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Liver transplantation arrests and reverses muscle wasting


Abstract: Muscle wasting, sarcopenia, is common in advanced cirrhosis and predicts adverse outcomes while awaiting and following liver transplantation. Frequent post-transplant worsening of sarcopenia has attracted recent interest. It is unknown whether this serious problem is an expected metabolic consequence of transplantation or results from confounding conditions such as recurrent allograft liver disease or avoidable post-transplant complications. To clarify this question, we studied pre- and post-transplant muscle mass in a retrospective cohort of 40 patients transplanted for three diseases – alcoholic cirrhosis, non-alcoholic steatohepatitis cirrhosis, and primary sclerosing cholangitis cirrhosis – in whom allograft disease recurrence was monitored and excluded, and who lacked common post-transplant muscle wasting complications such as sepsis, renal failure, ischemia, and cholestasis. We measured skeletal muscle index (SMI) using computed tomography before and 12–48 months after transplant. SMI as a categorical variable significantly improved, from 18 patients above the normal cutoff pre-transplant to 28 post-transplant (p = 0.008). SMI increases were greatest in patients with the lowest pre-transplant SMI (p < 0.01). As a continuous variable, mean SMI remained stable, with a non-significant trend toward improvement. We conclude that after liver transplantation sarcopenia does not progress but is arrested and frequently improves in the absence of confounding conditions.

Muscle wasting is a common and serious manifestation of advanced cirrhosis. Deficient skeletal muscle mass measured on body imaging, termed sarcopenia, predicted death after liver transplantation in three recent reports (1–3), and non-lethal post-transplant morbidity in another study (4). Sarcopenia also predicted death in patients evaluated for or awaiting transplantation (5–7). Muscle mass had predictive value independent of other indicators of liver disease severity such as Model for End-stage Liver Disease (MELD) score and Child class.

Whether sarcopenia worsens, persists, or recovers after liver transplantation has accordingly attracted growing interest, as shown in an analysis of post-transplant sarcopenia reported in six studies involving 304 patients (8). Potential causes of post-transplant sarcopenia cited in that review included ongoing signaling by a muscle wasting mediator, myostatin; persistent disturbances involving the metabolic syndrome; adverse effects of immunosuppression; muscle wasting complications such as sepsis, cholestasis, and renal failure; and allograft recurrence of such diseases as hepatitis B and C, autoimmune hepatitis, and non-alcoholic fatty liver disease (NAFLD).

A new study, the first to measure pre- and post-transplant muscle mass using computed tomographic (CT) imaging, reported that sarcopenia regularly progressed or failed to improve after transplantation in the majority of a cohort of 53
patients and suggested that post-transplant up-regulation of myostatin could account for the finding (9).

Given the clinical importance of understanding mechanisms involved in post-transplant sarcopenia, a central question is whether the problem is an expected or obligate consequence of persisting abnormalities after transplantation as suggested above or results from potentially avoidable confounding post-transplant complications. To answer this question accurately, we evaluated skeletal muscle mass before and after liver transplantation in 40 patients selected for absence of potentially confounding influences on skeletal muscle mass in the post-transplant period.

Methods

Patients

This retrospective observational cohort study was approved by the University of Pittsburgh Institutional Review Board under protocol O12030073. We selected a cohort of all patients who had analyzable serial abdominal CT imaging obtained before and between 12 and 48 months after an initial liver transplant performed for alcoholic cirrhosis, non-alcoholic steatohepatitis (NASH) cirrhosis, or primary sclerosing cholangitis (PSC) with cirrhosis. We chose these three diseases because their post-transplant recurrence in the observation period between transplantation and a follow-up scan could be excluded by clinical monitoring for relapse in the case of alcoholic cirrhosis, or by review of post-transplant imaging in the case of NASH and PSC.

We reviewed 547 patients who had an initial liver transplant for alcoholic cirrhosis, NASH cirrhosis, and PSC cirrhosis among the 2061 transplants performed at our center from 2000 to 2012. We did not study patients with combined liver/kidney, multivisceral, or repeat transplants. Patients were not included if they had evidence of coexisting hepatitis B or C infection or other alternative causes of cirrhosis in their pre-transplant evaluation. We did include patients in whom a hepatocellular carcinoma confined to the native explanted liver was present if there was no evidence of recurrence or metastasis in the post-transplant observation period.

