tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 levels [9].

Protein-energy malnutrition predisposes a patient to complications, such as a compromised respiratory function and delayed physical rehabilitation, and it also increases a patient's stay in the hospital and intensive care unit, blood usage and hospital charges [7, 8]. PEM adversely affects both the patient and graft survival, the patient quality of life after OLT and the response to stress, including the stresses of infection and surgery [3–7].

A loss of skeletal muscle mass (SMM), called sarcopenia, reflecting preoperative malnutrition, is the most common complication of liver cirrhosis (LC). Sarcopenia has been found to be closely associated with post-LT mortality in patients undergoing living donor LT (LDLT) [10]. Sarcopenia confers a vulnerability to preoperative infections, including spontaneous bacterial peritonitis and pneumonia due to the deteriorated immune function, as well as post-LT bacteremia, sepsis and wound dehiscence [11, 12].

There is no doubt that ensuring adequate nutritional intake, as well as correcting vitamin and micronutrient deficiencies, is paramount to alleviating some of these complications and reducing the perioperative morbidity and mortality after LT [1–3].

Etiology of Malnutrition

Patients with liver disease have decreased caloric intake due to the anorexia caused by zinc deficiency, hyperglycemia and increased levels of pro-inflammatory cytokines, such as TNF-α, IL-6 and leptin [13–16]. Other causes of the loss of appetite in patients with liver disease are the unpalatable specialized diets; low-salt and low-protein diets for ascites and hepatic encephalopathy (HE), respectively, and altered gustatory sensation due to the hypomagnesemia and autonomic neuropathy in LC, which also causes gastroparesis and a delayed bowel transit time. This, together with bacterial overgrowth and tense ascites, causes nausea, early satiety and increased protein loss [13–17]. In addition, in up to 45 % of patients with cirrhosis, a coexisting infection with *Helicobacter pylori* may cause dyspepsia and a decreased desire for food [14]. Moreover, nil per os (NPO) or limited intake for, during and after diagnostic or therapeutic procedures may further contribute to PEM [15–18].

Patients with liver disease are in a hypercatabolic state. Many cirrhotic patients also have increased basal energy expenditure (BEE), which may be related to increased sympathetic nervous system activity, decreased glycogen stores and impaired glycogenolysis. Although hyperinsulinemia is present, glucose intolerance ensues due to insulin resistance. Increased gluconeogenesis may further exacerbate the muscle wasting due to impaired muscle glucose uptake [19, 20].

Protein malnutrition is the predominant feature of advanced liver disease due to inflammation, impaired liver synthesis and increased protein breakdown, along with low glycogen stores that lead to gluconeogenesis from amino acids [18]. Patients with protein malnutrition have increased protein requirements to maintain a positive nitrogen balance. The low plasma levels of insulin-like growth factor (IGF-1), which mediates most of the growth-promoting effects of growth hormone, also explain the severe growth hormone resistance seen in patients with ESLD [21]. Protein-losing enteropathy has been suggested to play a role in the development of hypoalbuminemia in ESLD patients [22].

Moreover, patients with ESLD may have impaired synthesis of polyunsaturated fatty acids from their essential fatty acid precursors, with increases in the levels of n-6 and n-9 fatty acids and decreases in n-3 moieties in plasma and adipose tissue [23]. Enhanced gluconeogenesis, especially after fasting, with a preference for fat metabolism, lipid peroxidation and lipolysis, also increases upon impaired glycogen storage and utilization [24], further exacerbating the condition.

Other contributing factors include impaired hepatointestinal extraction, large volume paracentesis, intestinal and drug-induced diarrhea (due to drugs like neomycin, lactulose, diuretics, antimetabolites, cholestyramine) and malabsorption in alcoholic and cholestatic liver diseases, especially sclerosing cholangitis with inflammatory bowel disease or concomitant pancreatic insufficiency [13, 25].

Evaluation of the nutritional status

All patients being prepared for LT should undergo a complete nutritional assessment. Traditional assessment tools are not accurate in patients with liver disease due to fluid retention, which is found in a significant number of patients, and the effects of liver dysfunction on protein synthesis. No gold standard for assessment exists at this time [6, 26].

The initial assessment should begin with a careful history to document weight loss, nausea, anorexia and the use of specialized diets and supplements. A complete physical examination should be performed to search for changes in the oral mucosa, skin and hair, thickness of subcutaneous fat and for muscle wasting, all of which are associated with chronic liver disease. A subjective global assessment (SGA) combines a thorough history-taking and physical examination and rates patients as either "well-nourished", "moderately malnourished", or "severely malnourished" [6].

