

Nutritional Status and Liver Transplantation

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Chronic liver disease has a profound effect on nutritional status and undernourishment is almost universally present in patients with end-stage liver disease undergoing liver transplantation. In the last decades, due to epidemiological changes, a trend showing an increase in patients with end-stage liver disease and associated obesity has also been reported in developed countries. Nutrition abnormalities may influence the outcome after transplantation therefore, the importance to carefully assess the nutritional status in the work-up of patients candidates for liver transplantation is widely accepted. More attention has been given to malnourished patients as they represent the greater number. The subjective global nutritional assessment and anthropometric measurements are recognized in current guidelines to be adequate in identifying those patients at risk of malnutrition. Cirrhotic patients with a depletion in lean body mass and fat deposits have an increased surgical risk and malnutrition may impact on morbidity, mortality and costs in the post-transplantation setting. For this reason an adequate calorie and protein intake should always be ensured to malnourished cirrhotic patient either through the diet, or using oral nutritional supplements or by enteral or parenteral nutrition although studies supporting the efficacy of nutritional supplementation in improving the clinical outcomes after transplantation are still scarce. When liver function is restored, an amelioration in the nutritional status is expected. After liver transplantation in fact dietary intake rapidly normalizes and fat mass is progressively regained while the recovery of muscle mass can be slower. In some patients unregulated weight gain may lead to over-nutrition and may favor metabolic disorders (hypertension, hyperglycemia, hyperlipidemia). This condition, defined as 'metabolic syndrome', may play a negative role on the overall survival of liver transplant patients. In this report we review data on nutrition and liver transplantation. (J CLIN EXP HEPATOL 2011;1:190-198)

Liver transplantation (LT) has dramatically changed the prognosis of end-stage liver disease. The amelioration in the immunosuppressive regimens and surgical techniques has progressively improved the outcome of these patients and survival after LT is nowadays 70–80% at 5 years.¹ From 2002, the introduction of the model for end-stage liver disease (MELD) for prioritization of the patients in need of a new liver has led to a significant reduction in mortality in the waiting list, favoring the transplantation of the sickest patients;^{2–4} at the same time, it has been clearly demonstrated that there is no transplant benefit when patients are transplanted with a MELD score below 15.⁵ As a consequence in the past years, patients submitted to liver transplant are likely to have a more compromised clinical status, and complications of cirrhosis, such as malnutrition, are expected to be even more

prevalent in liver recipients than before. Those patients with a more advanced liver insufficiency are in fact known to experience a higher prevalence of severe protein/calorie malnutrition.⁶ The possible impact of malnutrition on the outcome of LT and the need of dietary counseling and nutritional supplementation in patients with end-stage liver disease has become therefore a subject of growing interest and debate. From another point of view, countries with an increasing prevalence of overnutrition have recently reported that the number of obese patients in the waiting list for LT is increasing and there is a concern that also severe obesity may affect the morbidity and mortality after transplantation.⁷

The purpose of this review was to examine the recent literature to estimate the prevalence of malnutrition in advanced liver disease, evaluate the possible methods to recognize nutritional alterations in these patients, consider the role of nutritional status in liver transplant, and underline the main recommendation and guidelines for nutritional support in advanced liver disease.

METHODS

Bibliographic searches were performed in MEDLINE for the following words (all fields): 'nutrition' (MeSH) or 'malnutrition' (MeSH) or 'obesity' (MeSH) or 'nutritional status' (MeSH) and 'liver transplantation' (MeSH) or 'liver transplant' (MeSH) or 'cirrhosis' (MeSH) or 'end-stage liver disease' (MeSH). Reference lists of the studies

Keywords: Body weight, cirrhosis, end stage liver disease, malnutrition, nutritional assessment, nutritional support or nutritional therapy, obesity, outcomes

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Abbreviations: BCAA: branched chain amino acids; BMI: body mass index; LT: liver transplantation; MELD: model for end-stage liver disease; SGA: subjective global assessment for nutrition

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identified during electronic searching were also hand-searched to identify the additional relevant studies for the inclusion. Studies eligible for the review were those published between 1990 and 2011; however, older studies were utilized, when needed, to support the information about the physiopathology of malnutrition in liver disease. Studies published in abstract form only, or in non-English language, were excluded. Preference was given to studies presenting original data than to review studies.

