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EDITORIAL

NUTRITIONAL STATUS IN FRAIL CIRRHOTIC PATIENTS UNDERGOING LIVER TRANSPLANTATION

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The liver is the largest and most important metabolic organ, playing a pivotal role in the integration of biochemical pathways of carbohydrates, fats, proteins, and vitamins (1). End-stage liver disease (ESLD) has an important negative effect on nutritional status (2) and malnutrition is a common problem in patients waiting for liver transplantation (LT). The mean weight loss during ESLD is about 9 Kg and this contributes to further morbidities and mortality (3).

The etiology of malnutrition in ESLD is multifactorial:

i) abnormal nutrient and caloric intakes secondary to anorexia (often related to unpalatable diets with sodium restriction), early satiety, and increased proinflammatory cytokine levels;
ii) malabsorption secondary to reduction in biliary salt pool, impaired bowel motility (which also promote bacterial proliferation) and portal hypertension;
iii) iatrogenic factors (i.e. assumption of antibiotics as neomycin);
iv) increased energy expenditure, although still debated (3, 4).

The decrease in liver glycogen stores activates gluconeogenesis to support the metabolic necessity (5). Thus, lipolysis (6) and proteolysis (7) are activated in order to guarantee the availability of glycerol and amino acids (for gluconeogenesis) and free fatty acids (as alternative energy source). Unfortunately, these processes have the negative effect of causing muscle wasting, which is further aggravated by ammonia (8). It is not surprising that the prevalence of muscle loss in liver cirrhosis is extremely high, and reported ranging between 10% and 70% according to gender and severity of liver failure (2). Such estimates are probably underestimated due to the fact that peripheral edema or associated obesity may mask the muscle atrophy (9-11).

The depletion of muscle mass in cirrhotic patients is an independent predictor of survival, quality of life, outcome and response to stress and surgery (12, 13). It deeply contributes at generating a state of precarious homeostasis, rendering the cirrhotic patients highly vulnerable even to slight stressor, or frail (14). This condition of frailty is surely driven by the severity of the cirrhosis but is also determined by the wide spectrum of age-related conditions (15, 16). In the last years, many tools have been used to measure frailty in ESLD, and even a specific Liver Frailty Index has been developed (17).

Patients with ESLD should have adequate protein intake (about 1.2-1.5 g/kg /daily) (3) to avoid the progression of muscle wasting and protein deficiency. LT leads to a significant improvement in nutritional deficiencies and metabolic disorders. However, pre-transplant frailty does not reverse completely after the intervention. Moreover, transplant surgery is a major stressor for the body, which may even transiently experience a worsening of the frailty despite the reversal of the liver failure (15).

In the early post-surgical period, protein catabolism is noticeably (but temporarily) increased, as shown by the urinary excretion of great amounts of nitrogen. Protein requirements in the first weeks after surgery are of 1.5-2.0 g/kg/daily. Furthermore, electrolytes abnormalities (due to abdominal drains, gastrointestinal losses, fluids overload, and diuretics) should be constantly monitored (1, 3).

Modifications in the energy metabolism may also play a role in the changes of nutritional status after LT. However, evidence on the resting energy expenditure in the pre-surgery period is still quite controversial (18-21).

Nonprotein energy requirements vary according to the metabolic and inflammatory status (1). When indirect calorimetry is not available, physicians should estimate a caloric need of 25-30 kcal/kg/daily (1, 22).

Enteral nutrition after LT is advisable when the patient is hemodynamically stable and does not present nausea or vomiting. LT patients should be advised to avoid fasting during the day, and encouraged at consuming small, frequent meals to reduce protein catabolism. These recommendations seem to improve quality of life and survival (23-27).

Most of the weight gain generally occurs during the first 6 months after LT. However, patients do not completely stop gaining weight also for the subsequent years. Fat mass progressively increases whereas muscle mass does not. Consequently, a sarcopenic condition may still residue after LT and concurs at increasing the individual's risk profile for negative health-related outcomes (28-30). At the same time, the excessive accumulation of adipose tissue can trigger the onset

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of or worsen hypertension, dyslipidemia and diabetes mellitus (31).

The immunosuppressant therapy prescribed after LT also exert substantial metabolic effects. Corticosteroids increase appetite and centripetal fat deposition, decrease fat oxidation and promote proteolysis. Calcineurin inhibitors, such as cyclosporine and tacrolimus, impair muscle growth and muscle regeneration by inhibiting calcineurin in the muscle and stopping its differentiation. Moreover, cyclosporine is an independent predictor of weight gain. Sirolimus and everolimus inhibit the mammalian target of rapamycin complex (m-TOR), consequently compromising the protein synthesis (3). Patients need to receive nutritional advice for avoiding foods interactions with immunosuppressants (grapefruit, pomegranates, or Seville oranges) (32-34).

Osteoporosis is another important metabolic complication occurring after LT. The amount of bone loss varies (from 1.4 to 24%) (1). However, preexisting osteopenia/osteoporosis are certainly risk factors for aggravating bone loss after LT as well as prolonged immobilization, malnutrition and immunosuppressants. No pre- or post-transplant parameter of bone metabolism or hepatic function can be mentioned as robust predictor of the entity of bone loss after surgery. The incidence of pathologic fractures (20-30%) is particularly high during the first year of follow-up. For these reasons, patients should receive 1000–1200 mg of elemental calcium daily (depending on their age) and at least 400–800 IU of vitamin D daily (1, 35).

In conclusion, patients with ESLD waiting for LT, show several nutritional and metabolic disorders that are associated with an increased risk of morbidity and mortality after LT. Patients with ESLD are extremely complex and represent clear candidates for designing multidisciplinary, adapted care models for the management of their frailty status (36). In this context, a closer collaboration and interaction among the involved healthcare professionals and disciplines is amenable.

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