Of these 547 patients, 152 had a clinical record of abdominal CT imaging before and between 12 and 48 months after transplant. Post-transplant scans were performed for clinical indications such as abdominal distress, evaluation of potential abdominal inflammation or infection, or concern for recurrent hepatocellular carcinoma or other tumors. Pre- and post-transplant images were available in our picture archiving and communication system for 48 of these patients for body composition analysis.

We reviewed the records of these 48 patients using pre-defined criteria to exclude those with potentially confounding causes of post-transplant muscle wasting. Exclusion criteria were any critical care unit readmission in the post-transplant observation period, hepatic artery thrombosis/ischemic cholangiopathy, alcohol relapse, persistent renal failure with creatinine above 2 mg/dL, post-transplant lymphoproliferative disorder, opportunistic infection requiring hospitalization, post-transplant imaging suggesting either allograft PSC recurrence by presence of typical duct abnormalities or NAFLD by presence of steatosis, and new malignancy or recurrent hepatocellular carcinoma. We excluded eight patients, including two with PSC recurrence, two with de novo cancers (one lung, one colon), two with renal failure, one with alcohol relapse, and one with severe recurrent acute pancreatitis and mesenteric vein thrombosis. The 40 remaining patients comprised our study cohort.

Body composition analysis

We measured skeletal muscle as the skeletal muscle index (SMI), and measured visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), using segmentation analysis of cross-sectional CT images at the midpoint of the third lumbar vertebra. Measurements were expressed as surface area in cm² divided by the square of patient height in m² as previously reported (1–6). To define presence or absence of sarcopenia as a categorical variable, we used previously reported SMI cutoff levels for sarcopenia of <38.5 cm²/m² in women and <52.4 cm²/m² in men (10).

We used the MITK software package, an open source application for body segmentation developed by the German Cancer Research Institute (11). MITK is similar to applications such as the commercial Slice-O-Matic and the open source NIH ImageJ software packages; the latter have been compared and found to produce congruent results (12). We found that intra-observer reproducibility for the MITK package was satisfactory, with serial measurements within 5% of each other (data not shown). We assessed inter-reader agreement for MITK among three observers for measurements of SMI, VAT, and SAT as described by Bland and Altman (13). Contrast-enhanced CT scans from 40 healthy living organ donor candidates (20 men and 20 women) were analyzed.
by each observer. As shown in Table 1, intraclass correlations, mean measurement differences, and coefficients of repeatability were acceptable and comparable with previously published analyses of body composition software performance (12, 14).

**Statistical analysis**

For each of the variables of interest – SMI, VAT, and SAT – data were described before and after transplant. For SMI, the cutoffs noted above were used to categorize sarcopenia as present or not. Normal quantile plots were visually inspected to assess whether data were at least approximately normal. Paired differences were tested using a paired *t*-test, and paired differences between categories for sarcopenia were tested using McNemar’s test (15). McNemar’s test measures whether the discordance (at, e.g., time 1 vs. time 2) is beyond what would be expected by chance. Paired *t*-tests were performed overall and repeated within gender and within condition (i.e., alcoholic cirrhosis, NASH, and PSC). McNemar’s test was not repeated within groups, given the small counts in the resulting contingency tables.

Linear regression analysis was conducted to assess the significance of potential associations of disease diagnosis, age, sex, MELD score, BMI, and waiting list time to transplant (adjusting for the other variables in the model) for predicting the paired differences in the continuous measures from before to after transplant (i.e., post-transplant value minus pre-transplant value). The coefficients for the linear regression thus represent the association between values (or categories) of a given variable and the paired differences, where a positive coefficient represents a larger change in post-minus pre-transplant difference. For comparison of disease groups, NASH was used as the baseline category so that the coefficients for the alcoholic and PSC groups were compared with the NASH group using the *F* statistic. Variables which were at least marginally significant (i.e., *p* ≤ 0.10) in the unadjusted analysis, or in the analysis adjusted for initial muscle mass, were included in a multivariable model. Variables that achieved a *p*-value of ≤0.05 in the multivariable model were considered statistically significant. Use of logistic regression as an alternative to linear regression in the case of binary outcomes was considered for modeling the binary categorical measure of sarcopenia, but the sample size was insufficient for doing so (given that at least 10 events of sarcopenia are needed for each variable and presence of sarcopenia would also have to be adjusted for in the model). All analyses were run in STATA statistical software (StataCorp LP, College Station, TX, USA).

