



# Malnutrition, frailty, sarcopenia, obesity—optimizing nutrition care in liver transplantation

Lori Fortier

Vancouver General Hospital, Vancouver Coastal Health, Solid Organ Transplant Clinic, Gordon and Leslie Diamond Health Care Centre, Vancouver, Canada

*Correspondence to:* Lori Fortier, RD, BHEc. Liver Transplant Dietitian, Vancouver General Hospital, Vancouver Coastal Health, Solid Organ Transplant Clinic, Gordon and Leslie Diamond Health Care Centre, 2775 Laurel Street-5th Floor, Vancouver, B.C. V5Z 1M9, Canada. Email: Lori.fortier@vch.ca.

**Abstract:** Protein calorie malnutrition is widely present in individuals with end-stage liver disease undergoing liver transplant. Nutritional depletion of lean body mass (sarcopenia) and fat reserve may increase surgical risk, morbidity, mortality, and health care costs. Patients may present with sarcopenic obesity or obesity prior to transplant which carries into the post-transplant setting. Obesity is associated with many comorbid conditions including metabolic syndrome affecting long-term mortality. Identifying malnourished patients and optimizing protein and energy intake throughout the transplant process is discussed. Strategies to preserve and improve lean body tissue and mitigate excessive weight gain are presented.

**Keywords:** Malnutrition; frailty; sarcopenia; obesity; liver transplant (LT); nutrition therapy

Received: 12 December 2017; Accepted: 25 January 2018; Published: 06 February 2018.

doi: 10.21037/amj.2018.01.15

**View this article at:** <http://dx.doi.org/10.21037/amj.2018.01.15>

## Introduction

Chronic illness accounts for 75% of health care costs (1). In the United States alone 750,000 adults have cirrhosis (1). The time frame from diagnosis to death averages 10 years and approximately 20% of patients with cirrhosis will be hospitalized within 1 year (2). Rates of readmission to hospital increase in decompensated cirrhosis due to ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy (HE) and compromised renal function (3). Frequent readmissions are not only costly to the healthcare system (approximately \$20,000 per admission) but also to patients as they are often deconditioned from their hospital stay (3).

Complications related to disease progression may result in changes in treatment modalities. Patients have multiple physicians involved in their care and subsequently may receive conflicting advice (3). Of concern, is patients are coming for liver transplant (LT) assessment following low-protein diets on advice from their family physicians and medical specialists. The intent of this review is to address

protein and energy requirements throughout the transplant process and offer strategies to preserve lean tissue and mitigate excessive weight gain.

## Nutritional status pre-LT

Malnutrition is prevalent among patients with end-stage liver disease (ESLD) and has been reported in 20–100% of all patients (4-7). The cause of malnutrition is multifactorial. Inadequate dietary intake may occur from nausea, vomiting, early satiety, delayed gastric emptying, ascites, HE and frequent hospitalizations (8,9). Impaired digestion and absorption from bile salt deficiency, altered motility, and bacterial overgrowth may cause nutrient loss (10,11). Altered metabolism may occur from accelerated starvation (protein and lipids are used as an energy source as carbohydrate stores are diminished), insulin resistance and reduced synthesis of hepatic proteins (8,12). Patients with malnutrition have longer hospital stays, increased incidence of ascites and hepatorenal syndrome, as well as increased mortality (13,14).

## Body mass index (BMI)

BMI is calculated by using the following formula  $W/H^2$  where  $W$  represents weight in kilograms and  $H$  represents height in meters. From the Global BMI Mortality Collaboration Study of over 10 million participants, all-cause mortality in the BMI range of 20 to below 25  $\text{kg}/\text{m}^2$  was minimal however, mortality increased significantly for BMIs below 20  $\text{kg}/\text{m}^2$  and for BMIs of 25 or greater (15). BMI is considered a simple tool to detect malnutrition in patients with cirrhosis (16). Dick and colleagues reviewed the United Network for Organ Sharing (UNOS) database (1987–2007) and found that patients at the extremes of the BMI range, underweight ( $<18.5 \text{ kg}/\text{m}^2$ ) and severely obese ( $>40 \text{ kg}/\text{m}^2$ ), had significantly lower survival. The underweight patients had more hemorrhagic complications and the severely obese had more infections and cerebral vascular accidents (17). A low BMI ( $<18.5 \text{ kg}/\text{m}^2$ ) was associated with increased mortality in the surgical intensive care unit mainly due to more pulmonary complications (18). The impact of BMI in the context of the model for ESLD (MELD) was investigated using the UNOS database from 2002 to 2011. Overweight or obese recipients did not have an increased risk for graft loss or death regardless of MELD but underweight patients were at increased risk for poor outcomes. Interestingly, the underweight recipients with low MELD scores had an increased risk for both graft loss and death (19).

From the starvation/famine literature, fat rather than lean tissue is used as an energy source. Females have a greater amount of adipose tissue which may be one reason why women withstand starvation to a lower BMI level than men. A BMI level of 13 in males and 11 in females may be the lowest limit for survival (20). In the hunger strikers, a weight loss of 40–50% of body weight with a BMI of 10  $\text{kg}/\text{m}^2$  was not compatible with life (21). Patients undergoing assessment for LT with low BMIs warrant a detailed review of comorbid conditions and functional status (19). Is the patient able to improve nutritional status through optimal nutrition therapy and exercise? If not, what is the lowest BMI acceptable for LT? As BMI does not differentiate between fat and lean body tissue, is there a critical amount of lean tissue necessary to withstand the surgery and post-transplant complications?