This test has shown high specificity, but very low sensitivity, for diagnosing malnutrition in patients with alcoholic liver disease. However, it has not been found to be a reliable tool for evaluating the nutritional status in LT patients [6, 26].

Biochemical tests such as evaluations of the serum transferrin levels, retinol binding protein plus creatinine-height index, 24-h urine nitrogen and 3-methylhistidine excretion, as well as the total lymphocyte count and delayed hypersensitivity testing, have been used [27, 28]. However, such parameters have not been shown to be accurate indices of the nutritional status given the fact that their levels correlate with the severity of liver damage, rather than malnutrition due to the catabolic nature of the liver disease and associated protein turnover. Serum albumin frequently serves as an important indicator of the liver function. However, it has a long half-life (17–21 days), and because exogenous albumin supplements are frequently administered in clinical practice, the serum albumin levels cannot sensitively or dynamically reflect early liver damage. The shorter half-life (2–3 days) of prealbumin (transthyretin) renders it a more sensitive indicator of damaged synthetic functioning in the liver and fluctuations in the nutritional status than albumin [29].

Anthropometric measurements, such as the body mass index, mid-arm muscle circumference, triceps skin fold thickness or subscapular skin fold thickness have also been used as part of a nutritional assessment in patients with liver disease [27, 28]. However, these measures have been questioned regarding their reliability in patients with ascites and peripheral edema [27, 30].

The non-protein respiratory quotient (npRQ), a unitless number estimated from the carbon dioxide production, was used to evaluate the nutritional status of patients with LC [31]. The homeostasis model assessment (HOMA), a method used to quantify insulin resistance and β-cell function, has been reported to reflect the nutritional status in patients with nonalcoholic fatty liver disease [31]. The BEE can either be predicted using several formulas, such as the Harris-Benedict equation using ideal body weight plus 20 %, or measured with indirect calorimetry [32].

The body cell mass (BCM) is defined as the sum of the intracellular water and fat-free mass, including skeletal muscle and viscera, without the bone mineral mass. The BCM comprises the metabolically active and protein-rich compartments in the body responsible for the BEE, and is known to be depleted in patients with PEM [9, 33, 34]. The BCM is thus considered to be a highly reliable parameter of the nutritional status, especially for patients undergoing LT, who usually have abundant extracellular fluid, such as edema and ascites. A low BCM in patients with LC suggests a decrease in the skeletal muscle volume, which could interfere with early post-operative mobilization and result in pulmonary complications, including aspiration pneumonia and atelectasis [7, 12].

In the nutritional assessment for patients undergoing LDLT, Kaido et al. [10] used a direct segmental multi-frequency bioelectrical impedance analysis (BIA) with the InBody720 (Biospace, Tokyo, Japan) device, which allowed the body mass index, intra- and extracellular water and body fat percentage to be automatically measured within two minutes. The SMM was measured and shown as a percent against a standard SMM calculated based on the sex and height of each patient. The BCM was automatically calculated by the InBody 720 and displayed against a normal range (e.g., 23.0–28.1 kg).

Bioelectrical impedance analysis measures the body's resistance to flow (impedance) of alternating electrical current at a designated frequency between points of contact on the body. The water in body tissue is conductive; therefore, BIA can indirectly provide information on the body's tissue contents, including the total body water, fat-free mass and SMM, and is accurate in over-hydrated subjects [7, 10]. BIA is increasingly being used because it is easy to perform, portable, non-invasive and quick. It has been highly correlated with hydrostatic weighing, dual energy X-ray absorptiometry, in vivo neutron activation analysis and deuterium isotope dilution, without the radiation exposure hazards [35–38]. BIA is thought to be superior to measuring the psoas muscle cross-sectional area at the L_3 vertebral level by computed tomography (CT) scanning or magnetic resonance imaging (MRI), since it might be more appropriate to evaluate not only the psoas muscle mass, but also the whole body SMM. Other frailty parameters of skeletal muscle function, such as the hand-grip strength, walking speed or levels of exhaustion can be used in conjunction with BIA [39, 40].

Considering the feasibility, the current guidelines of the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend only SGA and/or anthropometry parameters to identify patients at risk for poor nutritional status, and recommend that BIA should be used to quantify undernutrition, in spite of the limitations of all techniques in patients with ascitic decompensation [41, 42]. According to the ESPEN, other composite nutrition scores provide no additional prognostic information [41, 42].

Nutritional therapy before liver transplantation

The main goals of pre-LT nutritional therapy are to prevent further nutrient and muscle depletion and to correct any vitamin and mineral deficiencies present to minimize the risk of infections and debility [25]. An early, planned, preoperative nutritional intervention can be performed in most cases of LDLT, since the date of LT is known in

advance, unlike in deceased donor LT (DDLT). Nutritional therapy, as well as rehabilitation at the time of referral of a potential recipient, should start a few months before LT to most effectively increase the SMM and BCM [7].