Prevalence and Consequences of Nutritional Alterations in Patients With End-stage Liver Disease

Malnutrition is frequently associated with chronic liver disease: the prevalence may range from 20% to 80% depending on the methods used for the nutritional assessment and the severity of liver disease.^{6,8,9} A large multicenter study has shown that the prevalence of malnutrition is considerably higher in patients with a more severe liver impairment (20–25% in Child A–B patients but >50% in Child C).⁶ The correlation between malnutrition and the origin of liver cirrhosis is controversial. Some authors have suggested a higher prevalence of malnutrition in patients with postalcoholic disease;¹⁰ alcohol abuse may in fact represent a cause of malnutrition per se due to the replacement of nutrient foods with empty calories, or secondary to the conditions of maldigestion and malabsorption, induced by the reduction of the bile and pancreatic enzyme secretion, which can lead to increase nutrient losses.^{11,12} Malnutrition, however, is not limited to post-alcoholic cirrhosis and a number of studies have demonstrated that the prevalence of malnutrition is similar in patients with non-alcoholic liver disease.^{6,8,13,14} Concerning the gender, a more pronounced loss of body fat has been described in woman while men experience more frequently a depletion in the lean body mass. This alteration may be present even in the early stages of liver cirrhosis and is further accelerated in the advanced stages of the disease.^{15–17}

In the past decade, a new scenario with a higher prevalence of overweight/obese cirrhotic patients has been pointed out. Data from the United Network of Organ Sharing have shown that, in the past decade, obesity-associated liver disease has become an increasing indication for LT. At the same time, the prevalence of obese patients in the waiting list has been reported to be as high as 20%.¹⁸ Although these data mainly refer to the United States where a high prevalence of overnutrition exists, a similar trend could also involve other developed countries in the near future. Data on the nutritional status of patients with end-stage liver disease in other populations are not always available. It is expected in fact that in countries in developing transition, both under-nutrition and obesity may coexist.¹⁹ The impact of these double burden in cirrhotic patients is unknown and data about the nutritional status

of patients awaiting for LT in developmental countries is still scarce. In a recent study on Malaysian patients with decompensated cirrhosis, the prevalence of malnutrition was as high as 50%.²⁰ In our unit, which is a tertiary referral center, among 205 cirrhotic patients consecutively hospitalized in the year 2010, a mid-arm muscular circumference <5th percentile was detected in 35%. After correcting body weight for ascites and edema (estimated dry weight), body mass index (BMI) (Kg/m^2) <18, denoting malnutrition, was reported in 21% of patients and BMI >35, denoting obesity, was found in 5%.

Malnutrition in cirrhotic patients is known to be associated with a higher prevalence of complications, such as hepatic encephalopathy, ascites, hepatorenal syndrome, and bacterial infections;^{21,22} furthermore, malnourished patients may experience a deterioration in the quality of life. The independent role of malnutrition on survival in patients with liver disease has been extensively documented; patients comparable for the severity of liver insufficiency show a higher rate of mortality when nutritional status is severely impaired.^{23–25}

Main Causes of Malnutrition and Methods to Recognize Nutritional Alterations in Patients With End-stage Liver Disease

A variety of mechanisms are considered to be responsible for malnutrition in patients with chronic liver disease and usually two or more may coexist (Table 1). All these abnormalities may precede protein-calorie malnutrition which arises when the diet does not provide adequate calories and proteins to maintain the nutritional status or when the body is unable to fully absorb or utilize the food eaten secondary to the liver disease. The most common findings in cirrhotic patients are a reduction in the muscle mass and function and a depletion in fat deposits;^{6,8,17,23,26} the body composition profile may be modified in cirrhotic patients even in the initial stages.^{15,16} These changes may, however, be masked due to fluid retention which increases both intra- and extracellular water even before ascites and edema become clinically apparent.²⁷

