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TOPIC HIGHLIGHT

2016 Liver Transplantation: Global view

Nutrition therapy: Integral part of liver transplant care

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Abstract

Managing malnutrition before liver transplantation (LTx) while on the waiting list and, excessive weight gain/metabolic disturbances in post-surgery are still a challenge in LTx care. The aim of this review is to support an interdisciplinary nutrition approach of these patients. Cirrhotic patients are frequently malnourished before LTx and this is associated with a poor prognosis. Although the relation between nutritional status versus survival, successful operation and recovery after LTx is well established, prevalence of malnutrition before the operation is still very high. Emerging research has also demonstrated that sarcopenia pre and post-transplant is highly prevalent, despite the weight gain in the postoperative period. The diagnosis of the nutritional status is the first step to address the adequate nutritional therapy. Nutritional recommendations and therapy to manage the nutritional status of LTx patients are discussed in this review, regarding counseling on adequate diets and findings of the latest research on using certain immunonutrients in these patients (branched chain amino-acids, pre and probiotics). Nutrition associated complications observed after transplantation is also described. They are commonly related to the adverse effects of immunosuppressive drugs, leading to hyperkalemia, hyperglycemia and weight gain. Excessive weight gain and post-transplant metabolic disorders have long been described in post-LTx and should be addressed in order to reduce associated morbidity and mortality.

Key words: Nutritional status; Malnutrition; Obesity; Metabolic syndrome; Nutrition therapy; Liver transplantation

Core tip: Cirrhotic patients are frequently malnourished before liver transplantation (LTx) and this is associated with a poor prognosis**.** Emerging research has also demonstrated that sarcopenia pre and post-transplant is highly prevalent, despite the weight gain in the postoperative period. The diagnosis of the nutritional status is the first step to address the adequate nutritional therapy. Nutritional recommendations and

therapy to manage the nutritional status of LTx patients are discussed in this review. Nutrition associated complications observed after transplantation is also described. Excessive weight gain and post-transplant metabolic disorders have long been described in post-LTx and should be addressed to reduce associated morbidity/mortality.

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INTRODUCTION

Nutritional therapy is an integral part of liver transplant care. Although many nutritional aspects of liver transplantation patients have previously been addressed, it is still a challenge to manage malnutrition[1] in the pre-transplant phase and, excessive weight gain/metabolic disturbances[2,3] postoperatively. Recent reports still show that little has changed in the last years with increased prevalence of both entities[4,5].

Interdisciplinary teams should definitely prioritize nutritional therapy as an integral part of liver transplant care in order to change this reality. The aim of this article is to review the nutritional status of liver transplant patients as well as the recommendations and therapy before and after liver transplantation.

NUTRITIONAL STATUS

Malnutrition is still highly prevalent in cirrhotic patients, despite the medical advances in liver transplantation care[1]. Causes of malnutrition in these patients are well described and, essentially, include the effects of a catabolic chronic illness accompanied by reduced food intake[6,7] leading to negative energy balance[8] (Table 1). Many reasons are cited to explain decreased diet intake in cirrhotic patients such as: anorexia caused by zinc deficiency, hyperglycemia and, increased inflammatory cytokine productions (*e.g.,* TNF-α and IL-6) and leptin[7,9,10]; frequent fasting periods for medical examsand procedures as well as iatrogenic diet counseling, usually indicating the avoidance of protein sources, especially for those patients at higher risk of encephalopathy[11] and/or low-salt unpalatable diets. Furthermore, autonomic neuropathy observed in liver cirrhosis causes altered gustatory sensation, gastroparesis and delayed bowel transit time, which together with bacterial overgrowth and tense ascites, cause nausea and early satiety[7,12]. Protein losses due to gastrointestinal bleeding and frequent parecentesis also contribute to malnutrition, which may further be worsened by protein-losing enteropathy, contributing to the development of hypoalbuminemia[13]. Adequate nutrient utilization may be impaired because digestion, absorption and metabolism seem also to be affected in cirrhotic patients. When there is associated excessive alcohol intake or diseases affecting the biliary system, malabsorption is impaired[14,15]. The latter is also influenced by the use osmotic laxatives, as lactulose. Also, liver impairment negatively impacts the capacity of macronutrient metabolism, specially the reduction of protein synthesis, the decrease in glycogen storage and glycogenolysis[7]. Patients with end-stage liver disease may have impaired synthesis of polyunsaturated fatty acids from essential fatty acids precursors, with increases in the levels of n-6 and n-9 and decreases in n-3 fatty acids in plasma and adipose tissue[16]. Also, some authors have reported increased resting energy expenditure in cirrhotic patients[17,18].