**Results**

Baseline data for the 40 patients comprising our study cohort are shown in Table 2. There were nine patients, all men, with alcoholic cirrhosis, 21 (10 men and 11 women) with NASH cirrhosis, and 10 (seven men and three women) with PSC cirrhosis. There were five living donor transplants. Hepatocellular carcinoma confined to the explanted liver was present in 14 patients. The tumor was a new finding on pathologic examination of the explant in four patients and detected on pre-transplant imaging in the other 10. Patients with evidence of tumor recurrence or spread during the post-transplant observation period were not included in the study cohort.

Pre- and post-transplant muscle mass expressed as SMI is shown in Table 3. Overall, pre-transplant sarcopenia was prevalent in all groups, especially with PSC cirrhosis, where only one of the 10 patients was not sarcopenic prior to transplant. When SMI was considered as a categorical variable, either normal or sarcopenic based on gender-specific cutoffs, 89% of the 18 patients with a normal pre-transplant SMI remained normal post-transplant, and 55% of the 22 patients with a sarcopenic pre-transplant SMI improved to normal. The categorical change was significant (*p* = 0.008). As a continuous variable, after transplant the mean SMI in each patient group and overall showed a non-significant trend toward improvement compared with pre-transplant values. SMI as a continuous variable did not worsen in any gender or disease subgroup.

An unadjusted linear regression model, a model adjusted for pre-transplant values, and a multivariable regression model are shown in Table 4 for SMI. For change in muscle mass after transplantation, results of the unadjusted linear regression model showed that pre-transplant muscle mass was significantly and negatively associated with the

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**Table 1. Inter-reader agreement among three observers for measurements of skeletal muscle index (SMI), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT)**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Intraclass correlation coefficient, all three observers</th>
<th>Mean measurement difference (bias), % (1 vs. 2, 1 vs. 3, 2 vs. 3)</th>
<th>Coefficient of repeatability (2 SD), % (1 vs. 2, 1 vs. 3, 2 vs. 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMI</td>
<td>0.991</td>
<td>-3.6, 1.1, 4.7</td>
<td>10.1, 10.8, 13.3</td>
</tr>
<tr>
<td>SAT</td>
<td>0.998</td>
<td>-5.4, 4.9, -10.3</td>
<td>8.7, 13.4, 14.4</td>
</tr>
<tr>
<td>VAT</td>
<td>0.994</td>
<td>9.2, -1.2, -10.3</td>
<td>25.8, 33.8, 35.1</td>
</tr>
</tbody>
</table>
Table 2. Baseline data for 40 patients with liver transplants for alcoholic, NASH, and PSC cirrhosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Age (years)</th>
<th>BMI</th>
<th>MELD</th>
<th>Albumin</th>
<th>HCC</th>
<th>Living donor</th>
<th>Waitlist time, months</th>
<th>Time from transplant to second CT, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol cirrhosis</td>
<td>59.6 ± 7.0</td>
<td>27.6 ± 5.0</td>
<td>18.8 ± 7.0</td>
<td>3.0 ± 0.3</td>
<td>5</td>
<td>0</td>
<td>4.1 ± 5.1</td>
<td>20.3 ± 7.4</td>
</tr>
<tr>
<td>9 men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NASH cirrhosis</td>
<td>58.0 ± 10.6</td>
<td>32.3 ± 5.9</td>
<td>12.8 ± 3.7</td>
<td>3.0 ± 0.5</td>
<td>8</td>
<td>4</td>
<td>3.7 ± 2.6</td>
<td>23.9 ± 9.5</td>
</tr>
<tr>
<td>10 men, 11 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSC cirrhosis</td>
<td>52.0 ± 12.9</td>
<td>25.1 ± 2.9</td>
<td>16.4 ± 7.6</td>
<td>3.1 ± 0.7</td>
<td>1</td>
<td>1</td>
<td>2.4 ± 0.9</td>
<td>24.7 ± 10.7</td>
</tr>
<tr>
<td>7 men, 3 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56.8 ± 10.9</td>
<td>29.4 ± 6.0</td>
<td>15.1 ± 6.2</td>
<td>3.0 ± 0.5</td>
<td>14</td>
<td>5</td>
<td>3.5 ± 3.2</td>
<td>23.3 ± 9.6</td>
</tr>
<tr>
<td>26 men, 14 women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; MELD, Model for End-stage Liver Disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
Data are mean ± 1 SD.