Considering the predictive role of malnutrition for the patient's outcome, an accurate assessment of the nutritional status in patients with advanced liver disease is mandatory. However, the methods to be used for the assessment of the nutritional status in liver cirrhosis are controversial.²⁸ Malnutrition in these patients may develop insidiously and is frequently jeopardized by multiple confounding factors (Tables 2 and 3). The main tools commonly used to investigate the nutritional status can be inappropriate in the setting of chronic liver disease: body weight and BMI can be misleading because of edema and ascites, although one study has validated BMI in cirrhotic patients using an appropriate cut-off;²⁹ plasma protein concentration is influenced by the functional reserve of the

Table 1 Causes and mechanisms of malnutrition in end-stage liver disease.

Reduced nutrient intake	<ul style="list-style-type: none"> • Decreased appetite and anorexia • Nausea and early satiety • Starvation 	<ul style="list-style-type: none"> – Unpalatable diet (sodium and water restriction for peripheral edema and ascites, protein restriction for hepatic encephalopathy) – Disgeusia due to micronutrient deficiencies (zinc or magnesium) – Anorexic effect caused by increased levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and leptin – Tense ascites – Gastroparesis – Small bowel dysmotility – Bacterial overgrowth – Hospitalization – Invasive diagnostic procedures requiring fasting – Gastrointestinal bleeding and endoscopic therapies
Reduced intestinal absorption	<ul style="list-style-type: none"> • Maldigestion • Bacterial overgrowth • Diarrhea 	<ul style="list-style-type: none"> – Pancreatic insufficiency in alcohol abuse and/or cholestasis – Intestinal dysmotility and increased transit time – Drugs (i.e., nonabsorbable disaccharides, antibiotics, and cholestyramine)
Metabolic alterations	<ul style="list-style-type: none"> • Protein catabolism • Increased energy expenditure • Insulin resistance • Increased fat turnover 	<ul style="list-style-type: none"> – Reduced hepatic protein synthesis and increased protein breakdown – During ascites and bacterial infections – Hepatocellular carcinoma – Hyperinsulinemia and reduced nonoxidative glucose metabolism – Increased lipolysis due to more rapid transition to starvation – Fats are utilized as alternative energy source

Table 2 Factors influencing the accuracy of common indices used for nutritional assessment in patients with chronic liver disease.

Body weight	<ul style="list-style-type: none"> • Water restriction and fluid accumulation • Changes in body composition
Visceral proteins	<ul style="list-style-type: none"> • Decreased liver synthesis • Increased volume of distribution
Anthropometry	<ul style="list-style-type: none"> • Fluid retention (barely influential)
Immunological status	<ul style="list-style-type: none"> • Hypersplenism • Abnormal immunological reactivity
Creatinine excretion	<ul style="list-style-type: none"> • Renal insufficiency
Bioelectrical impedance analysis	<ul style="list-style-type: none"> • Presence of ascites

liver more than the degree of malnutrition; the creatinine-height index is influenced by liver and renal function; nitrogen balance to assess protein catabolism is difficult to be measured in clinical practice. Although anthropometry may be affected by the presence of severe water retention, some studies have shown a good correlation between the assessment of body composition through anthropometric measurements (arm-muscle circumference and triceps skinfold) and more sophisticated techniques such as dual exchange X-ray absorption.^{30,31} The arm-muscle circumference and triceps skinfold thickness have also been shown to correlate with mortality in cirrhotic patients.^{23,24} To overcome the difficulty to assess the nutritional status in patients with chronic liver disease, some authors have applied a combination of different parameters to obtain what is widely known as the ‘Subjective Global Assessment (SGA)’ of nutrition.³² This is in fact a method based on the clinical history, physical examination, dietary interview and gastrointestinal symptoms and it has been frequently

Table 3 Advices for nutritional assessment in a cirrhotic subject.