## Sarcopenia

Muscle mass is an objective tool utilized to predict LT

outcomes (22). Healthy adults lose 1% of muscle mass every year after the age of 30 (22). Sarcopenia (age related muscle loss) may be defined as 2 or more standard deviations below the mean muscle of healthy young adults (23,24). The prevalence of sarcopenia in adults older than 60 years ranges from 7–50% (22–24) and greater than 50% in those over 80 years (23). The overall presence of sarcopenia was 40% in patients being evaluated for LT and the mortality risk was 2-fold higher in the patients with sarcopenia (25,26). Sarcopenia in cirrhosis presents earlier in men than women and it appears men are more susceptible to sarcopenia than women (50% *vs.* 18%) (25,26).

Sarcopenia can be defined by total abdominal muscle mass on computed tomography (CT) at the level of the third lumbar vertebrae (L3) (25). With appropriate software (SliceOmatic V4.3, Tomovision, Montreal, Quebec, Canada), muscle and adipose tissue can be quantified and normalized for stature. The L3 skeletal muscle index (SMI) was expressed as muscle area ( $\text{cm}^2$ )/height ( $\text{m}^2$ ). The cutoffs for sarcopenia were L3 SMI of 38.5  $\text{cm}^2/\text{m}^2$  or less for women and 52.4  $\text{cm}^2/\text{m}^2$  or less for men (25). LT candidates with sarcopenia have a higher wait list mortality and patients are more likely to die of sepsis (25,26). In patients with sarcopenia measured by the total psoas area (TPA) on CT scan at L4, increased morbidity and mortality was found post LT (27) as well as an increased risk of infection (28). Sarcopenia may also occur in obese individuals and is a better predictor of abnormalities in physical function (gait, balance, and falls) than in either sarcopenia or obesity alone (29). In the New Mexico Elder Health Survey, two or greater self-reported physical disabilities odds ratio in men for sarcopenic obesity was 8.72 compared to 3.78 for sarcopenia alone or 1.34 for only obesity (29).

Cirrhotic patients require routine imaging for surveillance of hepatocellular cancer (HCC) therefore, with appropriate software, an objective level of muscle mass can then be determined without additional exposure (22).

## Frailty

Sinclair and colleagues investigated the impact of frailty on number of hospital days in patients waitlisted for LT (30). The Fried Frailty Index was used which consists of handgrip strength (HGS), unintentional weight loss, exhaustion, gait speed, and physical activity (31). The results demonstrated that physical frailty is associated with an increased number of days in hospital independent of disease severity as determined by the MELD score (30). Functional decline

in LT candidates is associated with increased risk of death and delisting (32,33). Functional tests such as HGS and gait speed, can be done quickly, are economical and practical in a clinical setting and do not require imaging (34). Canadian reference values for grip strength for ages 6–79 are available from Statistics Canada (35).

As both low muscle mass and low muscle function predict morbidity and mortality, the European Working Group on Sarcopenia in Older People recommend the definition of sarcopenia to include both low muscle mass and muscle function (34). In 2011 the Society of Sarcopenia, Cachexia and Wasting Disorders added walking speed less than 1 meter/second or distance walked during the 6-minute walk test (less than 400 meters) to a definition of sarcopenia with limited mobility (36).

## Obesity

Obesity is becoming one of the most serious health problems globally (37). Canadian 2015 statistics reported that 28.1% of Canadians are obese (BMI >30 kg/m<sup>2</sup>) (38). Obesity is associated with diabetes, hypertension, hyperlipidemia, coronary artery disease, compromised pulmonary function, liver disease [mainly non-alcoholic steatohepatitis (NASH)], and recurrent disease post LT (NASH, HCC) (37,39-41). Obesity is associated with surgical complications (infection, wound dehiscence) (42) and long-term mortality (37).

Weight loss is recommended for all obese patients waiting for LT, especially those with a BMI above 35 kg/m<sup>2</sup> to a weight target below 30 kg/m<sup>2</sup> (37). A BMI of greater than 30 kg/m<sup>2</sup> before transplantation is a strong predictor of BMI above 30 kg/m<sup>2</sup> at 3 years after LT (43).

Malnutrition, sarcopenia, frailty, and obesity all affect pre- and post-transplant morbidity and mortality. This underscores the pivotal role of nutrition assessment and intervention in LT patients.

## Nutritional assessment

Nutrition assessment is critical in identifying malnourished patients. An accurate height and weight should be obtained. An estimated dry weight can be determined by subtracting the volume of ascites reported on imaging (3–5 kg for small ascites, 7–9 kg for moderate, 14–15 kg for large) from the actual weight (44). Previous paracentesis and amount removed is helpful but generally not all ascites is removed. Of note, ascites itself can increase the relative risk

for post-LT mortality. In a study of over 1,300 patients, ascites volume increased relative risk for mortality by 7% [hazard ratio (HR), 1.07] for each liter of ascites removed at transplant and graft failure by 6% (HR, 1.06) (45). Edema must be estimated and deducted from the weight (1 kg for mild edema, 5 kg for moderate, 10 kg for severe) (43). An estimation of dry weight is subjective but it is better than gross overestimation, especially in assessing energy and protein requirements and in refeeding the malnourished patient. BMI can then be determined using the estimated dry weight.