For adult recipients preparing for LDLT, Kaido et al. [10, 12] described a detailed preoperative nutritional therapy regimen. This regimen starts approximately 2 weeks before LDLT after the BIA assessment. The therapy consists of the following three components: a nutrient mixture enriched with BCAAs (Aminoleban® EN; Otsuka Pharmaceutical Co., Tokyo, Japan) or BCAAs nutrients (Livact®; Ajinomoto Pharma Co., Tokyo, Japan) as a late evening snack; synbiotics using a supplementation product enriched with glutamine, dietary fiber and oligosaccharide (GFO®; Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily, and a lacto-fermented beverage containing 5×10^8/mL of *Lactobacillus casei Shirota* strain (Yakult 400®; Yakult Honsha Co., Tokyo, Japan) once a day via feeding tube or orally until discharge. Additionally, patients with a low serum zinc level receive 1.0 g/day of polaprezinc (Promac D®; Zeria Pharmaceutical Co., Tokyo, Japan).

Dietitians should adjust the type and amount of food for each patient to maintain a total caloric intake at least 1.2 times the BEE (approximately, 35–40 kcal/kg and a protein intake of 1.2–1.5 g/kg), including BCAAs nutrients (scaled according to the degree of hepatic decompensation), adherent to the ESPEN guidelines [11, 41, 42]. Of the total non-protein energy requirements, 60–70 % should be administered as high-complex and simple carbohydrates, whereas lipids should make up the other 30–40 %. In malnourished patients, a daily energy intake of 50 kcal/kg is required for caloric repletion [25]. Excess calories should be avoided, as this promotes hepatic lipogenesis, liver dysfunction and increased carbon dioxide production, leading to increased work required for breathing [25, 43, 44].

Route of nutritional support

Enteral nutrition (EN) with a gastric or jejunal small-bore feeding tube is the preferable route of delivery of nutrition for all patients who are not able to maintain adequate oral intake so that they can still benefit from topical nutritional factors in the gut, and to maintain the integrity of the gastric mucosa and gut barrier. It is also less costly, being associated with fewer complications and a decreased hospital length of stay compared with parenteral nutrition (PN), which carries a risk of infection, fluid overload and electrolyte imbalance [45].

Enteral nutrition provides antigenic stimulation to the gut-associated lymphoid tissue and is a stimulus for biliary secretion of immunoglobulin A [11, 46]. These factors help to maintain the barrier against the translocation of luminal bacteria to the portal circulation, thus decreasing infectious complications, as indicated by the differential urinary excretion of carbohydrates of varying molecular weights [11, 46].

With EN, excessive feeding will lead to intolerance, causing diarrhea, bloating and vomiting. Because the gut provides a "gate-keeper" role, major complications related to excessive tube feed administration are generally kept to a minimum. However, with PN, there are no means of regulation, and the patient is forced to assimilate the entire substrate load [11, 45].

Feeding tubes do not increase the risk for esophageal variceal hemorrhage, but may be associated with an increased risk of epistaxis, sinusitis, impaired gastric emptying and tube feeding-associated diarrhea on long-term use, as well as with tube retraction, clogging and small intestinal obstruction. However, complications related to malpositioned feeding tubes are usually preventable if care is taken to ensure correct initial placement and by regularly monitoring the position [11, 47].

The indications for PN use in liver disease have recently been reviewed and published by the ESPEN for patients with fulminant hepatic failure and coma, and for patients who are moderately or severely malnourished and cannot achieve adequate caloric intake, either orally or through EN due to gastrointestinal dysfunction, such as esophageal bleeding, ileus or intestinal obstruction [41, 48]. Given the low glycogen stores in patients with liver disease, it is important to provide a glucose infusion in patients who require fasting and are not able to take oral nutrients or EN for more than 12 h [41, 42]. The use of "standardized" formulas should be restricted to stable patients with no fluid overload who need only maintenance fluid administration [48].

Considerations for carbohydrate supplementation

Glucose infusion should supply 2–3 g/kg body weight per day of glucose. The administration of glucose in excess will result in severe hyperglycemia, lipogenesis and increased carbon dioxide production [48, 49]. Patients with liver failure can have alterations in glucose homeostasis; therefore, careful monitoring of the serum glucose level is needed to avoid complications associated with hyperglycemia [49].

Considerations for lipid supplementation

Patients with advanced LC have decreased plasma levels of essential fatty acids and their polyunsaturated derivatives, such as arachidonate, that have been associated with lower survival. These are cell membrane components and

precursors of a wide array of biologically active compounds [24, 50].