Physical examination and anthropometry	<ul style="list-style-type: none"> • Consider body weight modification in the last months with particular attention at the last 2 weeks. • Calculate body mass index using the estimated dry weight if needed. • Evaluate subcutaneous fat and muscle mass (arm circumference and triceps skinfold). • Measure hand-grip strength as a tool to identify patients at nutritional risk.
Dietary interview	<ul style="list-style-type: none"> • Perform a detailed diet history to evaluate the recent reduction or modification (intentional/unintentional). • Estimate the amount of calorie and protein intake in the diet. • Evaluate the presence of gastrointestinal symptoms (anorexia, vomiting, nausea, diarrhea, and dysphagia).
Subjective global assessment (SGA) of nutrition	<ul style="list-style-type: none"> • Integrate objective and subjective data to obtain SGA.
Total energy balance	<ul style="list-style-type: none"> • Estimate calorie needs with formulas or measure resting energy expenditure in difficult case by indirect calorimetry. • Calculate energy balance as: total energy intake subtracted total energy expenditure.

utilized to evaluate the nutritional status both in patients with chronic liver disease and in those waiting for LT.^{22,31,33} In some of these studies, SGA has been proved to be an excellent predictor of outcome.^{33,34} The hand-grip strength test, a simple and bedside useable tool which investigates muscle function, has also been applied in cirrhotic patients, demonstrating to be a powerful instrument to predict a poor clinical outcome.³⁵

Although a gold standard to assess the nutritional status in patients with end-stage liver disease is still lacking, both SGA and anthropometry have been recommended by the European Society of Parenteral and Enteral nutrition to be adequate in identifying those patients at a risk of malnutrition.³⁶ Main suggestions for the evaluation of the nutritional status in cirrhotic patients are summarized in Table 3.

Nutritional Status and the Outcome After Liver Transplantation

Malnutrition is known to be associated with a greater risk of postoperative complications and mortality in patients with liver disease,^{37,38} it is therefore conceivable that a deteriorated nutritional status may also exert a detrimental effect in patients undergoing LT. A number of studies have addressed this problem^{34,39-44} although the results have been controversial (Table 4).

Some studies have shown that pre-operative malnutrition impacts negatively on the post-transplant outcomes. Among them, one prospective study on 68 cirrhotic patients undergoing LT³⁹ demonstrated a lower postoperative survival rate in patients with severe malnutrition, while a retrospective study on 99 patients transplanted between 1996 and 1999³³ showed that patients classified as severely malnourished according to SGA required more blood products during surgery and needed a prolonged postoperative

hospital stay. This latter study, however, could not evaluate the relationship between nutritional status and peri-operative mortality because of the small number of events. In a series of 102 cirrhotic patients with a high prevalence of cholestatic liver disease (59%), malnourished liver recipient, defined as those with mid-arm circumference and triceps skinfold thickness below 25th percentile, were found at higher risk for postoperative infections; however, the time spent in the intensive care unit, the total time spent in the hospital, and survival were not significantly different in well-nourished and in malnourished patients.⁴² Selberg et al⁴¹ also found that a body cell mass depletion >35% and hypermetabolism were associated with lower survival rates after transplantation; in this study, however, at variance with other reports, the survival rate was evaluated considering a rather long-term (5-year) follow-up.

Different results have been reported by two prospective investigations dealing with a series of 61 and 53 LT candidates where the authors failed to find any association between the pre-operative nutritional status and the patient's survival or the global resource utilization.^{40,43} These authors suggest that other factors (surgical risk, donor risk index, immunosuppressive therapy, and so on) may play a major role on the transplantation outcome and may therefore blunt the influence of the recipients' nutritional status. A further study failed to find a correlation between the nutritional status and the different posttransplant outcomes in 31 liver recipients; however, the results were

Table 4 Relationship between nutritional status and outcome after liver transplantation.