Table 1 Factors associated with malnutrition in patients on the waiting list for liver transplantation

Factors
Anorexia
Ascites
Altered taste perception
Metabolic and inflammatory derangements
Inadequate diet restrictions
Decreased social status
Polypharmacy
Multiple paracentesis
Variceal bleeding
Long fasting periods for labs and diagnostic procedures

As a consequence, nowadays, the prevalence of malnutrition is still very high[1] and seems not to have decreased from what was reported more than twenty years ago[4,19]. Thus, malnutrition may currently affect almost all cirrhotic patients. This could be justified by the fact that patients undergoing transplantation today are generally sicker than those who underwent it before the use of the model of end-stage liver disease (MELD) score. Therefore, it could be hypothesized that nutrition could play a more significant role today than in the past, placing patients at additional nutrition challenges for post-operative recovery[20].

Malnutrition related outcomes have been well recognized with many studies showing the negative impact after transplantation, which is associated to longer hospital andintensive care unit stay, infections, graft impairment and mortality[21-24]. Nevertheless, a recent metanalysis of randomized clinical trials has failed to demonstrate that nutritional therapy improves clinical outcomes[25]. Some reviews, however, reported beneficial effects of oral supplements, enteral and parenteral nutrition[26-28] in reducing complications and mortality of cirrhotic patients.

One fact that may have influenced the previous study results is related to the diagnosis of malnutrition in cirrhotic patients as well as the surrogate outcome measures used to assess nutrition interventions. Due

Table 2 Subjective Global Assessment for patients on waiting list for transplantation[31] performance

Subjective Global Assessment
I. History
A. Weight
Height_____ Current weight_____
Pre-illness weight _____
Weight in past 6 months: High_____ Low_____
Overall change in past 6 months:_____
B. Appetite
Dietary intake change relative to normal
Appetite in past two weeks: ____good ____fair ____poor
Early satiety: _____none _____1-2 weeks _____ > 2 weeks
Taste changes: _____none _____1-2 weeks _____ > 2 weeks
C. Current intake per recall
Calories____ Protein_____
Calories needs _____ Protein needs_____
D. Persistent gastrointestinal symptoms
Nausea: _____none _____1-2 weeks _____ > 2 weeks
Vomiting: _____none _____1-2 weeks _____ > 2 weeks
Diarrhea (loose stools, > 3/day)
Number of stools per day_____/Consistency_____
_____none _____1 weeks _____ > 1 weeks
Constipation: _____none _____1-2 weeks _____ > 2 weeks
Difficulty chewing: _____none _____1-2 weeks _____ > 2 weeks
Difficulty swallowing: _____none _____1-2 weeks _____ > 2 weeks
E. Functional capacity
_____ No dysfunction ____Dysfunction
_____ weeks
_____ working suboptimally
_____ ambulatory
_____ bedridden
II. Physical exam
A. Status of subcutaneous fat (triceps, chest)
_____ good stores _____ fair stores _____poor stores
B. Muscle wasting (quadriceps, deltoids, shoulders)
_____none _____mild to moderate _____ severe
C. Edema and ascites
_____none _____ mild to moderate _____ severe
III. Existing conditions
A.Encephalopathy
_____ none _____ stage I-II _____stage III _____ stage IV
B.Chronic or recurrent infection
_____ none _____ 1 week _____> 1 week
C.Kidney function
_____good/_____decreased (no dialysis)/_____decreased (with dialysis)
D.Varices
_____none/_____ varices (no bleeds)/_____ varices (with bleeds)
IV. Subjective Global Assessment Rating (based on sections I, II, III)
A._____ Well nourished
B._____ Moderately malnourished (or suspected of being malnourished)
C._____ Severely malnourished