The Subjective Global Assessment (SGA) method developed by Detsky and colleagues in Toronto, Canada in the 1980's (46) is considered a gold standard for bedside nutrition assessment and is universally utilized (47-50). SGA consists of a medical/nutritional history including weight change over time, dietary intake compared to usual intake, gastrointestinal symptoms lasting longer than 2 weeks and functional status. The physical exam component of the SGA includes subcutaneous fat loss (triceps, biceps, orbital fat pads, mid axillary line, back), muscle wasting (temple, clavicle, shoulder, scapula, and quadriceps) and fluid retention (edema, ascites). The medical diagnosis and the effect on metabolic stress are considered. The patient is then classified as A—well nourished, B—mild to moderately malnourished and C—severely malnourished (46). SGA is a predictor of outcomes after LT. Malnourished patients (SGA B and C) required prolonged ventilator support, increased ICU days, increased incidence of tracheostomies (4) and longer hospital stays (5).

Nutrition assessment is performed with the intent of optimizing patient outcomes. Nutrition goals are to provide adequate protein and calories via the oral, enteral or parenteral route to optimize nutritional status, increase or at least preserve lean body mass, and help modulate inflammation and the immune response (51). As there is such a variation in energy needs due to disease severity, muscle mass and other comorbidities, indirect calorimetry (IC) is the best tool for assessing resting energy expenditure (REE) but is not available in all settings. For predictive equations, the Harris Benedict Equation (HBE) using an estimated dry weight plus a 20% stress factor is reasonable (52,53). One can adjust calorie level for weight loss, weight gain and activity level. European guidelines recommend 35–40 kcals/kg dry weight/day for patients with cirrhosis (49). Critical care guidelines recommend 25–30 kcals/kg dry weight/day (51,54). Refer to *Table 1* for recommended energy and protein requirements.

**Table 1** Protein and energy requirements for liver transplant patients

Stage of transplant	Protein (g/kg/day)	Energy
Pre-transplant		
Stable	1.2–1.5	25–35 kcals/kg (105–147 kJ/kg); REE ×1.2–1.6
Malnourished	1.2–1.5	35–40 kcals/kg (147–168 kJ/kg); REE ×1.6–1.75
Critical Care	1.2–2.0	25–30 Kcals/kg (105–126 kJ/kg); REE ×1.2–1.4
Post-transplant		
0–3 months	1.5	35–40 kcals/kg (147–168 kJ/kg); REE ×1.6–1.75
CRRT	1.5–2.5	25–30 Kcals/kg (105–126 kJ/kg); REE ×1.2–1.4
Greater than 3 months (under 65 years)	1.0–1.3	25–35 kcals/kg (105–147 kJ/kg); REE ×1.2–1.6
Greater than 3 months, older than 65 years—moderately active	1.0–1.2	25–30 kcals/kg (105–126 kJ/kg); REE ×1.2–1.4
Greater than 3 months, older than 65 years—very active	1.2–1.5	30–35 kcals/kg (126–147 kJ/kg); REE ×1.4–1.6

CRRT, continuous renal replacement therapy; REE, resting energy expenditure.

Protein intake should not be restricted in patients with cirrhosis. Historically there were concerns that a high protein intake would contribute to HE. Cordoba and colleagues randomized patients with episodic HE to receive different amounts of protein. The incidence of HE was not significantly different between the two groups. The lower protein group had higher protein breakdown which disappeared when both groups were at 1.2 g/kg/day (55). Inadequate protein intake less than 0.8 g/kg/day was associated with increased mortality in cirrhotic patients awaiting LT (56). Recommended protein needs are 1.2–1.5 g/kg dry weight/day (54). Critical care guidelines recommend protein levels of 1.2–2.0 g/kg dry weight/day (51). Medical therapy with Lactulose and antibiotics may be required for persistent HE (51,54).

### Nutrition therapy

A diet of small frequent meals (6–10 a day) is recommended to optimize intake and reduce symptoms of bloating, fullness, nausea and vomiting (57). Cirrhotic patients will lose as much in an overnight fast as healthy volunteers will lose in 2–3 days of fasting due to increased fat oxidation and early onset gluconeogenesis (58). A late evening meal improves nitrogen retention (59). A bedtime snack of about 50 g of carbohydrate (two slices of bread and jam) shortened nocturnal fasting and diminished fat and protein oxidation (12). The Association for the Study of Liver Diseases (AASLD) guidelines recommend multiple feedings with emphasis on a nighttime snack and breakfast feeding to improve nitrogen balance (60).

If oral intake is not adequate within 5–7 days of admission, enteral nutrition (EN) via a tube feed is recommended (61,62). There is often patient resistance to having a tube placed but once the tube is in and the patient feels better from being adequately fed, the benefits of tube feeding become apparent to the patient. In addition, it takes the pressure off the patient of having to “push” oral intake to try and meet their nutritional goals.

In patients with an upper gastrointestinal bleed (GIB) it is recommended to wait 24–48 hours after the resolution of the bleed prior to feeding tube placement (61). Coagulopathy may be a risk for tube placement. The patient may require platelet transfusion, fresh frozen plasma or vitamin K to improve the international normalized ratio (INR) and platelet count (61). Percutaneous endoscopic gastrostomy (PEG) placement is contraindicated in decompensated cirrhosis because of risk of ascites, peritonitis, variceal puncture and coagulopathy (63–65).

