Nutritional optimization in liver transplant patients: from the pre-transplant setting to post-transplant outcome

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Abstract

Background and study aims: **malnutrition and its clinical phenotypes, sarcopenia, and frailty, are prevalent conditions that affect patients with cirrhosis awaiting liver transplantation. The link between malnutrition, sarcopenia, and frailty and a higher risk of complications or death (before and after liver transplantation) is well established. Accordingly, the optimization of nutritional status could optimize both access to liver transplantation and the outcome following the surgery. Whether optimization of nutritional status in patients awaiting LT is associated with improved outcomes after transplant is the focus of this review. This includes the use of specialized regimens such as immune-enhancing or branched-chain amino-acids-enhanced diets.**

Results and conclusion: **we discuss here the results of the few available studies in the field and provide an expert opinion of the obstacles that have led, so far, to an absence of benefit of such specialized regimens as compared to standard nutritional support. In the next future, combining nutritional optimization with exercise and enhanced recovery after surgery (ERAS) protocols could help optimize outcomes following liver transplantation.** (Acta gastroenterol. belg., **2023,** 86, **335-342**).

Keywords: preoperative optimisation, nutritional status, liver transplantation, malnutrition, sarcopenia, frailty.

Background

Malnutrition is a common complication of end-stage liver disease and a well-recognized predictor of pre-liver transplant (LT) morbidity and mortality (1,2). It is associated with an increased risk of complications, including hepatic encephalopathy in the pre-LT setting, and adversely affects the quality of life (3). Recent practice guidance by the American Association for the Study of Liver Diseases (AASLD) has clarified the theoretical and operational definitions of malnutrition, frailty, and sarcopenia as they have been often misinterpreted so far (4).

Operational definitions of malnutrition, frailty, and sarcopenia have helped to translate these gerontologic constructs into the field of liver diseases. Malnutrition is now further specified as "an imbalance (deficiency or excess) of nutrients that causes measurable adverse effects on tissue/body form (body shape, size, composition) or function and/or clinical outcome" (4). Frailty is now defined as "the phenotypic representation of impaired muscle contractile function" and sarcopenia by "the "phenotypical representation of loss of muscle mass" (4). Accordingly, frailty and sarcopenia are two distinct clinical phenotypes of malnutrition. In patients with cirrhosis, the pathophysiology of sarcopenia is complex and involves many different co-existing factors such as liver dysfunction-related endocrine disorders, portal hypertension, endotoxemia, systemic inflammation, hyperammonemia, and elevated myostatin levels. A review has recently summarized the available evidence in the field (5).

In patients awaiting for LT, the prevalence rate of malnutrition spans between 40% to 90% (6), while frailty prevalence ranges from 17% to 43% (7). Importantly, it is well established now that sarcopenia is sex-specific and affects more males than females with a prevalence ranging from 33% in females to 54% in males (3,8).

Whether optimization of nutritional status in patients awaiting LT is associated with improved outcomes after transplant is the focus of this review.

Assessment of malnutrition, sarcopenia and frailty in the pre-LT setting

Subjective Global Assessment (SGA) and Royal Free Hospital -Global Assessment (RFH-GA) are used to evaluate malnutrition. The technique of SGA (9-11) uses clinical information collected during history-taking and physical examination to determine nutritional status without recourse to objective measurements. It includes weight change, dietary intake change, gastrointestinal symptoms, functional capacity, disease and its relation to nutritional requirements and physical features including loss of subcutaneous fat, muscle wasting, oedema, and ascites providing a SGA rating (well nourished, moderately malnourished, and severely malnourished) (11).

RFH-GA incorporates a mixture of subjective and objective, anthropometric variables including Body Mass Index (BMI) and Mid-arm muscle circumference (MAMC). RFH-GA provides a validated assessment of nutritional status and is accepted as the gold standard for nutritional assessment of liver disease patients in the UK (3). Of note, RFH-GA has the disadvantage of being time-consuming. The Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT), which includes only easy-

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to-answer clinical questions, has been validated as a reliable tool to screen for malnutrition in the cirrhotic population. Importantly, it can also be used in patients with fluid retention without using the BMI. RFH-NPT discriminates patients into low, medium or high-risk patients by taking into account the patients' nutritional history (unplanned weight loss, dietary intake, body mass index) and their current complications of liver disease (12).