Authors and reference no.	Patients (n)	Parameters used for the assessment of nutritional status	Prevalence of malnutrition (%)	Outcomes related to malnutrition
Pikul et al ³⁹	68	SGA	79	Prolonged ventilator support Increased incidence of tracheostomy More days in intensive care unit and hospital
Selberg et al ⁴¹	150	Anthropometry Body composition analysis Indirect calorimetry	41-53	Low survival 5 years after liver transplantation
Harrison et al ⁴²	102	Anthropometry Dietary intake	79	Higher risk of infections
Figuerido et al ⁴⁰	53	SGA Hand-grip strength Body composition analysis	87	More days in intensive care unit Increased incidence of infections
Stephenson et al ³³	99	SGA	100	Increased blood product requirements More days in hospital
Shahid et al ⁴³	61	Hand-grip strength Anthropometry	Not defined	No correlation
De Luis et al ⁴⁴	31	SGA Body composition analysis Dietary intake	Not defined	No correlation
Merli et al ³⁴	38	SGA Anthropometry Indirect calorimetry Dietary intake	53	More days in intensive care unit and hospital Increased incidence of infections

SGA: subjective global assessment of nutrition.

probably influenced by the fact that the large majority of these patients were not depleted at the time of surgery.⁴⁴ In a recent study, we prospectively analyzed the nutritional status of 38 consecutive patients awaiting for LT in our University Hospital. Fifty-three percent of these patients were malnourished according to the SGA. Nutritional status, hemoglobin levels, and disease severity were all independently associated with the number of infection episodes before hospital discharge. We also found that the presence of malnutrition was the only independent risk factor for the length of stay in the intensive care and the total number of days spent in the hospital. Our results suggest that the recipients' nutritional status influences the rate of post-transplant complications and may therefore increase the costs of liver transplant.³⁴

Controversies exist not only regarding the morbidity and mortality of patients transplanted in undernourishment, but also for those with overnutrition or obesity. Liver transplantation in severely obese patients (BMI > 35 Kg/m²) has been associated with a higher rate of wound infection and the early death from multi-system organ failure.⁴⁵ These results have been confirmed by the analysis of a large database including 18,172 transplanted patients showing that primary graft nonfunction, and in hospital, 1-year, and 2-year mortality were significantly higher in the morbidly obese patients (BMI > 40 Kg/m²).⁴⁶ In the long-term, also the 5-year mortality was significantly higher in severely obese liver recipients mostly as a result of the adverse cardiovascular events. A potential limit of this study was the inability to correct BMI for the presence of ascites. A higher BMI may in fact also reflect the presence of severe ascites, frequently associated with renal dysfunction and more severe liver disease and these conditions may also have an impact on the posttransplant outcomes. A similar study, using the National Institute of Diabetes and Digestive and Kidney Disease LT database, after the correction of the BMI for ascites, found no significant difference in survival across all BMI categories.¹⁸ In a further attempt to investigate the impact of recipient's BMI on LT survival, Dick and co-workers reported that the patients at the extremes of the BMI (BMI < 18.5 and ≥ 40 Kg/m²) showed the higher rates of mortality. Underweight and very severe obesity were confirmed to be the significant predictors of death, also if evaluated in different transplant era.⁴⁷ It is important to point out that the effect of malnutrition on survival is difficult to demonstrate in studies including small series of liver recipients. In fact, the early post-transplant mortality in most transplant units is much <10% and other determinants including donor and recipient variables may also play a relevant role on the patients' outcome. The same applies to studies regarding the impact of pretransplant feeding on post-transplant survival; in fact, these interventional studies require a strict pretransplant nutritional protocol, which may last for a variable period and necessarily involve limited cohorts of patients.

