Editorial on Nutrition

Sarcopenia in liver transplant recipients: its relevance to peritransplant morbidity and mortality

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Introduction

Sarcopenia is defined as the loss of not only skeletal muscle mass but also its function (1). Although sarcopenia is mainly associated with aging, it may also be accompanied by chronic wasting illnesses such as cancer cachexia and end-stage liver disease (2). Most patients awaiting liver transplantation are more or less in a state of sarcopenia. As the disease has progressed and the patient becomes wheelchair-bound, that patient must be in a serious state of sarcopenia. Recently, investigations into the relationship between sarcopenia and outcomes of liver transplantation have attracted much attention because being in a state of sarcopenia has been reported to have a significant impact on the morbidity, the mortality, and the quality of life of the recipients after liver transplantation (3-7). Kaido *et al.* recently reported interesting facts regarding sarcopenia and liver transplantation—"effects of pretransplant sarcopenia and sequential changes in sarcopenic parameters after living donor liver transplantation." In this report, by assessing sarcopenia by bioimpedance analysis and hand grip, they revealed that the overall survival was significantly lower in sarcopenic patients, and that skeletal muscle mass rather decreased even after liver transplantation and did not return to the pretransplant level even 1 year after transplantation (8). I would like to summarize my opinions on their results by citing some relevant articles.

Assessment of sarcopenia in patients awaiting for liver transplantation

The European Working Group on Sarcopenia in Older People recommended that the definition of sarcopenia include not only low muscle mass but also low muscle function (1). The Asian Working Group for Sarcopenia (9) agreed that sarcopenia should be described as low muscle mass plus low muscle strength and/or low physical performance. They recommended cutoff values for muscle mass measurements (7.0 kg/m^2 for men and 5.4 kg/m^2 for women by using dual X-ray absorptiometry, and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women by using bioimpedance analysis), handgrip strength (<26 kg for men and <18 kg for women), and usual gait speed (<0.8 m/s).

The measurement of muscle mass using dual X-ray absorptiometry or bioimpedance analysis may be influenced by the status of fluid retention from which, manifested as ascites or systemic edema, almost all liver transplant candidates suffer at least to some degree (4). In addition, some patients might be in a state of hepatic encephalopathy or hepatopulmonary syndrome, which may affect the coordination of muscles or the duration of muscle sustain. Therefore, these conditions may affect the results of their handgrip strength and usual gait speed.

So far, measuring muscle mass by CT or MRI seems to be the best way in assessing skeletal muscle mass in liver

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transplant candidates (1), because these measurements are not only hardly influenced by the degree of fluid retention but also are completely objective. Therefore, many studies relating to sarcopenia in patients with end-stage liver disease were analyzed by the measurement of muscle mass by CT or MRI (4).

In order to compare studies relating to the impact of sarcopenia on outcomes of liver transplant recipients, it is necessary to standardize the assessment process of sarcopenia. Because almost all candidates for liver transplantation undergo abdominal CT as a preoperative work-up and a considerable number of these candidates have problems relating to water retention such as intractable ascites or systemic edema which may influence the results of dual X-ray absorptiometry or bioimpedance analysis, measuring muscle mass calculated by CT or MRI seems, at present, the best way in assessing sarcopenia of liver transplant candidates. Irrespective of patients' confused mental statuses caused by hepatic encephalopathy, patients' inabilities to stand unaided, or massive ascites, skeletal muscle mass can be measured in all patients.

Montano-Loza *et al.* used L3 skeletal mass index—the cross-sectional area of muscles consisting of the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis at the third lumbar vertebra normalized for stature—in assessing sarcopenia of liver transplant candidates (3). This measurement of a single abdominal image of the third lumbar vertebra is reported to provide an excellent estimation of the total body skeletal muscle (10). Now that software capable of instantaneously calculating such muscle areas on CT or MRI is broadly available, L3 skeletal mass index may be the first choice in assessing sarcopenia for liver transplant recipients. Ideally, each gender-specific cut-off value should be determined for each ethnicity.

It should be noted that only decreased skeletal muscle mass, by definition, does not necessarily mean sarcopenia. Diagnosing a patient as sarcopenia needs to describe not only decreased skeletal muscle mass but also decreased muscle function of that patient (1,9). If an investigator reports worse prognoses of liver transplant recipients only in view of skeletal muscle mass without describing muscle function, the condition should not be mentioned as sarcopenia, but should be directly mentioned as "the state of decreased skeletal muscle mass."