Because fat is important for the nutrient repletion of malnourished patients, dietary fat should not be restricted unless true fat malabsorption has been diagnosed using a fecal fat test. Medium chain triglycerides, an alternative form of fat not requiring bile salts for absorption, can provide a concentrated source of calories to patients with fat malabsorption, and are available in both EN and PN formulations [24, 50].

Clinical essential fatty acid deficiency takes approximately 5–6 weeks to develop without linoleic acid or linolenic acid intake, so it is not likely to become an issue for most patients with liver failure except in those who are severely malnourished. Therefore, a short course of "fat-free" total parenteral nutrition (TPN) can be used in most patients [24, 51].

Many EN formulas provide a wide range of lipid dosages, from a variety of sources, for fatty acids. When prescribing TPN, many hospitals compound "three-in-one" TPN solutions containing amino acids, dextrose and lipids. The minimum lipid dose in such combinations should be 20 g/L or 2 % of the final concentration. More dilute lipid formulas are unstable in the presence of hypertonic dextrose and amino acids, resulting in separation of the lipid emulsion into oil and water [51].

A large dose of PN lipid can result in reticuloendothelial system blockade, which aggravates the infection risk and is exacerbated by rapid "piggyback" infusion techniques, and is ameliorated by slower continuous infusion. Lipid administration should not exceed 1 g/kg per day using the pre-hospital dry weight, and should be given over a period of 24 h if possible [50, 52].

Considerations for protein supplementation

Hyperammonemia results from the production of ammonia in the gut and kidneys and the decreased breakdown by the liver and skeletal muscle, which is caused by sarcopenia in malnourished patients with liver disease. It is well known that ammonia is directly toxic to brain astrocytes. This effect definitely contributes to HE. In addition, inflammation, infection and oxidative stress also play a role [53].

The protein intake should not be limited, as this may aggravate protein deficiency, and improvement in the nitrogen balance may be achieved without aggravating HE [54]. Supplementation with vegetable-sourced, rather than animal-sourced protein may be advantageous [55].

In practice, whole-protein formulas are generally recommended, and BCAA-enriched formulas should be used in patients who develop HE during re-feeding. The protein intake should be at least 1 g/kg/day initially, and then the 24-h urinary urea nitrogen level can be measured to assess the catabolic rate in patients with normal renal function. Further increases in protein intake can be adjusted accordingly. Progressive increases in protein supplementation should be implemented, up to 1.8-2.0 g/kg/day, as tolerated [52, 55].

Branched-chain amino acid supplementation

Branched-chain amino acid supplementation (leucine, isoleucine and valine) are not metabolized by the liver, and thus are preferentially used as amino acid sources in patients with liver failure. On the other hand, aromatic amino acids (AAAs) (phenylalanine, tryptophan and tyrosine) are not metabolized effectively in patients with liver failure, and thus accumulate [55–57]. The expected ratio, the so-called Fisher's ratio, or the BCAAs/tyrosine ratio (BTR) should be 3.5:1; however, this ratio often falls to 1:1 in patients with ESLD, allowing preferential transport of the AAAs to occur across the blood–brain barrier [56]. The AAAs are then metabolized to octopamine, phenylethylamine and phenylethanolamine, which are weak false neurotransmitters that inhibit the excitatory stimulation of the brain, competing with endogenous neurotransmitters, thus aggravating HE [56, 57]. In addition, tryptophan is metabolized to 5-hydroxytryptophan (serotonin), which can produce further lethargy [56, 57]. There has been a debate on the use of BCAA-enriched versus standard amino acid formulas [58–60] based on the hypothesis that a decreased BTR contributes to HE [61]. However, the ESPEN guidelines do not recommend using specialized formulas [41, 42].

Branched-chain amino acid supplementation induce the secretion of hepatocyte growth factor and glutamine production [62, 63]. Leucine activates the mammalian target of rapamycin signaling pathway, thus inhibiting protein degradation and activating glycogen synthase [7, 12]. Shirabe et al. [64] reported that preoperative oral BCAA supplementation reduced the incidence of post-transplant bacteremia and sepsis in LDLT patients. Nakamura et al. [65] reported that the phagocytic functions of neutrophils and killer lymphocytes obtained from LC patients were restored by oral BCAAs supplementation.

Recently, a pre-LT BCAA-enriched formula has been demonstrated to lower ammonia, and to improve the albumin and prealbumin levels, the total lymphocyte count, BTR, glucose intolerance, liver regeneration, immune system function, maturation of dendritic cells and the ability of peripheral blood mononuclear cells to proliferate in response to mitogens, thus preventing post-operative sepsis [7, 64, 66].