Sarcopenia assessment has been validated with Bioelectrical impedance analysis (BIA), MAMC, Dual-Energy X-ray Absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI). BIA is a noninvasive and inexpensive test that evaluates the body's electrical conductivity and resistance (impedance) and has been used to determine lean body mass and fat in patients with end-stage liver disease. It is based on the principle that conduction through fat tissue tends to be decreased due to increased impedance, in contrast with more rapid conduction through the water. For this reason measurement of body cell mass in patients with edema may be inaccurate (13). DEXA has been used to measure total body bone mineral, fat, and fat-free mass, although its accuracy may also be influenced by fluid retention (14). In patients with cirrhosis, DEXA can assess both fat mass and fat-free mass, without providing accurate information about the quality of the fat-free mass, particularly its water content (15). CT is the gold standard for sarcopenia assessment in patients waiting for LT as a wide majority of patients undergo this procedure during the pre-LT work-up (16). Among others, lumbar 3 skeletal muscle index (L3-SMI) seems to be one of the most reliable methods to assess sarcopenia by CT with a threshold of 39 cm^2/m^2 in cirrhotic females and 50 cm^2/m^2 in cirrhotic males (1). Besides, CT allows assessing body composition including fat deposition within the muscle (myosteatosis) as well as fat surface areas and radiodensity. These latter have been increasingly associated with clinical events in the liver field (17). Sarcopenia can also be assessed by ultrasonography (especially on lower limb muscle mass) (18). It is a promising tool for patients who cannot be transported to a CT (e.g., patients in the intensive care unit) but it still needs further evaluation in patients with liver diseases.

Frailty assessment is usually done with Liver Frailty Index (LFI) (19) (which includes grip strength, timed chair stands, and balance testing) and Fried Frailty Score (20). The latter is a single 5-point score based on a combination of subjective reports (exhaustion, unintentional weight loss, and low physical activity) and objective measurements (walk speed and hand grip).

Impact of malnutrition and its clinical phenotypes on patients on the waiting list

The natural history of liver cirrhosis is characterized by ongoing, chronic effects of hepatic synthetic dysfunction, ascites, and hepatic encephalopathy with intermittent, acute catastrophic events such as acute variceal hemorrhage or spontaneous bacterial peritonitis. These factors impair the patient's physiologic reserve, ultimately manifesting in malnutrition and its clinical phenotype of frailty and sarcopenia commonly reported in patients with cirrhosis awaiting liver transplantation (21).

As shown in a large cohort of liver transplant waitlisted patients, the patients usually have a very low protein intake that is independently associated with mortality (22). As high as 76% of patients have been reported to have a protein intake below the 1.2 g/kg/d intake recommended for patients with cirrhosis. Malnutrition has been also shown to be one of the main predictors of mortality in patients with low MELD-Na scores especially in waitlisted patients (a population usually poorly underserved by the MELD scoring systems) (23).

Sarcopenia is associated with worse outcomes (including death, infections, hepatic encephalopathy, hepatorenal syndrome, and development of acute-on-chronic liver failure [ACLF]) as well as increased health-related costs in patients on the waiting list. An extensive literature was produced on this topic within the last 10 years (1,4,8,24-31) (Table 1). For instance, the MELD-psoas score, combining MELD and transversal psoas muscle thickness (TPMT) TPMT/height (mm/m) showed superior mortality discrimination to MELD score and similar to that of the MELD-Na score (25). Some differences in outcome prediction might be seen according to etiology. In patients with non-alcoholic fatty liver disease (NAFLD) sarcopenia was not associated with mortality but frailty was correlated with length of stay and risk of delisting, conversely in alcohol-related liver disease (ALD) sarcopenia was associated with transplant list de-listing (32).

