Original Article

Longitudinal CT study of sarcopenia due to hepatic failure after living donor liver transplantation

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Background: The quantity and quality of skeletal muscle have been observed to be closely related with post-transplantation mortality in patients undergoing living donor liver transplantation (LDLT). However, the effect of LDLT on skeletal muscle has not been thoroughly investigated. The aim of this study was to investigate the change of trunk muscle mass and adiposity in recipients of LDLT.

Methods: The study population included LDLT recipients at Hokkaido University Hospital who underwent pre- and post-operative computed tomography (CT) scans (31 recipients; 14 males, and 17 females). The cross-sectional area of the dorsal muscle group at the 12th thoracic vertebra (Th12) was measured with the dorsal muscle group mass index (DMGMI), while the psoas muscle at the upper border of 4th lumber vertebra (L4) was measured with the psoas muscle mass index (PMI). Muscle adiposity of the dorsal muscle group was also measured with the intramuscular adipose tissue content (IMAC). For these data, the correlation between pre-operative values and follow-up changes (post-operative values minus pre-operative values) were analyzed. Each sex was evaluated separately.

Results: A statistically significant correlation was detected between pre-operative values and follow-up differences in DMGMI for both sexes (male: r=–0.675, P=0.008; female: r=–0.687, P=0.002) and in PMI for both sexes (males: r=–0.739, P=0.003; females: r=–0.641, P=0.006). The correlation of pre-operative values and follow-up differences for IMAC was not statistically significant with r=0.132 (P=0.700) and r=–0.498 (P=0.071) for males and females, respectively.

Conclusions: Improvement of sarcopenia in recipients of LDLT can be demonstrated regardless of sex using volumetric CT.

Keywords: Computed tomography (CT); sarcopenia; hepatic failure; living donor liver transplantation (LDLT)

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Introduction

The liver plays a major role in metabolism, but when affected by disease may lead to inadequate food intake, abnormal nutrient metabolism and altered digestion and absorption, together with an increased protein catabolism and an increase in protein-energy requirements (1,2). In patients with liver cirrhosis, this nutritional deficiency can cause a decrease in skeletal muscle mass, namely sarcopenia. Sarcopenia is characterized by lower skeletal muscle quantity, higher fat accumulation in the muscle, lower muscle strength, lower physical performance, leading to

Table 1 Characteristics of study population

Characteristics	Male	Female	P value
Number	14	17	
Age at LDLT (year)	49.5±11.4	57.5±7.0	0.023*
Height (cm)	170.0±0.1	154.0±0.1	<0.001*
Weight (kg)	71.6 ±12.1	55.6±9.4	<0.001*
BMI (kg/m^2)	24.8 ±3.8	23.5±4.1	0.384*
Period between CT exam before LDLT and LDLT [day]	12 [5.5–22]	15 [12–26]	0.512**
Period between LDLT and 1-year follow up CT exam [day]	365.5 [360.3–372.8]	386.0 [367.0–394.0]	0.026**

Mean ± standard deviation, median (interquartile range). *, *t*-test; **, Mann-Whitney's U test. BMI, body mass index; LDLT, living donor liver transplantation; CT, computed tomography.

poor quality of life (QOL) (3-6).

As radiologic imaging analysis provides direct visualization of body and tissue components, its use in body composition and nutritional assessment is specifically valuable for quantifying nutritional deficiency for which traditional measures of nutrition (biochemical markers, body weight, or anthropomorphic measurements) have proven less accurate (7). Especially, computed tomography (CT) scanning provides an exact measure of muscle mass and has proven more accurate than externally measured muscle circumference (8). For example, the psoas muscle area measured using CT images is reported to be a prognostic factor for liver transplantation (LT) recipients; small psoas muscle area is associated with mortality (6,9-11). The dorsal muscle group area is also a useful prognostic factor (12). Furthermore, dorsal muscle group quality (i.e., fat accumulation of the muscle) has been demonstrated to be an indicator of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (13,14).

To the best our knowledge, there are no reports in the literature concerning follow-up evaluations of LT recipients in terms of trunk muscle area and adiposity. Changes in the size of trunk muscle are thought to best reflect log-term chronic illness and systemic health (3,13,15).

