Editorial on Nutrition

Is sarcopenia a prognostic factor after living donor liver transplantation?

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We read with great interest the article by Kaido *et al.* (1) entitled "Effects of Pretransplant Sarcopenia and Sequential Changes in Sarcopenic Parameters after Living Donor Liver Transplantation," published in the journal *Nutrition*. The authors previously reported that the preoperative skeletal muscle mass (SMM) was significantly correlated with the branched-chain amino acid (BCAA) to tyrosine ratio and the body cell mass (2). They also found that a low preoperative SMM was an independent risk factor for mortality after a living donor liver transplantation (LDLT) (2). Therefore, they conducted this prospective clinical study to investigate the effects of pretransplant sarcopenia on survival, and to examine any sequential changes in the sarcopenic parameters after an LDLT. In this article, sarcopenia was defined by measuring the SMM and grip strength (GS). The overall survival rates after an LDLT were significantly lower in those patients with sarcopenia than in those without sarcopenia ($P<0.001$). Based on the recovery after an LDLT, the GS returned to the preoperative levels more smoothly than the SMM (1).

Sarcopenia was initially described by Rosenberg in 1989 as an age-related decrease in the SMM (3). Today, sarcopenia is defined as a syndrome characterized by both a low SMM and low muscle function (4). The pathogenesis of sarcopenia in end-stage liver disease (ELD) is multifactorial, and has not been fully investigated. In ELD patients, the usual mechanisms that cause sarcopenia include an inadequate dietary intake, metabolic disturbances, and malabsorption (5). According to the SMM loss mechanism in ELD patients, there are several theories concerning the reduction in the SMM. For example, the primary source of amino acids for gluconeogenesis is proteolysis in the skeletal muscle, which generates both aromatic amino acids (AAAs) and BCAAs. However, only BCAAs are catabolized in the skeletal muscle, due to the localization of the branched-chain ketodehydrogenase and the oxidation of the carbon skeleton as an energy source. In contrast, AAAs are primarily metabolized in the liver, due to the portosystemic shunt and hepatocellular dysfunction. The amino acid imbalance promotes bioenergetic perturbations in ELD patients; therefore, the skeletal muscle starvation is accelerated and the SMM decreases (6). Ammonia is also generated by a number of mechanisms, including amino acid metabolism, purine metabolism, enterocyte glutaminase activity, and urea lysis in the gut. Although ammonia is well-known as a neurotoxic substance in ELD patients, ammonia in the skeletal muscle activates some intracellular signaling that contributes to sarcopenia (6). Based on these factors, the authors employed preoperative nutrient therapy using a nutrient mixture enriched with BCAAs and a symbiotic supplement enriched with glutamine to prevent or improve sarcopenia in this study.

Sarcopenia is not exclusively present in all underweight patients, and constitutes a hidden condition that can be present in ELD patients with any BMI (7). Moreover, the BMI is often affected by fluid retention from ascites and edema; therefore, cross-sectional studies including CT or MRI scans are warranted to quantify the SMM (7). In addition,

dual-energy X-ray absorptiometry (DXA) and a bioelectrical impedance analysis (BIA) are sometimes employed to define a low SMM for a sarcopenia diagnosis (8). Although DXA may be the most widely used method for the SMM assessment in many sarcopenia studies, a BIA is suitable, based on its portability, reasonable cost, fast processing, noninvasiveness, radiation-free function, and convenience (8). Based on these reasons, the authors employed CT and BIA to estimate the SMM of debilitated ELD patients. Unfortunately, it may be insufficient to define sarcopenia based on the SMM. Therefore, most investigators usually estimate the muscle strength; for instance, the GS has been widely used because it is inexpensive, easy to use, and is well correlated with most relevant health outcomes (8). However, the leg strength is more closely related to physical functions, like standing and walking. Overall, more feasible and reliable total body strength tests should be developed and validated. Because there is no clear linear relationship between the SMM and muscle strength that provides a basis for adopting both criteria for sarcopenia, an objective, available, and reproducible scoring system is lacking at this moment.

Emerging evidence suggests that sarcopenia is independently associated with a poor prognosis in many cancers, and linked with morbidity, mortality, and cancer recurrence after surgery (9). The author's institute previously evaluated intramuscular adiposity as a new parameter of sarcopenia, and showed that muscle steatosis was an independent risk factor for poor outcomes in patients having undergone an LDLT or hepatectomy for hepatocellular carcinoma (1,9). In this study, pretransplant sarcopenia negatively affected the short-term outcomes, including the one-year overall survival. It is believed that sarcopenia is associated with increased morbidity and mortality in ELD patients; however, it has also been reported that preoperative sarcopenia does not increase mortality after an LDLT (8). In some cases, it resolves after an LDLT; therefore, the way in which it impacts post-LDLT patients is now under debate, requiring further investigation.

In summary, the authors first confirmed that pretransplant sarcopenia is associated with the overall survival after an LDLT. This result provides an important message about the necessity of new inclusion criteria for LDLT patients that incorporate concrete factors associated with sarcopenia, such as the SMM and GS (1). In addition, the slow recovery of the SMM after an LDLT, due to the severe depletion of the skeletal muscle proteins, suggests that not only perioperative but also long-term intervention via rehabilitation and nutritional therapy is required for the earlier recovery of LDLT patients.

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Footnote

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

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