Indications for Malnourished Patients Waiting for Liver Transplantation

Despite these controversial results, the belief that malnutrition may increase the risk of patients undergoing LT, as is the case for other surgical procedures in cirrhotic patients,^{37,38} is generally recognized. Nutritional guidelines, published in the last years, have always underlined the importance to ensure an adequate calorie and protein intake to undernourished cirrhotic patients (35–40 Kcal/Kg/day; 1.2–1.5 g/Kg/day protein).^{36,48} According to these guidelines, energy should be provided by glucose and fat in a ratio of 65–50/35–50 of the nonprotein calorie requirements, and hepatic encephalopathy (grades I–II) should not be regarded as a reason for protein restriction. Even in patients with acute hepatic encephalopathy, a normal protein intake has been shown not to be harmful and able to avoid the increase in protein breakdown.⁴⁹ In malnourished patients, a dietary interview can be helpful to evaluate whether the intake is sufficient to meet the patient's requirements and to adopt an adequate nutritional counseling. It is highly recommended to make the periods of starvation shorter, by dividing the daily energy intake in multiple meals during the day. In fact, it has been shown that after overnight fast, cirrhotic patients experience a metabolic state similar to that of healthy subjects after 3 days of fasting,⁵⁰ with an increased gluconeogenesis from amino acids and increased lipolysis. A late evening snack has been found to be beneficial in cirrhotic patients to compensate the overnight fasting period.^{51,52} More recently, a randomized trial reported that a complete nutritional supplementation (710 Kcal and 26 g protein) given in the late evening hours (from 9 pm to 7 am) is able to improve the total body protein measured by the neutron activation analysis in patients with liver cirrhosis.⁵³ Nocturnal supplementations with snacks enriched with branched chain amino acids (BCAA) have also been suggested to be effective in improving the nutritional status of cirrhotic patients⁵⁴ being even better than the supplements of ordinary food.⁵⁵ Main nutritional recommendations in liver cirrhosis are summarized in Table 5.

Another important issue is how cirrhotic patients who are unable to meet their daily caloric requirements should be fed. According to the recommendations of the European Society of Parenteral and Enteral Nutrition, these kinds of patients are the candidates for tube feeding, while parenteral nutrition should be considered in patients with unprotected airways, or during deep encephalopathy when cough and swallow reflexes are compromised.⁵⁶ Nutritional support should also include the administration of vitamins, minerals and trace elements that may be depleted. For example, osteopenia and osteoporosis are frequent in patients with end-stage liver disease and vitamins and calcium supplementations are therefore recommended.^{57,58}

Prospective studies dealing with nutritional regimens in cirrhotic patients waiting for transplantation are still

Table 5 Main nutritional recommendations in end-stage liver disease.

Energy intake	Provide 30–35 Kcal/Kg dry body weight/day. Provide 50–60% of calories as carbohydrates. Provide 20–30% of calories as fat. Avoid unnecessary dietary restrictions.
Frequency of meals	4–6 meals every day including a late evening snack.
Protein intake	Provide 1–1.5g of protein per Kg of weight/day. In patients with hepatic encephalopathy, if the patient is protein-intolerant, consider to reach the protein need including vegetable proteins, dairy proteins, and/or branched chain amino acids oral supplementation.
Vitamins and trace elements	Consider the need of vitamins (A, D, E, and K) or trace elements (zinc and calcium) supplements based on patient's symptoms or serum levels.
Artificial nutrition	Patients who are unable to take adequate nutrition through diet or nutrition supplementation may require enteral or parenteral nutrition for maintenance.