The aim of this study is to analyze trunk muscle mass and adiposity change after living donor liver transplantation (LDLT).

Methods

Patients

Thirty-two adult (age ≥18 years) recipients underwent LDLT at Hokkaido University Hospital between January 2009 and December 2013. One recipient was not alive 1 year after LDLT. A total of 31 recipients (14 males, 17 females) of LDLT were therefore enrolled in the study. Each recipient had an abdominal CT exam (dynamic CT or non-dynamic contrast enhanced CT) at pre-LDLT and 1-year follow-up. *Table 1* shows the characteristics of the study population and *Table 2* shows the recipients' disease status.

Image analysis

Pre- and post-contrast axial CT images were used to carry out image analysis. Muscle areas and quality (fat accumulation of the muscle) were measured by a radiological technologist using a region of interest (ROI) precisely traced with the use of commercially available image analysis software (volume analyzer SYNAPSE VINCENT, Fujifilm Medical Co., Ltd., Tokyo, Japan). All CT images were acquired at 120 kVp and 5 mm slice thickness. We measured muscle area and adiposity using a single slice. Muscle areas were calculated after being normalizing by the square of the height of the patients. Both pre- and post-operative muscle were measured (16).

The bilateral dorsal muscle group area at the lower border of the 12th thoracic vertebra (Th12) divided by the square of the height of the patient was defined as the dorsal muscle group mass index (DMGMI) (mm^2/m^2) (12). The bilateral psoas muscle area at the upper border of 4th lumber vertebra (L4) divided by the square of the height of the patient was likewise defined as the psoas muscle mass index (PMI) (mm^2/m^2) (9).

The dorsal muscle group adiposity at the lower border of

Table 2 LDLT recipients' diseases status

	Male (n=14)	Female (n=17)
CTP score [median, interquartile range]	10 [7.5–11.75]	11 [9–12]
CTP class A	3	1
CTP class B	1	4
CTP class C	9	12
Hepatitis virus B (HBV)	4	1
Hepatitis virus C (HCV)	2	5
Hepatocellular carcinoma (HCC)	6	3
HBV cirrhosis	5	1
HCV cirrhosis	2	5
Alcoholic hepatitis	2	2
NASH	2	0
Cryptogenic cirrhosis	0	1
Cirrhosis (unknown cause)	0	1
Acute liver failure	1	0
Autoimmune hepatitis	0	1
Primary biliary cholangitis	1	3
Primary sclerosing cholangitis (PSC)	0	1
Familial amyloid polyneuropathy (FAP)	1	0
Multiple hepatorenal cyst	0	1
Unknown cause	0	1

LDLT, living donor liver transplantation; CTP, Child-Turcotte-Pugh; NASH, nonalcoholic steatohepatitis.

Th12 was furthermore defined as the intramuscular adipose tissue content (IMAC) following Kitajima *et al.* (13,14). The density of the dorsal muscle group was measured at the lower border of Th12 using plain CT images. CT values of subcutaneous adipose tissues (SAT) were also measured at four points, keeping away from major vessels using circle ROIs with a diameter of 6 mm. IMAC was calculated as previously described by Kitajima *et al.*; it was calculated as the mean CT value of the dorsal muscle group (Hounsfield units) divided by the mean CT value of SAT (Hounsfield units), which indicates the degree of steatosis (14). IMAC is normally a negative value. When IMAC is high, more fat infiltration is in the dorsal muscle group, whereas when IMAC is low, there is less fat in the dorsal muscle group. *Figure 1* shows examples of DMGMI, PMI, and IMAC measurement.

Statistical analysis

The pre-operative and post-operative values were compared using the paired *t*-test. Pearson's correlation coefficient (r) between the pre-operative value (pre-DMGMI, pre-PMI, and pre-IMAC) and follow-up change (post-operative value minus pre-operative value defined as ΔDMGMI, ΔPMI, and ΔIMAC) were evaluated. Each sex was separately evaluated. Differences were considered significant when $P<0.05$. All statistical analyses were performed with commercially available software (Microsoft® Excel and PASW® Statistics 18).