The initiation of oral BCAAs in patients in the early stage of liver disease may contribute to solving current LT problems, such as the donor shortage, and the availability

of only small liver grafts for patients awaiting LDLT. The use of oral BCAAs might also play a role in improving the post-LT mortality by preserving the hepatic reserve of scheduled liver transplant recipients [67, 68].

Micronutrient supplementation

Patients with ESLD are susceptible to severe deficiencies in folate and pyridoxal-5′-phosphate, the biologically active vitamin B6. Thiamine liver stores are depleted in alcoholic and hepatitis C-related LC [70, 71]. This depletion is associated with increased brain ammonia concentrations due to decreased activity of α-ketoglutarate dehydrogenase, a rate-limiting tricarboxylic acid cycle enzyme [69, 70]. Deficiencies in antioxidant micronutrients (selenium, vitamin E, vitamin C) are related to oxidative stress, which is common in such patients [71].

A typical feature of alcoholic liver disease is an increasingly severe reduction in hepatic vitamin A stores, which sometimes leads to infertility and night blindness [71–73]. In vitamin A-deficient cirrhotic patients, the supplementation of vitamin A, even at relatively moderate doses, may further aggravate liver injury, since high-dose vitamin A preparations may be hepatotoxic due to their polar retinoid metabolites, which cause hepatocellular apoptosis and may promote fibrogenesis [72, 73].

Magnesium and zinc deficiency are also common in patients with decompensated LC due to their decreased absorption and diuretic-induced increased urinary excretion [32, 33]. Clinically, zinc deficiency presents with alterations of smell and taste, alterations in protein metabolism and encephalopathy. Zinc supplementation improves the glucose intolerance and decreases the ammonia levels [32, 33, 74].

Bitetto et al. [75] observed that vitamin D may act as an immune modulator in LT, favoring the immune tolerance of the liver allograft. In addition, Bitetto et al. found that early vitamin D supplementation was independently associated with a lack of acute rejection, which is important, because low vitamin D levels are prevalent among LT candidates.

On the other hand, an excess of micronutrients can also be dangerous. Serum ferritin is associated with increased body iron, or can be a consequence of systemic necroinflammatory states. The level of serum ferritin can therefore serve as a predictor of mortality in LC patients [76].

Correction of liver osteodystrophy

Osteopenia and osteoporosis are highly prevalent in patients with ESLD, and represent a major cause of morbidity before and after LT [77]. These can be caused by hormonal changes in parathormone and calcitonin, increased circulating levels of bilirubin and cytokines, corticosteroids, and the use of immunosuppressive therapy in cholestatic diseases [78, 79]. Ingestion of alcohol can directly and indirectly promote bone loss; however, a poor diet, physical inactivity and the degree of liver insufficiency further contribute to the deterioration of bone [77, 78].

LT candidates should be encouraged to consume foods high in calcium and vitamin D. If consumption is low, calcium and vitamin D supplementation (1,200–1,500 mg/day) is highly recommended for patients with osteopenia, and should be given in combination with bisphosphonates for patients with established osteoporosis and/or a history of fractures. If steatorrhea is diagnosed, water-miscible forms of fat-soluble vitamins, including vitamin D, should be prescribed [79].

Protein metabolism generates a large amount of acid, which must be buffered by the skeleton and kidneys. The skeleton responds to high serum acidity by releasing a buffering agent, calcium, into the bloodstream, activating bone resorption. With more calcium entering the bloodstream, the kidneys respond by increasing urinary excretion, resulting in a net loss of calcium. There is also a link between high-fat diets and bone loss, as fat is suggested to inhibit osteoblast formation [77, 78].

Over-supplementation and the physical rehabilitation program

Patients with liver diseases commonly suffer from morbid obesity because of continued oral intake, along with the limitations in physical activity that are often recommended due to fear that exertion would hasten the progression of ESLD or worsen the complications. However, exercise has been documented to have no significant adverse effects on liver function tests or on symptoms. In fact, the adverse effects of inactivity and bed rest may not only worsen the complications of reduced physical functioning, muscle wasting and osteopenia, but may also be linked to decreased post-LT success [80, 81].

Obesity is also considered to be a predictor of hepatic steatosis in deceased [82] and living donors [13]. A fatty donor liver is strongly linked to decreased allograft function and decreased patient survival [83], and the presence of a fatty liver is the main reason for the discarding of potential donor livers [82]. Pre-LT obese patients may be more likely to have primary graft dysfunction or delayed graft function after LT [84, 85]. Weight loss is used to reduce the amount of liver fat among obese patients [84].