Frailty and its dynamic are also associated with mortality in patients on WL. Lai et al categorized the dynamic changes of LFI as improved, stable, moderate worsening, and severe worsening (21). Patients with severe worsening of frailty had worse baseline LFI and were more likely to have non-alcoholic fatty liver disease, diabetes, or dialysis dependence. The cumulative incidence of death/delisting increased by worsening ΔLFI group (21). The Multicenter Functional Assessment in Liver Transplantation (FrAILT) Study on 1166 LT recipients showed that pre-LT frailty was associated with an unadjusted 62% increased risk of post-LT mortality. Frail LT (LFI >4.5) recipients had a higher risk of post-LT death and greater post-LT healthcare utilization (33). Survival rates were lower for frail versus non-frail recipients: 94% versus 97% at 1 year, 89% versus 92% at 3 years, and 84% versus 90% at 5 years. (33).

Impact of malnutrition and its clinical phenotypes on post-LT outcome

Patients with a body cell mass (BCM) < 35% of body weight tended to have reduced survival after LT

Table 1. — **Studies (non-exhaustive list) evaluating the impact of sarcopenia on outcomes before and after liver transplantation. ACLF, acute-on-chronic liver failure; ALD, alcohol-related liver disease; ASM, appendicular skeletal muscle mass; BCM; body cell mass; CT, computed tomography; LOS, length of stay; MRI, magnetic resonance imaging; NASH, non-alcoholic steatohepatitis; PMA, psoas muscle area; PSMI, psoas skeletal muscle index; SMI, skeletal muscle index; SMM, skeletal muscle mass; SMMI, SMM index; TPMT, transverse psoas muscle thickness; WL, waiting list.**

Authors, year	N	Design	Technique	Parameters	Findings
Studies evaluating outcome on the waiting list					
Montano-Loza, 2012	112	Prospective	CT	SMI	↑ WL mortality independently MELD
Tandon, 2012	142	Retrospective	CT/MRI	SMI	↑ WL mortality; poorly predicted by BMI and SGA
Durand, 2014	562	Retrospective	CT	TPMT/Height	↑ WL mortality independent MELD
Carey, 2017	396	Retrospective	CT	SMI	↑ WL mortality
Van Vugt, 2018	585	Prospective	CT	SMI	↑ WL mortality particularly in patients with lower MELD
Engelmann, 2018	795	Retrospective	CT	SMI, PSMI	Associated with HE, infections, HRS, death.
Van Vugt, 2018	224	Retrospective	CT	SMI	↑ health-related costs for patients on WL
Sinclair, 2019	420	Retrospective	DEXA	ASM, SMMI	Upper limb lean mass associated with WL mortality
Banjhi, 2019	265	Retrospective	CT	SMI	↓prevalence of sarcopenia in NASH vs. ALD. Sarcopenia associated ↑ WL mortality an delisting ALD
Mauro, 2020	180	Retrospective	CT/MRI	SMI	Independent predictor of ACLF and WL mortality
Studies evaluating outcome after liver transplantation					
Englesbe,2010	163	Retrospective	CT	PMA	↑mortality
DiMartini, 2013	338	Retrospective	CT	SMI	↑mortality and length of stay in ♂ but not in ♀
Krell, 2013	207	Retrospective	CT	PMA	↑ infectious events and mortality
Kaido, 2013	124	Retrospective	BIA	SMM, BCM	↑ mortality
Hamaguchi, 2014	200	Retrospective	CT	PMI	↑ mortality
Montano-Loza, 2014	248	Retrospective	CT	SMI	↑ infectious events and LOS but not mortality
Underwood, 2015	348	Retrospective	CT	PMA	↑ complications and mortality
Harimoto, 2017	102	Prospective	CT	SMI	↑ complications, LOS and 6-month mortality
Golse, 2017	256	Retrospective	CT	PMA	↑ 1 and 5-year mortality
Kalafatelli, 2017	232	Retrospective	CT	PMI	↑ complications, LOS and 12-month mortality
Bhanji, 2019	293	Retrospective	CT	SMI	↑ LOS
Kuo, 2019	126	Retrospective	CT	SMI	↑ mortality in acutely ill patients (MELD Na ≥ >32)
Artru, 2021	314	Retrospective	CT	TPMT/height, PMI	↑ mortality in ACLF patients