scarce. Chin et al compared two pre-operative nutritional supplementations (a BCAA-enriched versus a matched standard semi-elemental formulation) in 19 children with end-stage liver disease waiting for liver transplant.⁵⁹ Twelve patients completed the study before being transplanted and 10 completed a full crossover study. Both regimens improved children's weight and height, and BCAA supplements caused a significant increase of mid-arm circumference and subscapular skinfold thickness. The authors concluded that BCAA-enriched formulas have advantages over standard semi-elemental formulas in improving the nutritional status in children with advanced liver disease. However, a randomized pilot study in adult patients could not demonstrate that an intensive pre-operative nutrition was able to improve the patients' outcome.⁶⁰ The authors included 82 consecutive patients, 42 received enteral supplementation, and the remainder acted as the control group. Although the supplemented group improved arm circumference, arm-muscle circumference, and hand-grip strength, the overall survival was not significantly different within the 2 groups ($P=0.07$) as a larger group of patients would have been needed. Despite the importance of nutritional therapy for patients waiting for LT, no clear data are therefore available to support the efficacy of nutritional supplementation in improving the clinical outcomes in these patients.

Nutritional Support After Liver Transplantation

After LT, surgical stress, postoperative fasting, and the possible occurrence of postsurgical complications suggest the need for nutritional supports. Only few studies have elucidated the role of postoperative nutritional support in these patients. In an old study, Reilly assigned 28 cirrhotic patients to receive, for a 7-day period after LT, total parenteral nutrition (either with standard amino acids or with

BCAA) or glucose infusion. Both the parenteral regimens improved nitrogen balance and respiratory muscle function, allowing an earlier weaning from ventilator support, and these patients also needed fewer days in the intensive care unit compared with the group receiving glucose.⁶¹ Hasse et al⁶² prospectively randomized 50 transplant patients to receive either an enteral formula via a naso-intestinal feeding tube or maintenance i.v. fluid until oral diet was initiated. Thirty-one patients completed the study, 14 in the enteral group. These latter patients showed higher nutrient intake, a better nitrogen balance and developed less infections; however, the costs of hospitalization, hours on the ventilator, lengths of stay in the intensive care unit and hospital, rate of re-hospitalizations, or rejection during the first 21 post-transplant days were similar to the control group. The authors concluded that early post-transplant tube feeding was both well tolerated and able to improve some outcomes and should therefore be considered in all liver transplant patients in the first days after surgery.⁶² Other studies compared the efficacy and tolerability of early enteral feeding versus the total parenteral nutrition after LT. Enteral feeding was shown to be as effective as total parenteral nutrition at maintaining nutritional status, and had potential benefits reducing complications and costs.^{63,64} An innovative approach has been proposed by Plank et al who showed an increase in the total body protein measured by neutron activation analysis in a small group of patients receiving an immunomodulatory oral supplementation before and immediately after LT.⁶⁵ Due to the small size of the study (15 treated and 17 controls receiving standard nutrition), the authors could not demonstrate any reduction in the number of infection episodes. No other studies have been performed to confirm these results in a larger number of patients.

Despite the lack of large validated studies in this field, some crucial points are widely accepted: after LT, nutrition should be initiated within 12–24 h postoperatively;³⁶ if the patient is unable to tolerate oral intake for a few days, the administration of nutritional supplements through a naso-enteric tube is preferable over total parenteral nutrition; nutrition should provide calories for an amount of 120–130% of the calculated basal energy expenditure and 1.2–1.5 g of proteins per Kg versus of dry weight as protein catabolism is expected to be further increased in the immediate post-surgical phase. Nutritional supplements should not be discontinued before the patient is able to maintain an adequate oral intake. Main nutritional recommendations in liver transplant patients are reported in Table 6.

Modification of Nutritional Status After Liver Transplantation

Nutrition abnormalities are expected to improve when liver function is restored. In fact, many metabolic alterations, which are involved in causing malnutrition in cirrhotic patients, are corrected when a new functioning liver

Table 6 Main nutritional recommendations after liver transplantation.