Table 3. Skeletal muscle index (SMI) before and after liver transplantation

<table>
<thead>
<tr>
<th>Liver disease</th>
<th>SMI, cm²/m²</th>
<th>p-Value t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-transplant</td>
<td>Post-transplant</td>
</tr>
<tr>
<td>Alcohol cirrhosis, n = 9, men</td>
<td>51.2 ± 9.6, 4/9</td>
<td>56.8 ± 6.4, 6/9</td>
</tr>
<tr>
<td>NASH cirrhosis, n = 10, men</td>
<td>43.9 ± 9.9, 6/10</td>
<td>49.1 ± 5.6, 8/10</td>
</tr>
<tr>
<td>PSC cirrhosis, n = 7, men</td>
<td>45.0 ± 4.4, 0/7</td>
<td>46.6 ± 8.4, 2/7</td>
</tr>
<tr>
<td>All men, n = 26</td>
<td>52.1 ± 12.0, 10/26</td>
<td>55.7 ± 12.3, 16/26</td>
</tr>
<tr>
<td>NASH cirrhosis, n = 11, women</td>
<td>43.9 ± 9.9, 7/11</td>
<td>49.1 ± 5.6, 11/11</td>
</tr>
<tr>
<td>PSC cirrhosis, n = 3, women</td>
<td>34.6 ± 5.5, 1/3</td>
<td>37.8 ± 12.2, 1/3</td>
</tr>
<tr>
<td>All women, n = 14</td>
<td>41.9 ± 9.9, 8/14</td>
<td>46.7 ± 8.8, 12/14</td>
</tr>
</tbody>
</table>

NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
Values in each cell are mean ± SD followed by the number of patients/total with normal SMI above the cutoff levels of 52.4 cm²/m² in men and 38.5 cm²/m² in women.
The overall categorical change after transplant from 18 to 28 in the number of patients with SMI above the normal cutoff was significant at p = 0.008 by McNemar’s test.
When assessed as a continuous variable, there were no significant differences between mean pre- and post-transplant SMI values in any patient group, based on continuous paired differences and the paired t-test.
Post-transplant SMI did not worsen in any gender or disease group.

extent of post-transplant change in muscle mass (p < 0.01). Lower pre-transplant muscle mass was associated with a greater magnitude of post-transplant recovery. After adjusting for pre-transplant muscle mass, both BMI and disease diagnosis were marginally significant and were included in the multivariable model. Only pre-transplant muscle mass was associated with the extent of its change in the multivariable model; as with the unadjusted model, lower pre-transplant muscle mass was associated with a greater post-transplant increase (coefficient -0.92, p < 0.01).

The time from transplant to the post-transplant CT scan was also checked as a covariate in both the unadjusted models and the models adjusted for the baseline measure. None of the results showed a p-value below 0.22.

Pre- and post-transplant VAT and SAT are shown in Table 5. Visceral adiposity increased significantly after transplantation in patients with NASH cirrhosis and for the entire cohort. Subcutaneous adiposity showed a non-significant increase in all disease groups.

Discussion

We found that post-transplant sarcopenia is not an expected or obligate consequence of liver transplantation. SMI improved or stabilized after liver transplantation in our patients in whom confounding causes of muscle wasting and recurrent allograft liver disease were excluded. Improvement was greatest in patients with the most severe pre-transplant sarcopenia.

Our findings contrast with and differ from those of Tsien et al. (9), who reported ongoing post-transplant muscle loss in a cohort of 53 patients evaluated for sarcopenia with equivalent methods to those we employed and managed with similar post-transplant immunosuppression regimens. Sarcopenia increased from 62% of their patients pre-transplant to 87% post-transplant. In our cohort, sarcopenia decreased from 55% of patients pre-transplant to 30% post-transplant. A key difference in design of the two studies was that patients with known post-transplant muscle wasting conditions and recurrent allograft diseases were not reported as excluded from Tsien et al.’s cohort as they were from ours. Taken together with earlier summarized data (8), it appears likely that complicating events and allograft disease recurrence, rather than abnormalities associated with transplantation itself, will
Muscle mass/C0 Waitlist time 0.53 (0.45)

Disease type
BMI/C0 MELD 0.24 (0.51)
Sex 1.19 (0.80)

Visceral adipose tissue, cm

Values in each cell are mean

NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis.

Denotes variables not included in the given model.