independently of the presence of ascites and clinical edema (34). In a study by, Kalafateli et al., severe malnutrition and MELD were independent predictors of post-LT infections as well as prolonged mechanical ventilation and ICU stay post-LT (3). Similar results were found for sarcopenia, assessed by total psoas muscle area measured in transverse CT sections at the third lumbar level (3). Moreover, patients with muscle depletion or malnutrition who received a steatotic liver graft with prolonged CIT (>12 h) had a significantly longer ICU and hospital stay and a higher rate of infections despite similar MELD scores, implying the need for allocation of more optimal grafts in malnourished patients with sarcopenia (3). Sarcopenia and malnutrition are not reflected in the MELD score, as they showed a wide overlap of values across different MELD scores. Similar results were presented by Merli et al. where the pretransplant nutritional status was independently associated with complication occurrence following LT and especially the number of infection episodes (35). The presence of malnutrition was the only independent risk factor for the length of stay in the ICU and the total number of days spent in hospital (35).

Sarcopenia negatively impacts survival after deceased-donor (3, 30, 36-38) as well as living donor LT (LDLT) (39-41) (Table 1). It strongly correlates with mortality after LT and its assessment can help clinical decision-making and, potentially, allocation policy (42). Moreover, sarcopenia predicts an increased risk of serious post-transplant infections (43) and length of stay (44). Similarly, in critically ill cirrhotic patients and ACLF, undergoing urgent inpatient evaluation and liver transplantation, sarcopenia (either assessed by L3-SMI, psoas muscle index, or TPMT/height) predicts post-transplant mortality and should be evaluated in this specific population (45). Importantly, there is increasing evidence that other parameters of body composition such as sarcopenic visceral obesity or myosteatosis are associated with post-LT early mortality and should be therefore evaluated at the same time as sarcopenia (41, 46-54)

Finally, frail patients have independently lower post-LT survival as compared to non-frail patients (33). Interestingly, the impact on post-LT seems to be delayed as compared to sarcopenia suggesting underlining their distinct phenotypes.

Results of nutritional interventional studies on pre- and post-LT outcome

Considering the evidence in the field detailed above, nutritional intervention before and in the perioperative to optimize malnutrition, sarcopenia, and/or frailty could optimize access to LT and improve the outcome following LT. Nutritional supplements are preparations intended to supplement the diet and provide nutrients, such as vitamins, minerals, fibres, fatty acids, or amino acids, that may be missing or may not be consumed in sufficient quantities (55).

Vitamin supplementation and in particular vitamin D role in liver transplant has been evaluated as its deficiency is highly prevalent in the cirrhotic setting and may adversely affect clinical outcome (16). While there was no survival difference based on the pre-transplant vitamin D level, vitamin D deficiency post-transplantation was associated with worse survival and the post-transplant supplementation of vitamin D was associated with a lower risk of acute cellular rejection (ACR) (56). In an Italian cohort of 67 liver transplant patients, incomplete graft recovery and infections were associated with lower vitamin D levels (57).

Oral nutritional supplements (ONS) aim to decrease skeletal muscle proteolysis and provide adequate energy substrate. Several strategies have been used.

Specially designed products (HepaticAid®), standard casein products (Ensure®), as well as usual diet plus standard ONS, have been evaluated in adult patients on a waiting list for liver transplantation (55,58). ONS accompanied by nutritional advice showed to increase MAMC and grip test with a trend to improve WL survival but no impact on post-LT mortality, length of stay, or rejection (58). Postoperative feeding via nasojejunal tubes has been compared to the postoperative conventional intravenous electrolyte solution. Enteral feeding has been associated with decreased postoperative infection rates and fewer metabolic complications after transplant when compared to total parenteral nutrition (59). Of note, patients who were given Ensure® experienced significantly more acute rejections per number of patients and more new onset of diabetes (55).

