Editorial on Nutrition

Importance of sarcopenia parameter changes after living donor liver transplantation

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The systemic role of muscle tissue is strengthened by the large system of hormones, chemokines and other mediators that constitute a dense network of communication between the skeletal muscle and the liver (1,2).

This, associated with the evidence of a progressive malnutrition and depletion of muscle mass in end-stage liver disease (ESLD) patients, has led many to study the role of sarcopenia and its systemic effects in this setting, and to identify it as critical risk factor for post- liver transplantation (LT) mortality (3-5).

Englesbe and colleagues found a direct correlation between central sarcopenia, measured by computerized tomography (CT), the total area of the psoas muscle (psoas area right side + left side), and post-LT mortality in 163 patients (6). CT measurement of the psoas area is a standardized method, but its invasiveness (which does not allow for seriate follow-up at short time intervals), and the analysis limited to a minimum part of the skeletal muscle tissue, affects the reliability of the study. One Japanese study by Kaido *et al.*, in 2012, overcame this limitation by estimating body composition as a whole through the use of bioelectrical impedance analysis (BIA). They showed that a reduction of the values of the body cell mass (BCM), defined as the intracellular water and the sum of the fat free body mass, among which viscera and muscular tissue, excluding bone mineral, is an independent risk factor for sepsis and mortality from infections in patients who underwent living donor liver transplantation (LDLT) (7).

The same group, building on its previous results, did a retrospective study of 124 patients who underwent LDLT in order to determine the role of sarcopenia on transplantation outcome. To measure of the degree of sarcopenia they again used segmental BIA, measuring not only the BCM, but also the skeletal muscle mass (SMM). Analysis of the results found that both patients with low BCM and patients with low SMM presented survival rates (up to 60 months post-LDLT) that were significantly lower than patients with normal/high values of BCM or SMM. Sarcopenia, identified as low BCM or SMM, was an independent risk factor for post-LDLT mortality (8).

This study also had limitations: it was retrospective, had a low number of patients, and lacked data for patients with acute liver failure and, above all, used only BIA to define the degree of sarcopenia, which seems to be greatest limitation, as underscored by Safer *et al.* (9). In particular, BIA does not allow us to define sarcopenia, as the European Working Group on Sarcopenia (10) and the Asian Working Group for Sarcopenia (11) have pointed out. Both groups consider not only a reduction in muscle mass as a necessary condition, but also a reduction in muscle strength, and failure of physical performance.

In their latest paper, Kaido and colleagues overcame some of the limitations of their previous studies by prospectively analyzing 72 patients who underwent LDLT

between January, 2013 and October, 2015 (12). Essential exclusion criteria for the study, also tested as a new criterion of exclusion for LT, was a severe degree of sarcopenia, defined as an inability to walk unaided. Similarly to their previous work, SMM was calculated using BIA, while muscle strength was evaluated by grip strength tests. Of the 72 patients, 10 were defined as pre-LDLT sarcopenia patients.

They had an overall survival of 94% at one year, exceeding the 80% reported for similar populations belonging to the same transplant center. This seems to bolster the idea of considering severe sarcopenia as an exclusion criterion for LT. There was a very low survival rate at one year for sarcopenic patients (60%), significantly lower than non-sarcopenic patients. Finally, all the patients had reduced SMM and GS in post-LDLT, with recovery to the pre-LDLT level of about 12 months, and 6 months, respectively.

These data are in line with results of a study by Tsien *et al.* of 53 deceased brain donor liver transplantation (DDLT) recipients; of these, only 2 of 33 patients with sarcopenia pre-DDLT (defined on the basis of the sum of the psoas, para-spinal and abdominal wall muscles to L4 muscles obtained by CT) had a post-DDLT recovery, while 75% (15 patients) of the non-sarcopenic patients developed this condition pre-DDLT (13), possibly due to a post-DDLT upregulation of myostatin, a potent mediator of muscle depletion, high levels of which seem to be linked to hyperammonemia in patients with ESLD (14).