A standard feeding formula is generally used. Branched chain amino acid supplements in decompensated cirrhosis have not been shown to reduce HE recurrence or survival (66). Immune modulation nutrition (IMN) products containing some combinations of fish oils, arginine, nucleic acids and antioxidants have shown reduced infectious complications and reduced ventilator days in the general post-operative patients but no change in mortality (67). Plank and colleagues randomized 120 patients waitlisted for LT to receive IMN enriched with omega 3 fatty acids, arginine, and nucleotides (Impact) or an isocaloric control. Perioperative IMN did not demonstrate significant benefits in terms of nutritional status

pre-operatively or post-operative outcome (68).

If the patient is fluid overloaded a concentrated formula is more suitable. For patients at refeeding risk, starting at 15–20 kcal/kg and advancing slowly is recommended. Glucose, potassium, magnesium and phosphate levels should be checked daily until goal nutrition is reached and bloodwork is within normal limits (61). If cyclic EN is warranted, nocturnal tube feeding has been demonstrated to result in protein accretion and is better than daytime feeding in increasing lean tissue (69). For prolonged tube feeding of greater than 4–6 weeks, it is recommended the tube be placed in the other nostril (62).

Parenteral nutrition (PN) may be required in the severely malnourished patient where there is a contraindication to tube placement or an inability to use the gastrointestinal tract.

### Early post-transplant phase (0–3 months)

If there are no contraindications, a regular diet may be initiated in the first 24 hours. Traditionally the diet progression was clear fluid, full fluid and then regular diet however giving a regular diet as the first post-operative meal does not increase morbidity or mortality (67). Clear liquids may actually increase risk of aspiration when compared to solid foods as liquids are more easily aspirated (70). The occurrence of nausea is about 20% whether the patients are given clear liquids or solids (71).

Early feeding by oral or tube feeding within the first 24 hours results in better outcome as it maintains gut integrity, modulates the immune response, stress response, and attenuates disease severity (72,73). In cases of severe sepsis, shock or severe malabsorption, EN may be feasible in the first 24–36 hours once the patient has stabilized. Intraluminal nutrients help to reverse mucosal hypoperfusion from shock (74). EN may not be feasible if there is bowel discontinuity, risk of bowel ischemia, obstruction or ongoing peritonitis. If unable to establish oral or EN in the severely malnourished patient by post-operative day 5, PN is warranted.

As malnourished LT patients tend to have more infectious complications (viral, bacterial, fungal), increased requirements for ventilator support, increased incidence of tracheostomy, and longer hospital stays, it is critical to provide adequate nutrition (4-6,51,75).

Plank and colleagues quantified the sequential changes in energy expenditure and body composition in the first year post LT (76). Before transplant patients were significantly

protein depleted (82% of total body protein compared to pre-illness) and lost an additional 1% (approximately 1 kg) of total body protein within 10 days post LT (mainly from skeletal muscle) (76). Protein requirements are 1.5 g/kg dry weight/day (77,78). In patients on continuous renal replacement therapy (CRRT), an additional 10–15 g of protein is lost daily. In CRRT, protein requirements are 1.5–2.5 g/kg/dry weight/day (51). In patients with an open abdomen, 15–30 g of protein/liter of exudate is lost in the drains and should be replaced to mitigate loss of lean tissue. Patients with an open abdomen can be fed safely if there is no bowel injury. EN [when compared to nil per os (NPO)] was shown to decrease time to facial closure, pneumonia, abdominal complications and mortality (79-82).

Some patients develop persistent inflammation, immunosuppression and catabolic syndrome (PICS) and experience persistent cachexia. Provision of at least 1.5 g protein/kg/day is recommended to help with anabolic resistance (83).

Ferreira and colleagues measured REE before LT and at 5 intervals during the first year after LT (84). Energy requirements were elevated post LT reaching 42% above predicted values by post-operative day 10 and remained elevated for 3 months. Measured REE was higher than predicted REE and no patients were hypo-metabolic at 3 months post LT (84).

Generally, patients are able to be discharged within 2–3 weeks post LT. Some patients may benefit from inpatient rehabilitation which has been shown to decrease 30-day readmission rate (85).

### Late post-transplant phase >3 months

Hyper-metabolism is still present at 6 months post LT but reaches predicted values by 12 months (76). Hyper-metabolism before LT is associated with hyper-metabolism after LT. Higher levels of fat mass prior to LT are associated with hypo-metabolism after LT (84).

Just over half of protein lost is restored by 12 months however body fat is restored by 12 months (76). Over hydration of fat free mass (total body weight minus total body fat) evident in the pre-transplant phase is still present at 12 months post LT (76). Respiratory muscle strength does improve but it is significantly lower than predicted values at 12 months (76,86).

Sarcopenic obesity begins in the first month post LT (87). The liver is a metabolic sensor that relays information (humoral and neural) via the brainstem to the



hypothalamus (controller of feeding behavior) (88). In LT the normal hepatic innervations (afferent and efferent neural limbs) are lost which may affect energy metabolism and thus contribute to weight gain (88). Oral intake improves post LT contributing to a positive energy balance. Prednisone, in addition to steroid induced diabetes, is associated with weight gain by increasing appetite, decreasing fat oxidation and increasing fat deposition (84). Prednisone is also associated with increased proteolysis and decreased protein synthesis (89). Calcineurin inhibitors, tacrolimus and cyclosporine, may contribute to impaired muscle growth and regeneration as calcineurin has an effect on skeletal muscle differentiation and hypertrophy. Sirolimus and everolimus inhibit rapamycin complex involved in protein synthesis (89).

