCAAs due to reduced lean muscle mass and defective use secondary to hyperinsulinemia.<sup>[39]</sup>

BCAAs compete with the serotonin precursor tryptophan for the same amino acid transporter in the blood-brain barrier, and the imbalance between the 2 in cirrhosis influences brain ammonia levels directly or indirectly.<sup>[40]</sup> So supplementation with BCAAs may reduce brain uptake of tryptophan and improve encephalopathy.<sup>[41,42]</sup> Furthermore, BCAA supplementation by both enteral and parenteral routes of feeding has shown improved in cerebral perfusion by which encephalopathy may get improved but still basic mechanism is unclear. A large multicenter study showed that oral BCAAs given for 1 year improved the Child score, reduced hospital admissions, and prolonged/improved event-free survival.<sup>[43]</sup> However, there have been no controlled studies and no mention of the timing of BCAA supplementation in cirrhotic patients.<sup>[44]</sup> At 3 months, a significant increase in serum albumin level was observed in patients who were administered with nocturnal BCAAs but not daytime BCAAs. It is hypothesized that BCAAs when consumed in daytime are utilized as calories, whereas nocturnal BCAAs are utilized for protein synthesis.<sup>[39]</sup> European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines [Table 3]<sup>[45]</sup> recommends use of enteral feed enriched with BCAAs for patients who develop encephalopathy. The use of solutions rich in BCAA and low in aromatic acids and tryptophan in encephalopathy has been proposed.<sup>[46]</sup> However, a Cochrane analysis based on 11 trials found no convincing evidence regarding benefit from BCAA. The use of BCAAs remains controversial, and they are not widely available in many centres due to their expense and unpalatability.<sup>[47]</sup>

According to ESPEN Guidelines, for a positive effect on liver function and clinical outcome, non-protein energy

**Table 5: Major studies recommending use of nutrition supplementation**

Study	Recommendations	Outcomes
Bories and Campillo <sup>[32]</sup> (1994)	40 kcal/kg per day	Protein and energy intakes were significantly higher; improved nutritional status; improved biochemical parameters
Hirsch <i>et al.</i> <sup>[81]</sup> (1993)	1,000 kcal and 35 g of nitrogen/day for 1 year	Need for hospitalization was significantly lower in the supplemented; reduction of infectious complications; a lower mortality in the therapeutic group
Mendenhall <i>et al.</i> <sup>[82]</sup> (1993)	> 2,500 kcal/day	51% mortality in severe malnourished patients with inadequate caloric intake; 19% mortality in patients who received adequate oral nutrition
Le Cornu <i>et al.</i> <sup>[83]</sup> (2000)	Nutritional supplementation to pre-transplant candidates	Did not increase overall dietary energy or protein intake and did not significantly improve post-transplant outcome; regular dietary counselling is as effective in increasing energy intake
Kawaguchi <i>et al.</i> <sup>[84]</sup> (2008)	200-kcal nutritional supplement	Stress scores for physical and mental symptoms were significantly lower compared to those in the fasting group

was given in amounts of 35-40 kcal/kg per day plus protein up to 1.6 g/kg per day. In patients with encephalopathy, transient protein restriction can be instituted, but after a few days adequate nutrition should be reinstated. Patients in coma (encephalopathy grade III-IV) can safely be given total parenteral nutrition (TPN) regimens providing 25-30 kcal/kg per day from non protein energy plus 1.0 g/kg per day using BCAA-enriched solutions. Fasting periods should not exceed 6 h due to the limited glycogen stores in malnourished cirrhotic patients. Generally, the oral or enteral routes are preferred. Parenteral nutrition should only be used when enteral feeding is not possible or impracticable [Table 3].<sup>[45]</sup>

### Micronutrients requirements

Micronutrient deficiency has been observed in 10-50% of patients with cirrhosis. Multivitamin supplements may be considered in these patients.<sup>[48]</sup>

### Vitamins

Various vitamins deficiency occurs in LT recipients like folate deficiency is due to a combination of decreased intake, decreased absorption, as well as losses from renal excretion and poor hepatic storage. Supplementation of folate and B12 is crucial in alcoholic hepatitis to protect uninjured hepatocytes and stimulate the repair/replacement of damaged cells [Table 4]. The common recommendation for folate supplementation is 1 mg/day orally.<sup>[48]</sup> Vitamin B1 deficiency is linked to primary tissue damage such as alcoholic polyneuropathy and also Wernicke's encephalopathy. Usual supplementation is 100 mg/day orally or subcutaneously initially for 2 weeks or until repleted, the amount in a standard multivitamin should be sufficient.<sup>[48]</sup> Deficiency of vitamin B6 (pyridoxine) is due to decreased intake or altered metabolism and storage. Standard supplementation is 50-100 mg/day orally, or more in severely depleted individuals.<sup>[49]</sup> Liver stores are often depleted even in the setting of normal