In addition to myostatin, other potential causes of post-LT sarcopenia appear to be the progressive metabolic syndrome development, immunosuppressive therapy, recurrence of hepatopathy, and the occurrence of sarcopenic-related diseases. Because sarcopenia post-LT is likely multifactorial, the question arises, as to whether this is a consequence post-LT (13), or whether it can, in some way, be prevented by reducing some of the variables mentioned above.

A recent study at the University of Pittsburgh by Bergerson *et al.* deepened precisely this aspect (15). Retrospectively selecting 40 patients who underwent LT, CT images of which were available in the pre-LT and in the post-LT period so as to determine the skeletal muscle index, the authors found not only that the total sarcopenia did not worsen post-LT, but reduced from 55% pre-LT to 30% post-LT (an improvement, but not statistically significant). These results, while surely interesting, were obtained by excluding all those patients who in the post-LT course had developed conditions potentially capable of leading to sarcopenia (e.g., occurrence of liver disease, chronic renal failure, *de novo* neoplasm, sepsis, stenosis of the biliary tract). Though this population does not represent the real population of patients undergoing LT, the results suggest that sarcopenia is potentially reversible.

With the potential reversibility of sarcopenia, and its close association with protein-energy malnutrition, perioperative nutritional support is one of the possible means of preventing excess morbidity and mortality. Both sarcopenia and malnutrition can predispose to post-operative infections (e.g., bacteremia, sepsis, pneumonia) or to dehiscence of the surgical wound (15). The Kaido study underscores that perioperative nutritional support (from 15 days before to 92 days after LDLT) can positively affect LT outcome, significantly affecting (P=0.018) survival of patients with low SMM, or loss of BCM pre-LDLT (16).

Pre-LT nutritional intervention for patients undergoing LDLT should aim to prevent the loss of nutrients and SMM. An intake supplementation for at least 15 days pre-LT and preferably enterally by means of fortified food compounds of branched chain amino acids, glutamine, fibers, and oligosaccharides, supported by rich probiotic drinks would seem to be adequate (8), attempting to keep the caloric intake at least 1.2 times higher than the basal energy expenditure, as reported by the European Society for Parenteral and Enteral Nutrition (ESPEN) guidelines (3).

Post-LT, even with a perfectly functioning graft, there is persistence of an excessive protein catabolism. For this reason, the outcome of nutritional support should be the prevention of protein degradation, ensuring an adequate caloric and protein intake (6). Early (within 12 hours of LT and through the use of feeding tubes) enteral nutrition recovery seems to prevent viral infections (8), and improve the overall outcome if maintained until the patient is able to resume adequate intake of nutrients per os (9).

Post-LT physical activity should be aimed at restoring muscle tone, increased aerobic capacity, reducing obesity and insulin resistance and, ultimately, counteracting the effects of the accumulation of visceral adipose tissue and intrahepatic fat (1). The effect of sarcopenia pre- and post-LT in defining the outcomes of transplantation has been established, as has the need to correct it with nutritional and rehabilitative interventions. Hamaguchi and colleagues for example, have shown that not only SMM, but also steatosis of striated muscle, is an independent risk factor for mortality in LDLT. The same authors have proposed a new system, Muscle Model for End-Stage Liver Disease

(M-MELD) score, to predict post-LDLT mortality (3).

Through analysis of the receiver operator characteristic curve, the cut-off for Muscle-MELD was set at a value of 43.2. Analysis of survival evidenced the overall survival of patients with low M-MELD scores were higher than those of the patients with high M-MELD, and that the latter was identified as risk factor for mortality at 6 months. Though fascinating, this study has several limitations, including its retrospective design and an incorrect definition of sarcopenia with respect to the already-mentioned definitions (10,11).

In conclusion, sarcopenia pre or post-LT still is one of the most relevant unsolved problems in improving the outcomes of LT patients. It should therefore be mandatory: (I) to define a predictive model of post-LT survival that takes into account SMM and the quality of striated muscle; (II) to redefine the criteria for exclusion from the waiting list for LT, defining an objective parameter for identification of severe sarcopenia; (III) to determine appropriate nutritional support and rehabilitation programs pre- LT available not only for candidates for LDLT (with a scheduled OR date), but also for DDLT candidates; (IV) and to identify the nutritional support programs and rehabilitation post-LT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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