Obesity (BMI >30 kg/m<sup>2</sup>) is present in 36% of patients at 3 years post LT (43). The greatest weight gain appears to occur after the first 6 months (43). Of the patients who were not obese pre-transplant, 31% became obese by 3 years post LT (43). Obesity can lead to metabolic syndrome which is reported to range from 43% to 58% post LT compared to 24% in the general population (90). Cardiovascular risk is associated with metabolic syndrome and cardiovascular complications are the primary non-graft related cause of death in LT (91). Treatment goals include optimal blood glucose control, fast tapering of steroids, lipid normalization, weight reduction and increased physical activity (92).

Although physical activity generally increases after LT more than 75% of patients remain sedentary (84). LT recipients have impaired peak physical exercise performance that is approximately 40–50% below age-related values (93,94); however, improvement can be achieved with diet modification and exercise (95). Regular exercise can optimize functioning after LT and intensive training can reach normal levels or even higher levels of VO<sub>2peak</sub> (oxygen uptake at the highest tolerable level of exercise) (95). Regular exercise training should optimally begin in the pre-transplant setting as improvements in aerobic capacity and muscle strength can be achieved (96).

### Intervention strategies

Chronic disease care-management programs such as the one described by Morando and colleagues are cost effective and improve 12-month survival (97). In this model, patients with cirrhosis and ascites are seen by a team (hepatologists, physicians in training, nurses) while having access to a day

hospital for paracentesis, transfusions, and bandings. Addition of a dietitian and physiotherapist to this model would add a “pre-habilitation” component to optimize nutritional status and physical functioning to mitigate/improve sarcopenia, frailty, and obesity even before referral for LT.

Sarcopenia is already present in 10% of Child Pugh Class A cirrhosis patients (26) therefore, early screening is of benefit. Adequate protein intake, a high complex carbohydrate bedtime snack, and breakfast feeding are critical in the pre-transplant phase for mitigating loss of muscle tissue. Providing 25–30 g/meal of high quality protein (meat, fish, poultry, eggs, and dairy) is recommended to maximally stimulate muscle protein synthesis (98). In patients with sarcopenia, BCAA supplementation (leucine 7.5 g, isoleucine 3.75 g and valine 3.75 g) dissolved in a carbonated beverage may help to reduce proteolysis and activate muscle protein synthesis (99). Anabolic therapies known to increase muscle mass such as testosterone and growth hormone may be useful in some patients (99,100). Exercise guidelines of 20–30 minutes of aerobic activity and 20–30 minutes of resistance training 3 times a week are recommended (99,100).

For older and/or deconditioned patients, exercises for improving flexibility, strength and balance are illustrated at [www.nhs.uk/exercises-for-older-people](http://www.nhs.uk/exercises-for-older-people). Inpatient rehabilitation, both pre- and post-transplant is of benefit in the severely debilitated patient. Older adults (greater than 65 years of age) require protein intakes of 1.0–1.2 g/kg and very active older adults require 1.2–1.5 g/kg/day secondary to changes in protein metabolism that occur with aging (101).

Obese patients are advised to lose weight pre-transplant. A restricted energy intake to provide for a weight loss of 0.5 kg a week is considered safe weight loss. Adequate protein intake and exercise are advised to mitigate loss of muscle tissue, promote muscle synthesis while decreasing excess adipose reserve.

Regular monitoring of nutritional status and timely intervention in the post-transplant setting is necessary to help correct malnutrition and prevent metabolic syndrome. A healthy diet and regular exercise both aerobic and resistance training is strongly emphasized. The Mediterranean diet (olive oil, high intake of vegetables, fruits, legumes, moderate intake of fish, white meat, low intake of high fat dairy, red meats, homemade sweets) is considered one of the healthiest diets, has a positive influence on cardiovascular disease, improves the clinical profile of patients with fatty liver disease when combined with an active lifestyle, and is both palatable and sustainable (102).

LT requires a high resource allocation. A long-term commitment to optimize body composition, physical functioning, and attenuate co-morbidities is warranted (93).

## Acknowledgements

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the Guest Editor (Eric M. Yoshida, Trana Hussaini) for the series “Liver transplantation” published in *AME Medical Journal*. The article has undergone external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/amj.2018.01.15>). The series “Liver transplantation” was commissioned by the editorial office without any funding or sponsorship. The author has no other conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