Results

Table 3 shows DMGMI, PMI, and IMAC for pre- and post-LDLT. IMAC was measured for only 11 males and

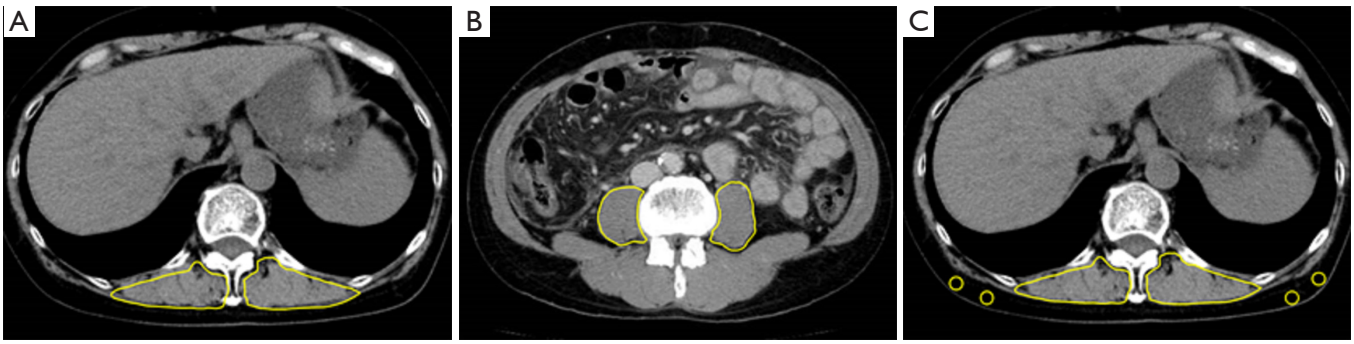

Figure 1 Measurement of DMGMI, PMI, IMAC for a 56-year-old male with hepatitis C, Child-Turcotte-Pugh class C. Outlines show the region of interest (ROI). (A) Dorsal muscle group mass index (DMGMI); bilateral dorsal muscle group area at lower border of 12th thoracic vertebra (Th12); (B) psoas muscle mass index (PMI); bilateral psoas muscle area at upper border of 4th lumber vertebra (L4); (C) intramuscular adipose tissue content (IMAC); dorsal muscle group adiposity at lower border of Th12. The density of the dorsal muscle group at the lower border of Th12 using a plain CT image was measured. CT values of subcutaneous adipose tissues (SAT) were also measured at four points, keeping away from major vessels using circle ROIs 6 mm in diameter. IMAC was calculated as mean CT value of dorsal muscle group (Hounsfield units)/mean CT value of SAT (Hounsfield units). CT, computed tomography.

Table 3 DMGMI, PMI, and IMAC for females (n=17)

	Pre-LDLT	Post-LDLT	P value
DMGMI (mm^2/m^2)	1,126.762±372.714	1,134.018±271.607	0.915
PMI (mm^2/m^2)	528.045±133.901	537.893±105.525	0.716
IMAC*	−0.320±0.094	−0.299±0.094	0.409

*, n=14, mean ± standard deviation, paired *t*-test. LDLT, living donor liver transplantation; DMGMI, dorsal muscle group mass index; PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content.

14 females because 3 males and 3 females did not undergo plain abdominal CT. *Figure 2* shows the relationship between pre-DMGMI and ΔDMGMI; r=−0.675 (P=0.008 for males), r=−0.687 (P=0.002 for females). *Figure 3* shows the relationship between pre-PMI and ΔPMI; r=−0.739 (P=0.003 for males), r=−0.641 (P=0.006 for females). *Figure 4* shows the relationship of pre-IMAC and ΔIMAC; r=0.132 (P=0.700 for males), r=−0.498 (P=0.071 for females). A summary of the results is shown in *Table 4*.

Discussion

The aim of this study was to analyze how trunk muscle mass and adiposity change at 1-year after LDLT in adult patients with liver disease. Our study, which assessed the volume of psoas and dorsal muscle group, demonstrates that sarcopenia is improved after LDLT especially in recipients with smaller muscle mass preoperatively. This tendency was observed both in males and females. On the other hand, those with larger muscle mass at pre-LDLT did not experience apparent muscle volume gain. This may implicate that the subjects in our study included recipients with diverse extent of sarcopenia before LDLT, and those with more severe sarcopenia seem to benefit from LDLT.