General recommendations	Provide calories for an amount of 120–130% of the calculated basal energy expenditure. Provide 1.5–2 g of protein per kilogram of dry weight in the early period.
Type of nutrition	Prefer nasogastric tube to the total parenteral nutrition to provide nutritional support until patients are able to tolerate oral intake.
Nutritional supplements	Should not be discontinued before the patient is able to maintain an adequate oral intake.

is given to the patient. Dietary intake is also expected to normalize as soon as the patients improve. Few studies reported data about the modification of the nutritional status after transplantation. In a small group of 14 unselected patients, the resting energy expenditure increased significantly (42% above the predicted values) during the first 10 days, and a significant degree of hypermetabolism was still present 6 months after LT while, after 12 months, the measured resting energy expenditure was completely normalized.⁶⁶ Using sophisticated techniques to estimate body composition, these authors also showed a loss of the total body fat during the early postoperative period which was fully regained at 3 months while a depletion in the skeletal muscle protein was still recognizable after 12 months. A retrospective study by Richards et al⁶⁷ suggested that a progressive weight gain is expected in all the patients after LT. In 597 patients transplanted between 1996 and 2001, the median weight gain at 1 and 3 years was 5.1 and 9.5 Kg above the dry pretransplant weight and by 1 and 3 years, 24% and 31% of the patients had become obese (BMI > 30 Kg/m²). In 46% of these patients, the arm-muscle circumference was below the 25th centile before LT. Among those who were not obese, 15.5% became obese 1 year after transplantation and 26.3% at 3 years. The obese population lost significantly more weight ($P < 0.05$) than the non-obese in the first 6 months, but, by the first year, there was no statistical difference in the weight gained between these 2 groups.

A more recent retrospective report examined the changes in the nutritional status in a mixed population of 70 cirrhotic and noncirrhotic patients transplanted between 1997 and 1999. The authors reported that after 1 year, 44% of patients were still classified as having some degree of malnutrition. The presence of malnutrition (based on anthropometry) was associated with a worse nutritional status before transplantation and fat stores (triceps skinfold thickness) remained inadequate in 70% of malnourished patients at the end of the first year.⁶⁸

In our experience, the main modifications in the nutritional status during the first year after transplantation are observed in those patients who are severely malnourished.⁶⁹ In our cohort, according to the subjective global nutritional assessment, 56% of patients were undernourished

at transplant. In these latter patients, the nutritional status further deteriorated at 3 months but improved 6 and 12 months after transplantation; the main changes were reported for fat mass (median triceps skinfold: basal 10.8 mm vs 12 months 15.2 mm, $P = 0.03$) while the parameters of muscle mass showed only minor variations (median arm-muscle circumference: basal 23.4 cm vs 12 months 24.0 cm, $P = 0.3$). The improvement of nutritional status was associated with a substantial amelioration of the calorie (basal 27 Kcal/Kg/die vs 12 months 32 Kcal/Kg/die, $P = 0.007$) and protein (basal 0.8 g/Kg vs 12 months 1.3 g/Kg, $P = 0.02$) intake.

A thorough knowledge of the modification of body composition and nutritional status after LT will also help in understanding why some of these patients gain an excessive weight and acquire a cohort of metabolic alteration leading to the development of a metabolic syndrome.⁷⁰ The metabolic syndrome has in fact been shown to be a prevalent cause of morbidity and mortality in the long-term follow-up of patients receiving LT⁷¹ also favoring 'graft loss'.⁷²

In conclusion, an impairment of nutritional status is a frequent finding in patients with end-stage liver disease. Malnutrition adversely affects the prognosis of these patients and has an impact on the morbidity and mortality after LT. Severe obesity may also affect the outcome of transplantation. A complete nutritional assessment is therefore always recommended to identify patients at a risk of complications and to introduce nutritional counseling and supplementations when needed. Artificial nutritional support may be indicated in malnourished patients while waiting for LT and after surgery although further large-scale interventional studies are needed to better define treatment guidelines. A close monitoring of the modification of the nutritional status and body composition in patients with a restored liver function will help to identify patients at risk for over-nutrition after LT.

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