- Volk ML. Identifying patients for intensive chronic disease management. *Dig Dis Sci* 2014;59:22-3.
- Johnson KB, Campbell EJ, Chi H, et al. Advanced disease, diuretic use, and marital status predict hospital admissions in an ambulatory cirrhosis cohort. *Dig Dis Sci* 2014;59:174-82.
- Volk ML, Tocco RS, Bazick J, et al. Hospital readmissions among patients with decompensated cirrhosis. *Am J Gastroenterol* 2012;107:247-52.
- Merli M, Giusto M, Gentili F, et al. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. *Liver Int* 2010;30:208-14.
- Pikul J, Sharpe M, Lowndes R, et al. Degree of preoperative malnutrition is predictive of postoperative morbidity and mortality in liver transplant recipients. *Transplantation* 1994;57:469-72.
- Stephenson GR, Moretti EW, El-Moalem H, et al. Malnutrition in liver transplant patients. *Transplantation* 2001;72:666-70.
- Merli M, Riggio O, Dally L, et al. Does malnutrition affect survival in cirrhosis? *Hepatology* 1996;23:1041-6.
- Cabr e E, Gassull M. Nutrition in chronic disease and liver transplantation. *Curr Opin Clin Nutr Metab Care* 1998;1:423-30.
- Van Thiel DH, Fagioli S, Wright HI, et al. Gastrointestinal transit in cirrhotic patients: effect of hepatic encephalopathy and its treatment. *Hepatology* 1994;19:67-71.
- Phillips JR, Angulo P, Petterson T, et al. Fat-soluble vitamin levels in patients with primary biliary cirrhosis. *Am J Gastroenterol* 2001;96:2745-50.
- Bauer TM, Steinbr ckner B, Brinkmann FE, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2001;96:2962-7.
- Chang WK, Chao YC, Tang HS, et al. Effects of extra-carbohydrate supplementation in the late evening on energy expenditure and substrate oxidation in patients with liver cirrhosis. *JPEN J Parenter Enteral Nutr* 1997;21:96-9.
- Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the model for end-stage liver disease score. *J Cachexia Sarcopenia Muscle* 2017;8:113-21.
- Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. *Liver Int* 2009;29:1396-402.
- Di Angelantonio E, Bhupathiraju S, Wormser D, et al. Body mass index and all-cause mortality: individual participant meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388:776-86.
- Campillo B, Richardet JP, Bories PN. Validation of body mass index for the diagnosis of malnutrition in patients with liver cirrhosis. *Gastroenterol Clin Biol* 2006;30:1137-43.
- Dick AA, Spitzer AL, Seifert CF, et al. Liver transplantation at the extremes of the body mass index.

- Liver Transpl 2009;15:968-77.
18. Gupta R, Knobel D, Gunabushanam V, et al. The effect of low body mass index on outcome in critically ill surgical patients. *Nutr Clin Pract* 2011;26:593-7.
  19. Bambha KM, Dodge JL, Gralla J, et al. Low, rather than high, body mass index confers increased risk for post-liver transplant death and graft loss: Risk modulated by model for end-stage liver disease. *Liver Transpl* 2015;21:1286-94.
  20. Henry CJ. The biology of human starvation: some new insights. *Nutr Bull* 2001;26:205-11.
  21. Sauerwein HP, Serlie MJ. Optimal nutrition and its potential effect on survival in critically ill patients. *Neth J Med* 2010;68:119-22.
  22. Carey EJ. Sarcopenia in solid organ transplant. *Nutr Clin Pract* 2014;29:159-70.
  23. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998;147:755-63.
  24. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc* 2011;12:249-56.
  25. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012;10:166-73.
  26. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: Its prevalence and independent prognostic value. *Liver Transpl* 2012;18:1209-16.
  27. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and post liver transplant mortality. *J Am Coll Surg* 2010;211:271-8.
  28. Krell RW, Kaul DR, Martin AR, et al. Association between sarcopenia and the risk of serious infection among adults undergoing liver transplantation. *Liver Transpl* 2013;19:1396-402.
  29. Baumgartner RN, Wayne SJ, Waters DL, et al. Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obes Res* 2004;12:1995-2004.
  30. Sinclair M, Poltavsky E, Dodge J, et al. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol* 2017;23:899-905.
  31. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146-56.
  32. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant* 2014;14:1870-9.
  33. Lai JC, Dodge JL, Sen S, et al. Functional decline in patients with cirrhosis awaiting liver transplant: results from the functional assessment in liver transplantation (FrALT) study. *Hepatology* 2016;63:574-80.
  34. Wang CW, Feng S, Covinsky KE, et al. A Comparison of Muscle Function, Mass, and Quality in Liver Transplant Candidates: Results From the Functional Assessment in Liver Transplantation Study. *Transplantation* 2016;100:1692-8.
  35. Wong S. Grip strength reference values for Canadians aged 6-79: Canadian Health Measures Survey, 2007 to 2013. Statistics Canada. Catalogue no. 82-003-X. *Health Rep* 2016;27:3-10.
  36. Kallwitz ER. Sarcopenia and liver transplant: The relevance of too little muscle mass. *World J Gastroenterol* 2015;21:10982-93.
  37. Nair S, Verma S, Thulavath P. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002;35:105-9.
  38. Statistics Canada. Table 117-0005-Distribution of the household population by adult body mass index (BMI)-Health Canada (HC) classification by sex and age group, occasional (percent). CANISM (database). Available online: <http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1170005>
  39. DiCecco SR, Francisco-Ziller N. Obesity and organ transplantation: successes, failures, and opportunities. *Nutr Clin Pract* 2014;29:171-91.
  40. Charlton MR, Burns JM, Pedersen RA, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011;141:1249-53.
  41. Mathur A, Franco ES, Leone JP, et al. Obesity portends increased morbidity and earlier recurrence following liver transplantation for hepatocellular carcinoma. *HPB (Oxford)* 2013;15:504-10.
  42. Schaeffer DF, Yoshida EM, Buczkowski AK, et al. Surgical morbidity in severely obese liver transplant recipients - a single Canadian Centre Experience. *Ann Hepatol* 2009;8:38-40.
  43. Richards J, Gunson B, Johnson J, et al. Weight gain and obesity after liver transplantation. *Transpl Int* 2005;18:461-6.
  44. Krenitsky J. Nutrition for patients with hepatic failure. *Prac Gastroenterol* 2003;6:23-42.
  45. Leonard J, Heimbach J, Malinchoc M, et al. The impact