There is also some evidence that nutritional supplementation with immunonutritional (IMN) formulas containing arginine, omega-3 fatty acids, or nucleotide in the preoperative period and as enteral feed early after transplant surgery may influence the outcome of liver transplantation (46). In a preliminary work, it was well tolerated and over the 6-month period following transplantation full recovery of body protein stores to the level immediately preceding the operation was evident. Post-transplant changes in respiratory muscle strength for the patients on enriched feed compared with those on standard feeds reflected the total body protein changes with better outcomes in terms of infectious complications (60). Benefits include also reducing postoperative infectious complications and length of hospital stay (61), postulating that IMN supplements can improve cell immunity and humoral immunity and might be helpful for the rehabilitation of patients undergoing liver transplantation at the perioperative stage. However, in the randomized controlled trial based on the preliminary results, 120 patients wait-listed for LT were randomized to either supplemental oral IMN or an isocaloric control. In this study, IMN did not provide significant benefits in terms of preoperative nutritional status or postoperative outcome (62). The rationale for high protein supplements is the reduction in catabolism and the decrease of fat accumulation in muscle. Diets with a normal content of protein, which are metabolically more adequate, can be administered safely to cirrhotic patients with episodic hepatic encephalopathy. Restriction of the content of protein in the diet does not appear to have any beneficial effect for cirrhotic patients during an episode of encephalopathy (63). A nutritional protocol with a higher rate of enteral nutrition and high-protein ONS resulted in a higher protein intake early after LT. However, there was no difference in severe postoperative outcomes compared to standard enteral nutrition (64). Long-term oral BCAA supplements have been beneficial in patients with advanced cirrhosis in order to improve event-free survival or quality of life (65). In patients with cirrhosis and sarcopenia BCAA supplementation determined a significant improvement in muscle mass and significant improvement in the Liver Frailty Index (66). While BCAA supplementation might be associated with increased survival on WL in sarcopenic patients (67), the scarce data on outcomes following LT have suggested an absence of benefit as compared to standard nutrition (68). Supplementation with BCAA-enriched nutrients might improve persistent nutritional and metabolic disorders associated with end-stage liver disease in the early post-transplant period, and consequently shorten the post-transplant catabolic phase after LDLT (69). So far, while β-hydroxy-β-methylbutyrate (HMB), could participate in the improvement of frailty, its supplementation has not been evaluated in the field of LT (70). Overall, considering the grade of evidence in the field, a recent expert panel has provided only weak recommendations supporting pre-transplant nutritional supplementation (71).

Important matters regarding optimization of nutritional status in liver transplant patients

Three points must be underlined here:

– In the absence of strong evidence showing an improvement of post-LT outcome due to the optimization of nutritional status, it is critical to recall that physicians still should apply recommendations dedicated to every patient with cirrhosis. Among them, reducing fasting periods is critical, minimizing the time of starvation that results in proteolysis and muscle loss. Late evening snacks have been shown to reverse anabolic resistance and sarcopenia of cirrhosis