Impact of pretransplant sarcopenia on mortality in liver transplantation

It has been reported that the longer the duration on a waiting list for liver transplantation, the more sarcopenic the patient has become, even though their Model for End-stage Liver Disease scores stay the same (11). Moreover, the faster the declining speed of their sarcopenic states, the poorer their prognoses. Therefore, they recommended that sarcopenia be incorporated into the liver allocation system (12). Patients in an advanced state of sarcopenia are confronted by their vulnerability to infection, and ultimately their imminent death.

In two reports (3,13), patients with sarcopenia tended to have postoperative complications, especially infectious complications. However, the overall survival after liver transplantation of patients with sarcopenia was comparable with that of patients without sarcopenia although Montano-Loza *et al.* reported that patients with "extreme" sarcopenia exhibited significantly worse prognosis (3). On the other hand, in other two reports, sarcopenia was a predictor of mortality after liver transplantation (6,7). We, however, cannot simply compare these results because the definitions of sarcopenia were totally different among these reports. Nevertheless, patients with severe sarcopenia must have worse prognoses because of the vulnerability to infectious problems.

In any event, if severe sarcopenia might sure lead to early mortality after liver transplantation, do we have to turn down patients with severe sarcopenia from a candidate list in order to avoid futile transplants? Should patients with severe sarcopenia be judged too late to be transplanted? When a liver transplant candidate becomes wheelchair-bound, that patient should be judged extremely sarcopenic and, as a result, the outcome of liver transplantation for that patient would be dismal. Kaido *et al.* stated in the main body of the manuscript that their selection criteria for living donor liver transplantation is "walk unaided," excluding patients with extreme sarcopenia (8). I completely agree with their opinion. Liver transplant candidates should undergo liver transplantation before being plunged into such extreme sarcopenia if possible, especially in the setting of living donor liver transplantation in which the date of transplantation can be scheduled to some extent according to the condition of the candidate recipient.

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Changes in sarcopenic status after liver transplantation

Jeon *et al.* reported that none of liver transplant recipients who were preoperatively diagnosed as sarcopenia regained muscle mass after liver transplantation. Moreover, 15% who were preoperatively non-sarcopenic developed sarcopenia after liver transplantation (5). Several reports also suggested that muscle depletion has not recovered in the first year after liver transplant (14). Kaido's results (8) were the same as these previous reports. It seems to reach a consensus that the skeletal muscle mass of the recipients, in general, decreases after liver transplantation and does not return to the preoperative levels. There may be a threshold of the level of sarcopenia beyond which reversal of sarcopenia after liver transplantation can never happen.

The main immunosuppressants used in liver transplant recipients are calcineurin inhibitors. Calcineurin inhibitors are known to inhibit skeletal muscle hypertrophy in animal models (15). Although liver transplant recipients usually gain weight after transplantation, that gain is mainly caused by the accumulation of fat, while skeletal muscle mass rather decreases (14). The state of sarcopenia rather worsen after liver transplantation. Jeon *et al.* (5) reported that sarcopenia continued to be a risk factor for mortality even in patients who managed to survive their early posttransplant periods. Because sarcopenia continues, or rather worsens in some recipients, after liver transplantation, their vulnerability to infections, frailty syndrome in general, caused by sarcopenia should be seriously cautioned in addition to the problems relating to immunosuppressants.

Conclusions

Now, we are never able to deny that the state of sarcopenia has a strong impact on outcomes of liver transplant recipients. This state of sarcopenia, in general, worsens even after liver transplantation, which is one of the most significant risk factors for mortality after liver transplantation. The more sarcopenic liver transplant candidates are, the poorer the transplant outcome would be, which would ultimately result in futile outcomes. Because there is no testified effective measure to ameliorate already-established sarcopenia, liver transplant candidates should be transplanted before they have been plunged into extreme sarcopenia.

I hope the above-mentioned measures for evaluating sarcopenia in liver transplant candidates will be incorporated into routine pretransplant evaluations in order to further improve overall outcomes of liver transplantation.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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