Dietitians need to resist the temptation to reach the impractical goal of producing anabolism. Attempts to replete the malnourished, metabolically stressed, pre-LT patient in excess of the patient's energy expenditure lead to

hyperglycemia and an increased incidence of infection. The goal of nutritional support for a patient with liver failure is to provide adequate protein and energy that is equivalent to, or slightly less than, the patient's energy expenditure. Therefore, energy restriction to 1,500 kcal/day is routinely used to encourage the mobilization of native fat stores [86].

Recently, a rehabilitation program has been introduced to encourage early post-operative mobilization and avert pulmonary dysfunction. Because LDLT is an elective procedure that differs from DDLT, a pre-LT rehabilitation program can be implemented until the day of LT [7].

Immunonutrition

The use of an immunomodulating diet (IMD) as a part of EN or PN is based on its downregulation of inflammatory cytokine production, its modulation of eicosanoid synthesis and its amelioration of post-LT immunosuppression, rather than its effects on nutrition per se [87, 88].

Glutamine dipeptide, arginine, nucleotides and ω-3 fatty acids (fish oil emulsion) intake have been suggested to minimize the ischemia or reperfusion damage of the donor organ [11, 64, 89]. Arginine stimulates the release of growth hormone and insulin, improves the nitrogen balance, promotes wound healing, strengthens immune function and enhances nitric oxide biosynthesis [87].

An IMD enriched with hydrolyzed whey peptide (HWP) (MEIN®; Meiji Dairies Co., Tokyo, Japan), which is a protein complex derived from milk, has been proven to decrease post-LT bacteremia, infections and mortality compared with a conventional elemental diet [90]. These benefits have been attributed to the antioxidant, antihypertensive, antiviral, antiinflammatory and antibacterial properties of HWP because it is rich in lactoferrin, β-lactoglobulin, α-lactalbumin, glycomacropeptide and immunoglobulins [11, 91]. Lactoferrin protects against the development of hepatitis caused by the sensitization of Kupffer cells by lipopolysaccharide, and inhibits the production of inflammatory cytokines, such as TNF-α, IL-1β and IL-6, by monocytes [4, 7, 74].

The considerable amount of steroids administered to patients after LT, as well as surgical diabetes and insulin resistance, can cause intra- and post-operative hyperglycemia, which has been associated with surgical site infections [92]. An IMD enriched with HWP contains isomaltulose disaccharide (glucose plus fructose with a glycosidic bond). Isomaltulose is often used instead of sugar in diets for patients with diabetes mellitus, since it prevents post-prandial hyperglycemia due to slow resolution. An IMD enriched with HWP has been found to significantly decrease the incidence of post-LT hyperglycemia [90, 92].

Patients undergoing emergency LDLT for acute liver failure (ALF) have little time to receive nutritional intervention. Therefore, early EN with an IMD enriched with HWP could be a good method to prevent post-LT complications due to infections [90].

Use of synbiotics

The bacterial translocation occurring in LC patients is usually related to bacterial overgrowth, increased intestinal permeability and immune alterations, and leads to intestinal edema, decreased peristalsis and infection. It also contributes to the pathogenesis of a hyperdynamic circulatory state and multiple organ dysfunction via pro-inflammatory cytokine responses [12, 93].

Probiotics are living bacteria found in fermented beverages, yogurt and sauerkraut that foster a hostile colonic environment against "bad" bacteria. Prebiotics are non-digestible dietary fiber that pass unchanged through the gastrointestinal tract and nourish probiotics. Synbiotics are a combination of both of these materials [94].

Sugawara et al. [95] reported that preoperative oral administration of synbiotics can enhance the immune response, attenuate the systemic post-operative inflammatory response and decrease the occurrence of post-LT infection and the duration of antibiotic therapy. These benefits of synbiotics are attributed to the ability of *Lactobacillus* to initiate immunoglobulin production, restore macrophage function, stimulate apoptosis and modulate lymphocyte function. In addition, *Lactobacillus* has been reported to attenuate cytokine release, increase mucin production, eliminate toxins and stimulate mucosal growth [96].

Probiotics such as *Enterococcus faecalis*, *Clostridium butyricum*, *Escherichia coli* strain Nissle 1917, *Lactobacillus casei* strain Shirota, *Bacillus mesentericus*, *Lactobacillus* and *Bifidobacterium* with fructooligosaccharides can all alter the gut microbiota, prevent bacterial translocation, decrease endotoxin levels and restore neutrophil phagocytic capacity [94], since the neutrophil function is impaired by endotoxemia upon bacterial translocation in patients with LC [97].

Lower ammonia levels, significant rates of minimal HE reversal and good adherence by patients, with greater improvement in all neuropsychological tests, have all been observed upon the use of probiotics compared with the use of conventional lactulose [98]. Furthermore, lactulose treatment was associated with occasional abdominal pain, cramping, diarrhea and flatulence. Synbiotic supplements were free of such adverse effects [98–100].