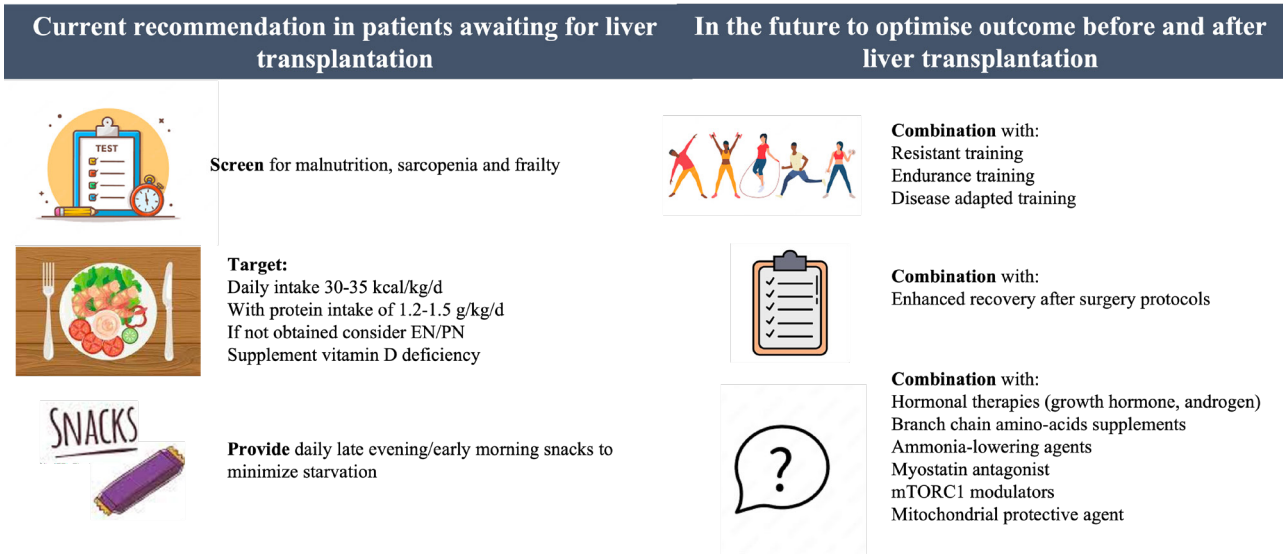

Figure 1. — Illustration of the current guidelines and the future direction to target malnutrition, sarcopenia and frailty to optimise access to liver transplantation and outcome after the procedure.

with improved quality of life in patients with cirrhosis (72). Provision of a nighttime feed to patients with cirrhosis results in body protein accretion equivalent to about 2 kg of lean tissue sustained over 12 months. This improved nutritional status may have important implications for the clinical course of these patients (73).

– Portal hypertension is one of the main drivers of malnutrition in patients with advanced liver disease. This is highlighted by the fact that reversing portal hypertension after transjugular intrahepatic portosystemic shunt (TIPS) is nowadays one of the most effective interventions to improve sarcopenia (74-76). Importantly, proof of concept results have been provided in a small prospective sample size study evaluating the impact of continuous terlipressin infusion in patients with hepatorenal syndrome or refractory ascites awaiting LT. Continuous terlipressin infusion was associated with an increase in energy and protein intake and to an improvement in nutritional and muscle parameters (77).
– Finally, so far, studies in the LT setting tested the effect of nutritional intervention alone while combining both nutritional intervention and physical exercise are more promising approaches (63,78). Enhanced recovery after surgery (ERAS) protocols are the illustration of multipronged approaches and have been associated with improved short-term complications after LT (79). These protocols especially include pre-operative carbohydrate loading and post-transplant enteral nutrition protocol.

Current guidelines and future direction

The most recent guidelines on this topic are by the European Society for Clinical Nutrition and Metabolism (ESPEN) (65) and the European Association for the Study of Liver (EASL) (16) and a recent position paper by the Enhanced Recovery after Liver Transplantation (ERAS4OLT.org) Working Group (71).

There is a global agreement to screen for malnutrition and sarcopenia in all cirrhotic patients listed for transplantation or scheduled for elective surgery. Sarcopenia can be treated prior to elective surgery, as this will enable improvement in body protein status and clinical outcomes. Preoperatively, a total energy intake of 30-35 kcal/kg/d (126-147 kJ/kg/d) and a protein intake of 1.2-1.5 g/kg/d should be aimed for. Standard nutrition regimens are recommended for preoperative nutrition since specialized regimens (including BCAA-enriched, immune-enhancing diets) were not superior to standard regimens regarding morbidity or mortality (16, 65) (Figure 1).

As discussed above, nutritional regimens and protein supplementation together with exercise should be evaluated in combination in this setting. Emerging therapies in the field are mostly represented by myostatin antagonists, direct mTORC1 modulation, and mitochondrial protective agents and should be primarily confirmed as efficient and safe in patients with cirrhosis before any translation into the pre-LT setting (78) (Figure 1).

Conclusion

Malnutrition, sarcopenia, and frailty are associated with an increased risk of complication and death on the waiting list and after liver transplantation and must therefore be assessed. There is an emergent evidence reporting that other parameter of body composition are associated with outcomes on the waiting list and after liver transplantation.

The nutritional intervention aims to maintain or improve nutritional status to optimize access to liver

transplantation and improve outcomes following liver transplantation.

Standard nutrition regimens are currently recommended since specialized regimens have not been shown to improve morbidity and mortality in this setting.

Multipronged and tailored approaches might help in obtaining significant results in the pre- and post-liver transplant setting.

Conflict of interest: None.

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