to the hepatic disease, some common nutritional parameters are generally altered, such as the weight - if the patient presents with fluid overload and, also albumin - since it can be lower because of impaired hepatic protein synthesis. Other anthropometric measurements, as triceps skinfold and mid-arm muscle circumference, which assess subcutaneous fat and muscle mass, can also be affected by fluid retention[29,30]. The adapted subjective global assessment, an essential clinical assessment tool has been suggested as probably the best reliable tool (Table 2)[31]. Also, functional instruments such as handgrip strength and the six minute walk test have been advocated as potential good parameters not only to asses but also to follow up nutritional interventions[1,2,32].

Therefore, despite the vast knowledge from research in the fields of metabolism, clinical nutrition and intervention, there is no generally accepted or standardized approach for the diagnosis and classification of malnutrition in these patients[33]. However, we suggest that because all cirrhotic patients are at high risk of malnutrition, it is strongly recommended that nutritional assessment be performed in every liver transplant candidate as an integral part of the evaluation protocol[1,6,32].

Recently, many researches have focused on sarcopenia, a condition defined as severe muscle wasting, and the related outcomes before and after liver transplantation have been reported[34-38]. The diagnosis can be done using dual energy X-ray absorptiometry, computed tomography and, bioelectrical impedance with sex-specific cutoffs for sarcopenia diagnosis[39,40]. Bioelectrical impedance testing is an easy, fast, a low cost tool that can be applied in nutritional transplant care to diagnose sarcopenia[41]. Prevalence of sarcopenia before transplantation is pointed in more than a half of cirrhotic patients[37,42]. It's absolutely important to stress that muscle wasting is a consequence od inadequate nutritional status - malnutrition -, thus, the relationship of sarcopenia and outcomes should be the same as that of malnutrition. After surgery, the prevalence of sarcopenia does not seem to decrease[43] although patients gain weight, sarcopenic obesity *co-exists*[44-48]. Greater food intake and physical inactivity are responsible for the positive energy balance, which is observed in up to 88% of patients after liver transplant[49]. This is a risk factor for metabolic syndrome, described in half of patients after liver transplant[50].

NUTRITIONAL RECOMMENDATIONS

Pre liver transplantation

Guidelines for nutritional therapy in cirrhosis have been proposed and updated in the last decades[33,51-53]. Recommendations to avoid malnutrition include a dietetic plan contemplating a caloric intake of 35-40 kcal/kg and a protein intake of 1.2-1.5 g/kg (Table 2). If patients present with water overload, the latter should be considered and discounted for dry weight estimation and nutritional requirement calculation. Obviously, this is absolutely a subjective decision and, that's why a probably better approach would be to estimate the ideal weight according to body height[54]. Indirectly calorimetry, if available, should be performed[30] as energy needs might be better estimated by this test, in liver transplant candidates[55].

A high protein intake may classically been known as a cause for encephalopathy. Nonetheless, there should be less fear in the prescription of higher amounts of protein, once modulation of nitrogen metabolism in not only due to the nutritional issue[56] and, on the other hand, protein restriction is no doubt one of the causes of malnutrition. For more than a decade, Cordoba *et al*[57] showed that diets containing 1.2 g/kg of protein can safely administered to patients with liver cirrhosis suffering from episodic encephalopathy. The authors also showed that protein restriction does not confer any benefit during an episode of encephalopathy. Besides, insufficient protein intake (< 0.8 g/kg) has been independently associated with malnutrition and mortality in a large cohort with 630 cirrhotic patients[22]. It is suggested that diets rich in vegetables and dairy protein may be beneficial and are therefore recommended, but tolerance varies considerably in relation to the nature of the diet[56].