- of obesity on long term outcomes in liver transplant recipients—results of the NIDDK Liver Transplant Database. *Am J Transplant* 2008;8:667-72.
46. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr* 1987;11:8-13.
  47. Hasse JM. Nutrition assessment and support of organ transplant recipients. *JPEN J Parenter Enteral Nutr* 2001;25:120-31.
  48. Tsiaousi ET, Hatzitolios AI, Trygonis SK, et al. Malnutrition in end stage liver disease: recommendations and nutritional support. *J Gastroenterol Hepatol* 2008;23:527-33.
  49. Plauth M, Cabre E, Riggio O, et al. ESPEN guidelines on enteral nutrition: Liver disease. *Clin Nutr* 2006;25:285-94.
  50. Fischer M, JeVenn A, Hipskind P. Evaluation of muscle and fat loss as diagnostic criteria for malnutrition. *Nutr Clin Pract* 2015;30:240-8.
  51. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016;40:159-211.
  52. Plevak DJ, DiCecco SR, Wiesner RH, et al. Nutritional support for liver transplantation: identifying caloric and protein requirements. *Mayo Clin Proc* 1994;69:225-30.
  53. Selberg O, Bottcher J, Tusch G, et al. Identification of high- and low-risk patients before liver transplantation: A prospective cohort study of nutritional and metabolic parameters in 150 patients. *Hepatology* 1997;25:652-7.
  54. Braga M, Ljungqvist O, Soeters P, et al. ESPEN guidelines on parenteral nutrition: Surgery. *Clin Nutr* 2009;28:378-86.
  55. Córdoba J, López-Hellín J, Planas M, et al. Normal protein diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol* 2004;41:38-43.
  56. Ney M, Abralde JG, Ma M, et al. Insufficient Protein Intake Is Associated With Increased Mortality in 630 Patients With Cirrhosis Awaiting Liver Transplantation. *Nutr Clin Pract* 2015;30:530-6.
  57. Dashti HS, Mogensen KM. Recommending Small, Frequent Meals in the Clinical Care of Adults: A Review of the Evidence and Important Considerations. *Nutr Clin Pract* 2017;32:365-77.
  58. Owen OE, Trapp VE, Reichard GA Jr, et al. Nature and quantity of fuels consumed in patients with alcoholic cirrhosis. *J Clin Invest* 1983;72:1821-32.
  59. Swart GR, Zillikens MC, van Vuure JK, et al. Effect of a late evening meal on nitrogen balance in patients with cirrhosis of the liver. *BMJ* 1989;299:1202-3.
  60. O'Shea RS, Dasarathy S, McCullough AJ, et al. Alcoholic liver disease. *Hepatology* 2010;51:307-28.
  61. Hasse JM, DiCecco SR. Enteral Nutrition in Chronic Liver Disease: Translating Evidence Into Practice. *Nutr Clin Pract* 2015;30:474-87.
  62. Stroud M, Duncan H, Nightingale J, et al. Guidelines for enteral feeding in adult hospital patients. *Gut* 2003;52 Suppl 7:vii1-12.
  63. Baltz JG, Argo CK, Al-Osaimi AM, et al. Mortality after percutaneous endoscopic gastrostomy in patients with cirrhosis: a case series. *Gastrointest Endosc* 2010;72:1072-5.
  64. Löser C, Aschl G, Hébuterne X, et al. ESPEN guidelines on artificial enteral nutrition—percutaneous endoscopic gastrostomy (PEG). *Clin Nutr* 2005;24:848-61.
  65. Phillips MS, Ponsky JL. Overview of enteral and parenteral feeding access techniques: principles and practice. *Surg Clin North Am* 2011;91:897-911, ix.
  66. Patel JJ, McClain CJ, Sarav M, et al. Protein Requirements for Critically Ill Patients With Renal and Liver Failure. *Nutr Clin Pract* 2017;32:101S-111S.
  67. Evans DC, Martindale RG, Kiraly LN, et al. Nutrition optimization prior to surgery. *Nutr Clin Pract* 2014;29:10-21.
  68. Plank LD, Mathur S, Gane EJ, et al. Perioperative immunonutrition in patients undergoing liver transplantation: a randomized double-blind trial. *Hepatology* 2015;61:639-47.
  69. Plank LD, Gane EJ, Peng S, et al. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. *Hepatology* 2008;48:557-66.
  70. Lassen K, Kjoever J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity. *Ann Surg* 2008;247:721-9.
  71. Pearl ML, Frandina M, Mahler L, et al. A randomized controlled trial of a regular diet as the first meal in gynecologic oncology patients undergoing intraabdominal surgery. *Obstet Gynecol* 2002;100:230-4.
  72. Hasse JM. Early postoperative tube feeding in liver transplantation. *Nutr Clin Pract* 2014;29:222-8.
  73. Ei S, Shinoda M, Itano O, et al. Effects of addition of early enteral nutritional support during the postoperative phase in patients after living-donor liver transplantation. *Ann Transplant* 2015;20:357-65.