Nocturnal meals

Periods of fasting should be avoided in cirrhotic patients. Frequent meals should be implemented to combat a

catabolic state during the overnight fasting period. For this reason, nocturnal supplementation with a small bedtime snack and nocturnal glucose supplementation increase the carbohydrate, along with decreased lipid and protein oxidation rates the next morning, without significant BEE changes, thus improving the nitrogen balance and total body protein gain, helping to prevent catabolic states and undernutrition [101–103]. It has been reported that nocturnal BCAAs administration as a late evening snack improves the serum albumin level and glucose tolerance in LC patients [103].

Nutritional support after liver transplantation (during the immediate post-LT period and short-term after LT)

Nutritional changes after liver transplantation

The total body water decreases and body fat increases after LT, whereas the BCM remains unchanged [104]. Deficiencies in vitamin A and zinc immediately normalize after LT [105, 106]. Although an increased BEE may persist for a long period after LT [105, 107], overweight status and hypercholesterolemia have been observed after LT [107], accompanied by an increase in the saturated fatty acid content of fat tissue [106].

In children, malnutrition and growth retardation are usually present in all cases before LT. Anthropometry derangement recovers as soon as 6 months after LT. Height recovery occurs later [108]. A marked catch-up growth is observed in the children with the most severe growth retardation before LT; however, some children experience failure to thrive even after LT [109].

The nutritional status after LT depends on the allograft function; if the allograft fails or is rejected, many of the nutritional derangements present before LT will persist. Even in a well-functioning graft, some nutritional disturbances are not completely normalized in the long term after LT. Increased protein breakdown is often present during the first 2 weeks post-LT; thus, optimizing the nutrient intake over this period is needed to promote wound healing and hepatocyte recovery [106, 110].

The goal of nutrition therapy in the acute post-LT phase is to ensure adequate protein and calorie provision to avoid protein breakdown [111]. Hypermetabolism has been found to be predictive of the transplant-free survival, independently of the MELD and Child-Pugh scores, and tends to persist for at least a year post-OLT [112].

Patients with ALF are generally well nourished and do not have a pre-hospital history of weight loss. Patients without protein-calorie malnutrition will tolerate 5–6 days of NPO before needing nutritional support. Malnourished patients should start nutritional support sooner. Withholding nutritional support and inducing a cumulative caloric deficit of over 10,000 kcal has been associated with decreased survival [86].

Resuming EN within 12 h of LT has been shown to reduce post-operative viral infections and to produce better nitrogen retention. Patients should be advanced from nutritional support to an oral diet using smaller and more frequent feedings as soon as tolerated after LT. EN should not be discontinued until patients are able to maintain an adequate oral intake consistent with their nutritional requirements [10–12].

The intraoperative placement of the tip of the feeding tube in the proximal jejunum allows early EN after LT. For adult LDLT recipients, Kaido et al. [10–12, 113] described, in detail, an early post-operative EN regimen using a 9F Witzel enteral tube jejunostomy placed in the proximal jejunum at surgery, through which EN was started within 24 h after surgery. The starting total daily caloric intake until post-operative day (POD) 3 was 10–15 kcal/kg, which was gradually increased to 25–35 kcal/kg using an IMD enriched with HWP (MEIN®; Meiji Dairies Co., Tokyo, Japan). The initial infusion rate was 20 mL/h. If well tolerated, this was increased to 40 mL/h by POD 5. In cases of severe edema of the small intestine or severe diarrhea, the speed of IMD was decreased to 20 mL/h (=20 kcal/h) or an oral rehydration solution was used. After confirmation of the improvement of the edema or diarrhea, the regimen was resumed. Oral nutrition was started after the swallowing function was confirmed, usually around POD 5. Dietitians calculated the daily amounts of protein and carbohydrates required for each recipient and adjusted the speed of the EN according to the patient's oral intake. EN was stopped when the patient could tolerate adequate oral intake containing solid food. All patients resumed preoperative synbiotic supplementation (i.e., GFO®; Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily and a lactic-fermented beverage once a day via the feeding tube or orally until discharge. This technique allowed for long-term feeding without discomfort or the risk of pneumonia carried by trans-nasal feeding, and avoided the need for concomitant TPN, with its risk of infection.