Considering other nutritional aspects of encephalopathy, a meta-analysis of randomized controlled trials pointed out that oral branched chain amino-acid (BCAA - valine, isoleucine and leucine) supplements have beneficial effects on manifestations of hepatic encephalopathy compared with control supplements, by improving the grade of encephalopathy, but not for the resolution or worsening of this condition[58]. Some reviews have addressed that BCAA supplementation appears to be associated with decreased frequency of complications of cirrhosis and improved nutritional status when prescribed as maintenance therapy[59,60]. BCAA supplementation is suggested to allow recommended nitrogen intakes to be attained/maintained in patients who are intolerant of dietary protein[56]. However, these observations are not universal[61]. A recent prospective study showed that an oral BCAA supplement enriched with leucine reverted the impaired mTOR1 signaling and increased autophagy in skeletal muscle of patients with alcoholic cirrhosis, and could be a promise in the treatment of sarcopenia[62]. Cost and palatability may limit the potential applicability of this treatment modality.

Caloric intake should be guaranteed by 50%-70% of carbohydrates[30,51]. It must be acknowledged that patients with liver failure are at a high risk of hypoglycemia, due to the limitation in storage of glycogen and, liver neoglucogenesis[53]. Reach caloric intake both with carbohydrates and less fats (to avoid slower gastric emptying) is important to prevent the utilization of amino acids for glucose production, and consequent depletion of protein tissue and production of ammonia[63]. Patients should be advised to avoid fasting for longer than 3-6 h during daytime and, should be encouraged to take small, frequent meals distributed throughout the day[56]. A late-evening snack of 50 g of complex carbohydrates is suggested to reverse aberrant substrate utilization and improve nitrogen retention. This has been described to improve quality of life, survival and, reduce the frequency and severity of hepatic encephalopathy episodes[64]. Regarding the consumption of non-digestible carbohydrate (prebiotics), patients should be encouraged to ingest approximately 25-45 g a day[56]. These can either be supplemented as prebiotic formula, or those present in a rich fiber diet, whose fermentation seems to have a beneficial effect on neuropsychiatric performance. On the other hand, probiotic (beneficial bacteria) and symbiotic (prebiotic + probiotic) supplementation should be discouraged in the treatment of hepatic encephalopathy[65,66], but, they may be an option for the prevention[67] and treatment of minimal cases of this condition[65]. Future researches are needed in this population for a consistent recommendation[56].

Fat is important in order to reach caloric recommendations (not more than 30%)[30], thus dietary fat should not be restricted, unless true fat malabsorption has been diagnosed using a fecal fat test or slower gastric emptying is reported[7]. Medium chain triglycerides are an alternative form of fat not requiring bile salts for absorption and can be used both in oral, enteral or parenteral nutrition formulations[68,69]. Essential fatty acids and their derivates should be provided, as patients with end stage liver disease may have impaired synthesis of them[7]. Supplementation of n-3 fatty acids have been suggested as a strategy to delay disease progression in liver cirrhosis and, in post-transplant, it reduces injury of the transplanted liver as well as it has been reported to decrease the incidence of infectious morbidities[70,71].

Oral supplements can be useful to help meet nutritional recommendations and some studies have shown that cirrhotic patients receiving daily supplements plus adequate oral nutrition had better outcomes compared with controls[72-75]. However, one randomized, controlled trial demonstrated that regular dietary counseling is as effective in increasing energy intake as providing a nutritional supplement, since patients who receive a nutritional supplement might decrease the amount of food intake[76]. Nonetheless, this is definitely a matter of adequate counseling, which should encompass various strategies to guarantee compliance, such as different supplement preparations/options (the use of healthy gastronomy). Another strategic action should be the use of supplements in modest quantities (*e.g.,* 50 mL) every time the patient as to take any medication. This ensures increased nutrition intake with probably low impact on satiety, however, diet-drug interactions must be addressed.

In relation to micronutrients, chronic liver disease generally courses with nutrient deficiencies, thus dietary counseling and planning should consider Dietary Reference Intakes[30].Thiamine, folate and magnesium, specially, when there is alcohol abuse[75], and deficiency of fat-soluble vitamins in advanced