74. Rosenthal MD, Vanzant EL, Martindale RG, et al. Evolving paradigms in the nutritional support of critically ill surgical patients. *Curr Probl Surg* 2015;52:147-82.
75. Chelala L, Kovacs CS, Taege AJ, et al. Common infectious complications of liver transplant. *Cleve Clin J Med* 2015;82:773-84.
76. Plank LD, Metzger DJ, McCall JL, et al. Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. *Ann Surg* 2001;234:245-55.
77. Zhang QK, Wang ML. The management of perioperative nutrition in patients with end stage liver disease undergoing liver transplantation. *Hepatobiliary Surg Nutr* 2015;4:336-44.
78. Singer P, Hiesmayr M, Biola G, et al. Pragmatic approach to nutrition in the ICU: Expert opinion regarding which calorie protein target. *Clin Nutr* 2014;33:246-51.
79. Burlew CC, Moore EE, Cuschieri J, et al. Who should we feed? Western Trauma Association multi-institutional study of enteral nutrition in the open abdomen after injury. *J Trauma Acute Care Surg* 2012;73:1380-7; discussion 1387-8.
80. Collier B, Guillaumondegui O, Cotton B, et al. Feeding the open abdomen. *JPEN J Parenter Enteral Nutr* 2007;31:410-5.
81. Moore SM, Burlew CC. Nutrition Support in the Open Abdomen. *Nutr Clin Pract* 2016;31:9-13.
82. Guillaume A, Seres DS. Safety of enteral feeding in patients with open abdomen, upper gastrointestinal bleed, and perforation peritonitis. *Nutr Clin Pract* 2012;27:513-20.
83. Moore FA, Phillips SM, McClain CJ, et al. Nutrition Support for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome. *Nutr Clin Pract* 2017;32:121S-127S.
84. Ferreira LG, Santos LF, Anastácio LR, et al. Resting energy expenditure, body composition, and dietary intake: a longitudinal study before and after liver transplantation. *Transplantation* 2013;96:579-85.
85. Kothari AN, Yau RM, Blackwell RH, et al. Inpatient Rehabilitation after Liver Transplantation Decreases Risk and Severity of 30-Day Readmissions. *J Am Coll Surg* 2016;223:164-71.e2.
86. Merli M, Giusto M, Riggio O, et al. Improvement of nutritional status in malnourished cirrhotic patients one year after liver transplantation. *e-SPEN* 2011;6:e142-7.
87. Schütz T, Hudjetz H, Roske AE, et al. Weight gain in long-term survivors of kidney or liver transplantation—another paradigm of sarcopenic obesity? *Nutrition* 2012;28:378-83.
88. Richardson R, Garden O, Davidson I. Reduction in energy expenditure after liver transplantation. *Nutrition* 2001;17:585-9.
89. Giusto M, Lattanzi B, Di Gregorio V, et al. Changes in nutritional status after liver transplantation. *World J Gastroenterol* 2014;20:10682-90.
90. Pagadala M, Dasarthy S, Eghtesad B, et al. Posttransplant metabolic syndrome: An epidemic waiting to happen. *Liver Transpl* 2009;15:1662-70.
91. Madhwal S, Atreja A, Albeldawi M, et al. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl* 2012;18:1140-6.
92. Sprinzl MF, Weinmann A, Lohse N, et al. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. *Transpl Int* 2013;26:67-74.
93. Stephenson AL, Yoshida EM, Abboud RT, et al. Impaired exercise performance after successful liver transplantation. *Transplantation* 2001;72:1161-4.
94. Kotarska K, Wunsch E, Jodko L, et al. Factors affecting exercise test performance in patients after liver transplantation. *Hepat Mon* 2016;16:e34356.
95. Krasnoff JB, Vintro AQ, Ascher NL, et al. A randomized trial of exercise and dietary counseling after liver transplantation. *Am J Transplant* 2006;6:1896-905.
96. Bernal W, Martin-Mateos R, Lipcsey M, et al. Aerobic capacity during cardiopulmonary exercise testing and survival with and without liver transplantation for patients with chronic liver disease. *Liver Transpl* 2014;20:54-62.
97. Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: A new model of care coordination by consultant hepatologists. *J Hepatol* 2013;59:257-64.
98. Paddon-Jones D, Rasmussen B. Dietary recommendations and the prevention of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2009;12:86-90.
99. Sinclair M, Gow P, Grossman M, et al. Review article: sarcopenia in cirrhosis - aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther* 2016;43:765-77.
100. Morley JE, Argiles JM, Evans WJ, et al. Nutritional recommendations for the management of sarcopenia. *J Am Med Dir Assoc* 2010;11:391-6.
101. Bauer J, Biola G, Cederholm T, et al. Evidenced-based recommendations for the optimal dietary protein intake in older people: A position paper from the PROT-AGE

Study Group. *J Am Med Dir Assoc* 2013;14:542-59.  
102. Gelli C, Tarocchi M, Abenavoli L, et al. Effect of a counseling-supported treatment with the Mediterranean

diet and physical activity on the severity of the non-alcoholic fatty liver disease. *World J Gastroenterol* 2017;23:3150-62.

doi: 10.21037/amj.2018.01.15

**Cite this article as:** Fortier L. Malnutrition, frailty, sarcopenia, obesity—optimizing nutrition care in liver transplantation. *AME Med J* 2018;3:22.