The glucose utilization by the transplanted liver is reduced in the first hours of engraftment due to impaired mitochondrial respiration and inactivity of the tricarboxylic acid cycle [114]. During this time, energy is generated mostly from fatty acid oxidation. After approximately 6 h, a shift from fat to glucose utilization occurs in normally functioning liver grafts, while a failing liver continues to utilize mainly fat [114, 115]. Glucose administration immediately after OLT has been recommended in small quantities and without insulin to avoid suppressing the peripheral fat mobilization, judged clinically by the blood

glucose, lactate and triglyceride levels and by the arterial ketone bodies [114, 115].

The energy requirements are not elevated in the uncomplicated patient after LT. Therefore, calories should be provided at approximately 120–130 % of the calculated BEE [116, 117]. On the other hand, due to the elevated nitrogen loss upon increased protein catabolism during the acute post-LT phase due to steroids, LT patients should receive 1.5–2.0 g of protein per kilogram of dry (pre-hospital) weight to facilitate the repletion of the muscle mass [118]. Diabetic patients with liver failure receiving EN should be covered with a long-acting isophane insulin suspension on a sliding scale for episodes of hyperglycemia [119].

Metabolic alkalosis and depletion of the serum potassium, phosphorus and magnesium levels often occur in the acute post-LT period due to routine chronic diuretic use in cirrhotic patients, so the amount of fluid from abdominal drains, gastrointestinal losses or fluid overload should be monitored. Ninety percent of cases of metabolic alkalosis are chloride-sensitive and easily correctable. Chloride can be delivered using TPN as a vehicle [10–12, 113].

Long-term nutritional support after liver transplantation

Metabolic syndrome, hyperlipidemia and obesity are common in patients after the first 6 months post-LT, especially those with immobility, and are associated with an increased risk of major vascular events, diabetes mellitus, hypertension, cancer and the progression of fibrosis. These conditions contribute to the long-term morbidity and mortality [7, 48, 119, 120].

The weight gain generally occurs between 2 and 16 months after LT, and has been attributed to the appetite stimulation by corticosteroids. Immediately after LT, patients are often instructed to ingest a high-protein, high-calorie diet to counteract the weight loss associated with pre-LT cachexia and increased energy requirements for surgical recovery, but this can induce unwanted weight gain. Depressive moods have also been implicated in over- and under-eating and should be considered a factor in LT recipients. Therefore, patients should be instructed on a diet that promotes a healthy body composition which is low in fat, with adequate amounts of lean protein to promote muscle gain. Calories should be sufficient to spare protein from being used as energy, yet not in excess of energy requirements. Regular follow-up with a dietitian will help ensure patient compliance. Dietitians should frequently re-assess the nutritional status to optimize the patient's diet during the transition from the acute to chronic post-LT phase [42, 50, 121–123].

Tacrolimus is thought to be associated with a less adverse cardiovascular risk profile than cyclosporine, with a significantly reduced prevalence of hypertension, hypercholesterolemia and obesity, together with significantly lower triglyceride levels. Corticosteroids also contribute to post-LT disturbances of these parameters. In patients with stable graft function, withdrawal of prednisolone over time reduces the prevalence of such disorders [112, 119]. Long-term administration of glucocorticoids results in lipid accumulation, weight gain, osteoporosis and muscle wasting by impairing the resting energy expenditure and substrate oxidation rates. Insulin resistance, the post-operative cytokine response and a post-menopausal status in females are other suggested mechanisms that inhibit a gain of muscle mass after LT [124].

Standard recommendations after LT include a "no added salt" diet (3 g sodium/day) to prevent water retention associated with steroid therapy. However, health professionals often encourage the addition of flavoring agents, including sodium, to foods to improve their taste to promote appetite. Therefore, the sodium intake may be higher than suspected [86].

Several risk factors for bone loss after LT include steroid use, malnutrition, muscle wasting, immobilization, pre-LT osteopenia or osteoporosis, previous fractures and immunosuppressive agents. Bone loss occurs mostly within the first three to 6 months after LT, and increases the risk of fractures within the first year. However, the osteopenia related to cholestasis tends to become stable at 1 year after LT following improved allograft function. Bisphosphonates may prevent bone loss after LT [79, 125–127].

Conclusion

Accurate assessment of the nutritional status and adequate intervention are prerequisites for perioperative nutritional treatment in patients who undergo LT. However, the metabolic abnormalities induced by liver failure make the traditional assessment of the nutritional status difficult. The presence of preoperative malnutrition and sarcopenia estimated by recently developed body BIA have a significant negative impact on the post-liver transplantation outcome. It is essential to provide adequate nutritional support during all phases of liver transplantation, including the preoperative administration of a BCAA-enriched nutrient mixture and the post-operative use of an IMD enriched with HWP. Perioperative nutritional therapy is indispensable to improve the outcomes after LT.

Conflict of interest None of the authors of this manuscript have any conflicts of interest to disclose.

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