Table 3 Nutritional recommendations in pre and peri liver transplant

Nutrients/Diet	Recommendations	Observations
Pre-transplant		
Calories	35-40 kcal/kg	Avoid fasting for longer than 3-6 h during daytime; encouraged to take small, frequent meals distributed throughout the day
Protein	1.2-1.5 g/kg	It is suggested diets rich in vegetables and dairy protein
Carbohydrates	50%-70%	A late-evening snack of 50 g of complex carbohydrates is suggested to reverse aberrant substrate utilization and improve nitrogen retention
Fat	30%	It should not be restricted, unless true fat malabsorption has been diagnosed using a fecal fat test or slower gastric emptying is reported
Fiber	25-45 g/d	Prebiotics fermentation seems to have a beneficial effect on neuropsychiatric performance
Vitamin and minerais	Dietary Reference Intakes	Or pharmacological doses in case of deficiency
Peri-transplant		
Calories	25-30 kcal/kg	Use indirect calorimetry if it is available
Proteins	1.5-2.0 g/kg	In the immediate phase after the operation, protein catabolism is markedly increased
Food/enteral nutrition		Early normal food or enteral nutrition (12 h) after liver transplant is advisable as long as the patient is hemodynamically stable and has no nausea or vomiting

liver disease, especially in those with cholestatic liver disease[76] are very common. Also, vitamin D deficiency in cirrhotic liver patients is universal[77,78] not only due to the malabsorption but also as a consequence of inadequate dietary intake and decreased UV light exposure. There is also impairment in hepatic activation of this vitamin in cirrhosis[79,80]. This condition leads to calcium deficiency, and eventually osteomalacia or osteoporosis, contributing to fractures seen in 40% of patients with chronic liver disease[81]. Vitamin D (800-1000 IU) and calcium (1.000 mg) supplementation should be implemented in deficiency and in the case of corticosteroid use[82]. Calcium supplementation should be 1.200 to 1.500 mg for those patients with osteopenia and osteoporosis[29,30].

Cirrhotic patients usually have salt retention, which leads to hypernatraemia demanding treatment with diuretics. Depletion of potassium, magnesium, phosphate, zinc and other intracellular minerals are, then, usually observed. However, cirrhotic patients seem to have decreased serum zinc, magnesium and selenium levels with the progression of liver disease and, it is suggest that micronutrient supplementation could play a role in preventing progression of liver disease and its complications[83]. Nonetheless, no routine recommendation on the requirement of micronutrients can be made on the basis of controlled studies and, administration of micronutrients has no proven therapeutic effect apart from the prevention or correction of deficiency states[51]. Sodium restriction to 2 g/d is recommended for those patients with ascites/edema[30]. But patients should be encouraged to use alternative seasonings, as herbs and spices,in order to avoid reducing food intake due to unpalatable diets.

PER AND EARLY POST LIVER TRANSPLANTATION

Per and postoperative nutrition recommendations are similar to those for other postoperative situations. It is specially important to stress that preoperative fasting from midnight and interruption of nutritional intake after surgery is unnecessary and even contra-indicated in most patients[84]. Because in deceased donor transplantation, no one can predict when a patient will receive a transplant[20], aggressive early post-operative nutrition support (by enteral route if possible) should be allocated to those patients with highest MELD scores, especially when they are undernourished and, if it is anticipated that patients will be unable to eat within for more than two days. Also, this approach should be considered when patients cannot maintain oral intake above 60% of the recommended intake for more than 10 d[84]. For those undergoing transplantation from living donors, new opportunities for nutrition therapy, as the transplant operation may be scheduled, preoperative nutrition interventions should be considered for recipients and donors when applicable based on the previous addressed discussion[20].

After the liver transplant operation, energy and protein requirements are still increased for weeks. Metabolism in liver recipients only improves at 4 wk after LTx, especially considering the non-protein respiratory quotient, serum non esterified fatty acids and nitrogen balance[85]. In the immediate phase after the operation, protein catabolism is markedly increased and patients should receive about 1.5-2.0 g/kg of protein (Table 3). Non-protein energy requirements, in this period, vary according to the metabolic and inflammatory status, with unstable patients demanding lower intakes while the others more. When indirect calorimetry is not available, estimates between 25 to 30 kcal/kg per day maybe used[30,51]. Electrolyte abnormalities, thereby, serum potassium, phosphorus, and magnesium levels should be monitored, due to routine diuretic use, abdominal drains and fluid overload. Also, refeeding syndrome

should be taken as a risk factor for these disorders[30].