serum levels.<sup>[50]</sup> Hypovitaminosis A has been linked to night blindness, impairment in immune function, and also to an increased risk of hepatic fibrosis [Table 4]. If malabsorption is suspected as a prime contributor to depletion, doses of 25,000-50,000 IU 3 times per week may be needed for repletion. Vitamin A supplementation improves the sense of taste and thereby may also improve dietary intake of the patients.<sup>[14]</sup> Inadequate intake of calcium and vitamin D and losses from malabsorption and renal excretion are related to lower serum levels of albumin and magnesium.<sup>[49]</sup> If the individual is unable to increase dietary intake to a consistent, adequate level of 1,000-1,500 mg/day, supplementation should be initiated, especially in those with suspected low bone mineral density. Osteoporosis has been confirmed in 17-23% of patients with liver disease. The role of vitamin D and calcium on bone mass in the setting of liver disease is unclear.<sup>[51]</sup> Serum levels should be monitored in 3 months to assess tolerance and success of repletion. Low serum levels of vitamin D are thought to be the result of poor dietary intake, malabsorption from cholestasis, pancreatic insufficiency, and decreased sunlight exposure.<sup>[52]</sup> Supplementation usually begins at 400 IU per day, with some patients requiring up to 800 IU per day of vitamin D or 12,000-50,000 IU per day of ergocalciferol, with serum levels reassessed in 2-3 months.<sup>[53]</sup> Serum vitamin E levels are typically decreased in alcoholic patients, pancreatitis or fat malabsorption [Table 4]. A dose of 400 IU per day either as standard vitamin E or as  $\alpha$ -tocopherol, if malabsorption is suspected, should provide for adequate supplementation in most individuals.<sup>[49]</sup>

### Minerals

During the pre-LT phase patients suffer from various mineral deficiencies because of metabolic changes due to liver impairment. Zinc deficiency is very common in cirrhotics.<sup>[54]</sup> Zinc supplementation may also be used for those patients with hepatic encephalopathy, with refractory response to vitamin A supplementation for night blindness, and

**Table 6: Guidelines for pre-transplant nutrition support**<sup>[31,37,63,89,90]</sup>

ESPEN Guidelines	Recommendations for nutrition
For organ transplantation 2006	Under nutrition majorly influence outcome after LT; use additional oral nutrition supplementation or even tube feeding; EN improves nutritional status and liver function, reduces the rate of complications, cost and prolongs survival; assess nutritional status regularly
For enteral nutrition for liver disease 2006	Use high-energy formulae in patients with ascites; increased protein requirements; use BCAA-enriched formulae (hepatic encephalopathy); EN and probiotic formula reduces the incidence of infections; hepatic encephalopathy must be treated with lactulose or rifaximin; normal protein diets can be given safely to patients with hepatic encephalopathy; recommended protein supplementation is based on “dry” body weight; recommended to insert fine bore nasogastric tubes in patients with esophageal varices
For parenteral nutrition in hepatology 2006	PN is indicated in unprotected airways, encephalopathy and moderately or severely malnourished cirrhotics; cirrhotics who have to abstain from food temporarily for > 12 h should be given i.v. glucose at 2-3 g/kg per day. When this fasting period lasts longer than 72 h TPN is required; the i.v. provision of all macro- and micronutrients must be ensured from the beginning of PN; carbohydrate should be given as glucose to cover 50-60% of non-protein energy requirements; in case of hyperglycaemia glucose infusion should be reduced to 2-3 g/kg per day and i.v. insulin infusion should be used; lipid should be provided using emulsions, should cover 40-50% of non-protein energy requirements

ESPEN: European Society for Parenteral and Enteral Nutrition; BCAA: branched-chain amino acids; LT: liver transplantation; EN: enteral nutrition; TPN: total parenteral nutrition

for potential improvement in immune function and taste perception.<sup>[49]</sup> Supplementation in the form of 220 mg zinc sulphate is given in 1-3 divided doses per day. Zinc and selenium deficiency has been observed in both alcoholic and non-alcoholic liver disease and may be associated with neurological symptoms.<sup>[55]</sup> Depleted serum iron levels, blood losses can cause deficiency in LT patients.<sup>[49]</sup> Hepatic iron overload is common and often secondary to increased intestinal iron absorption and transfusions, and may imitate hemochromatosis as well as increase the risk of developing progression of liver disease.<sup>[56]</sup> Patients undergoing LT are prone to hypomagnesemia, with potential deleterious effects. A study evaluated the efficacy and safety of routine intraoperative magnesium supplementation to prevent hypomagnesemia. The results<sup>[57]</sup> showed lower prevalence of postoperative hypomagnesemia in patients administered magnesium supplementation of 3 g [Table 4]<sup>[58-63]</sup> but may not affect the occurrence of arrhythmias.

## CHALLENGE IN PRE-TRANSPLANT NUTRITION SUPPORT

Ascites, defined as the accumulation of fluid within the peritoneal cavity as a direct consequence of portal

hypertension, is a common complication of ESLD and associated with a poor prognosis.<sup>[64]</sup> The squeal of impaired renal perfusion and fluid volume expansion can precipitate hyponatremia as well.<sup>[65]</sup> Spontaneous bacterial peritonitis may develop which is associated with increased mortality.<sup>[66]</sup> Nutrition issues may occur in cirrhotics with ascites due to decreased intake from early satiety, increase in REE before paracentesis. Also, imposing dietary restrictions of sodium and fluid reduces the palatability of food.<sup>[22]</sup>

The American Association for the Study of Liver Disease practice guidelines (2004), recommend sodium restricted diet and diuretic therapy as the mainstay of treatment for ascites, with their effectiveness demonstrated in about 90% of patients. A dietary sodium restriction of 2 g/day appropriately balances the need for adequate nutrition and fluid status. The reduction in ascitic fluid through careful diuresis can relieve early satiety. A 24-h urinary sodium excretion with a goal of  $\geq 78$  mEq urinary sodium per day can be measured to follow compliance to a sodium-restricted diet. A fluid restriction is appropriate in cirrhotic patients with dilutional hyponatremia or serum sodium levels  $< 125$  mg/dL [Table 4]. Small, frequent feedings and an adequate intake of protein, in addition to the sodium restriction, are important dietary