Table 5. Visceral and subcutaneous adipose tissue (SAT) before and after liver transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-transplant</th>
<th>Post-transplant</th>
<th>p-Value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral adipose tissue, cm²/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis, n = 9</td>
<td>73.8 ± 30.9</td>
<td>88.9 ± 37.1</td>
<td>0.14</td>
</tr>
<tr>
<td>NASH cirrhosis, n = 21</td>
<td>83.6 ± 30.7</td>
<td>99.4 ± 37.4</td>
<td>0.01</td>
</tr>
<tr>
<td>PSC cirrhosis, n = 10</td>
<td>46.9 ± 14.5</td>
<td>59.7 ± 25.0</td>
<td>0.08</td>
</tr>
<tr>
<td>All patients, n = 40</td>
<td>72.2 ± 31.5</td>
<td>87.1 ± 31.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAT, cm²/m² height</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis, n = 9</td>
<td>56.7 ± 45.2</td>
<td>59.0 ± 25.2</td>
<td>0.81</td>
</tr>
<tr>
<td>NASH cirrhosis, n = 21</td>
<td>83.6 ± 41.5</td>
<td>95.2 ± 31.0</td>
<td>0.17</td>
</tr>
<tr>
<td>PSC cirrhosis, n = 10</td>
<td>45.5 ± 26.5</td>
<td>51.1 ± 21.7</td>
<td>0.36</td>
</tr>
<tr>
<td>All patients, n = 40</td>
<td>68.0 ± 42.7</td>
<td>76.0 ± 34.3</td>
<td>0.11</td>
</tr>
</tbody>
</table>

NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis.
Values in each cell are mean ± SD.

emerge as the major drivers of post-transplant sarcopenia.

Our study’s key limitation is related to its intentional exclusion of potentially confounding causes of post-transplant sarcopenia to isolate the effect on muscle mass of transplantation alone, so that our patient cohort does not represent the general transplant population in whom these problems are frequent (8). Our highly selected cohort of 40 patients of the 547 screened could therefore contain elements of unintentional bias that we did not identify as we excluded known confounding muscle wasting conditions. In addition, the need for a clinically indicated post-transplant CT scan influenced patient selection. It appears unlikely, however, that need for post-transplant imaging based on concerns for pain, infection, inflammation, or recurrent cancer would have generated bias toward the improvement and stabilization in muscle mass that we observed. As shown in Table 3, 12 of our 40 patients had not recovered muscle mass into the normal range by the time of their post-transplant imaging. It is not known whether normalization of post-transplant muscle mass in this patient subgroup would eventually occur.

Our findings of ongoing visceral and subcutaneous adiposity are expected in light of current knowledge of the post-transplant state (16).

Muscle mass as an indicator of advanced liver disease severity and prognosis is attracting increasing recognition (17, 18). A new molecular connection between cirrhosis and sarcopenia is stimulation by elevated ammonia levels of muscle cell production of myostatin, a potent mediator of muscle wasting (19). Therapeutic interventions that promote recovery of muscle mass in other sarcopenic diseases have been shown to improve performance and quality of life (20).

Although the clinical and prognostic value of muscle mass is well described, it is not clear whether anatomic muscle mass measurements should become a therapeutic target for improving physical conditioning in cirrhosis. A review of 13 studies of exercise to improve physical performance in cirrhosis, for example, highlighted performance measurements of aerobic capacity and gait speed as important clinical endpoints (21). A new report described similar high prognostic value of physical performance testing in
liver-transplant-waitlisted patients (22). In appropriate settings, both anatomic muscle mass and physical performance measurements may have complementary value.

To conclude, our findings challenge the concept that sarcopenia should be expected as a consequence of liver transplantation. We found that successful liver transplantation without confounding muscle wasting complications improves and stabilizes muscle mass, a critical observation for guiding efforts to prevent and reverse transplant-related muscle wasting. Reversal of sarcopenia after transplantation should be considered an achievable goal.

Acknowledgements

We acknowledge with appreciation Dr. Chuanxing Qu, who contributed as a body composition analysis reader to the assessment of inter-reader reproducibility. This work was supported by Grant W81XWH-11-2-0133 from the United States Army Medical Research and Material Command.

Authors’ contributions

Joseph T. Bergerson, Achuthan Sourianarayanane, Amit D. Tevar, Andrea F. DiMartini, and Michael A. Dunn designed the study, obtained and analyzed the data, and wrote the paper. Jun-Goo Lee, Alessandro Furlan, and David T. Fetzer designed the image data, and wrote the paper. Jun-Goo Lee, Alessandro Dunn designed the study, obtained and analyzed the images. Douglas P. Landsittel designed and performed the statistical analysis. Michael A. Dunn obtained funding.

References