In summary, early normal food or enteral nutrition (12 h) after liver transplant is advisable as long as the patient is hemodynamically stable and has no nausea or vomiting[20,33,53]. A whole polymeric enteral formula is recommended and the use of immunonutrition (n-3 fatty acids, arginine, BCAA, nucleotides) in this period is still controversial[20,86].

After liver transplant, patients will have to take immunosuppressant medication to the end of their lives. Although modern drugs with less side effects are available, increased survival rates and decreased overall complications have led to many nutrition status implications associated with the use of cyclosporine, tacrolimus and corticosteroids. New onset diabetes or glucose impairment is common initially after the operation as the consequence of immunosuppressant regiment[87,88]. Diabetic dietary advice is usual required, and if necessary, the use of oral hypoglycemic or insulin regimens should be tethered according to the progression of diet. If hyperglycemia persists, it should be managed by reducing glucoseintake, since higher insulin might hamper increasedglucose oxidation in this period. Also, the diabetogenic potential of the immunosuppressant tacrolimus may be lowered by reducing its dose, without undue risk of rejection[51].

Many patients may concomitantly present with high potassium levels shortly after the operation. This usually results from the nephrotoxicity of the prescribed immunosuppressant medication. Thus, in the early post-transplant periods, it might be important to control potassium food sources as well as, it the recommendation of the use of dietary techniques which are able to reduce its content in nutrients[89]. In the long term, this is not indicated, as this condition mostly disappears. Hypomagnesemia also rises as a consequence of immunosuppression and, patients generally receive magnesium supplementation, however, some progress with diarrhea. The intake of magnesium rich food sources should be encouraged, such as dark cocoa, whole grains, nuts, legumes, fruits and green vegetables. Important to point that the consumption of this kind of food should not be restricted, even considering the immunocompromised host as a result of anti-graft rejection drugs. Patients should receive food safety advice to prevent food borne infections, which can be achieved with the correct handling of fruits and vegetables[90].

In the long-term after liver transplantation, weight gain is mostly observed. It is important to recover the nutritional status, since the patients lose an average of 9.1 kg during the course of liver disease[45]. Greatest relative weight gain occurs in the first six months after the operation[47] and, recovery of all weight loss happens in the first post-transplant year[45]. However, unfortunately, patients do not stop gaining weight in the subsequent years[44], resulting in the alarming prevalence of overweight and obesity[3]. During the first 12 mo, the fat mass progressively increases in those patients who had previously depleted overall body mass, but muscle mass recovery is subtle and non-significant by the end of the first year[91]. So, despite the weight gain, the high prevalence of sarcopenia does not change after transplantation and, new cases of this statusare incident leading to increased risk of morbidity and mortality[36].

LONG-TERM POST LIVER TRANSPLANTATION

Several metabolic complications related to weight gain and the immunosuppression are developed in long-term post-transplant. The risk of arterial hypertension, dyslipidemia and diabetes mellitus incidence increase after surgery and, impact outcomes as well as survival[92]. This set of metabolic disorders yield an increased risk of metabolic syndrome, described in approximately half of liver transplant recipients[2,50].

Every effort should be encouraged to avoid excessive weight gain and its consequences in the long-term after liver transplantation. There is, once again, the need for interdisciplinary, early, and close weight monitoring of all the patients, who certainly could benefit from counseling regarding weight gain and its consequences after surgery[44]. Beyond nutritional intervention, exercise counselingis essential to improve body composition (essentially sarcopenia),overall muscle function and metabolic parameters[32,91]. Specific nutritional and exercise guidelines are available and should be followed[93-98].

CONCLUSION

In summary, patients with terminal liver disease suffer from nutritional and metabolic disorders that are mostly associated to the disease *per se*, impacting morbidity, mortality and quality of life throughout their life spam either while on the waiting list for liver transplantation and thereafter. These derangements maybe prevented or decreased if adequate interdisciplinary approach is adopted, by providing adequate nutritional counseling and intervention, when necessary. These attitudes positively impact on overall outcomes in the perioperative period and in the long run after transplantation, avoiding future associated morbidity and mortality, such as metabolic syndrome.

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