In terms of muscle quality assessed by analyzing the adiposity of the dorsal muscle group, significant correlations were not found between before and after LDLT, although muscle adiposity tended to improve in females after LDLT (r=−0.498, P=0.071). This result might suggest that the effect of LDLT on muscle adiposity has sex difference (more benefit in female). Further study with a larger number of patients is need for confirmation. Anyway, sensitivity to change may be greater in muscle mass than muscle adiposity after LDLT for both sexes.

To the best of our knowledge, this is the first study to investigate the effect of LDLT on skeletal muscles according to different muscle mass. Tsien *et al.* reported that the prevalence of post transplantation sarcopenia is

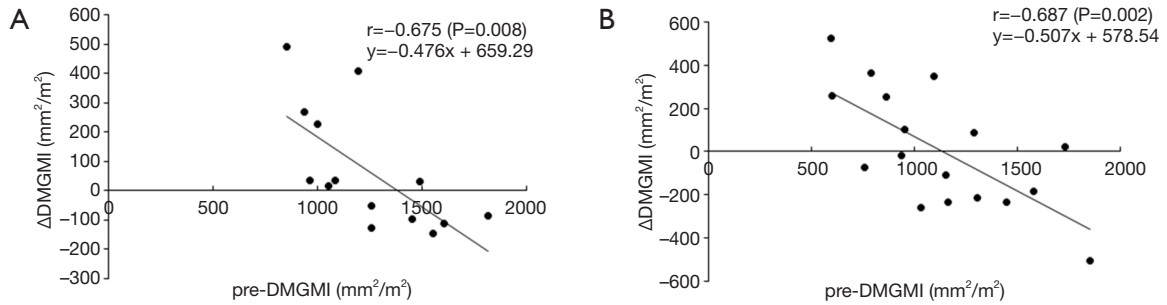

Figure 2 Relationship between pre-DMGMI and ΔDMGMI (A, males; B, females). (A,B) Significant negative correlation was found (A: r=−0.675, P=0.008; B: r=−0.687, P=0.002). pre-, pre-living donor liver transplantation; Δ, follow-up change (post-operative value minus pre-operative value); DMGMI, dorsal muscle group index; r, Pearson's correlation coefficient; x, pre-DMGMI; y, ΔDMGMI. DMGMI, dorsal muscle group mass index.

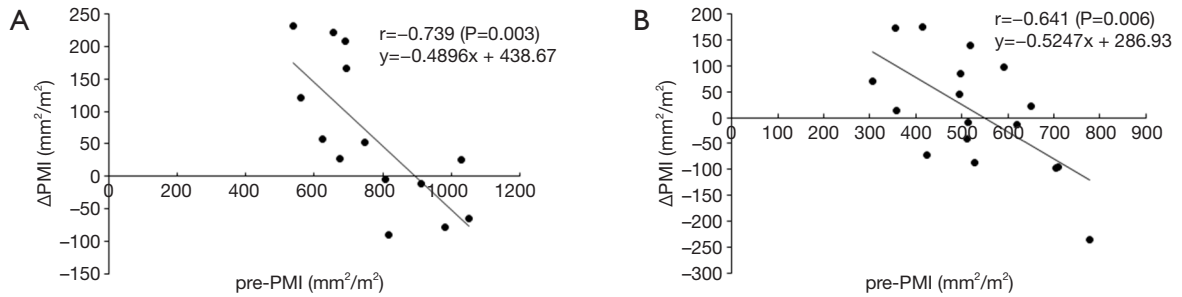

Figure 3 Relationship between pre-PMI and ΔPMI (A, males; B, females). (A,B) Significant negative correlation was found (A: r=−0.739, P=0.003; B: r=−0.641, P=0.006). pre-, pre-living donor liver transplantation; Δ, follow-up change (post-operative value minus pre-operative value); r, Pearson's correlation coefficient; x, pre-PMI; y, ΔPMI. PMI, psoas muscle mass index.

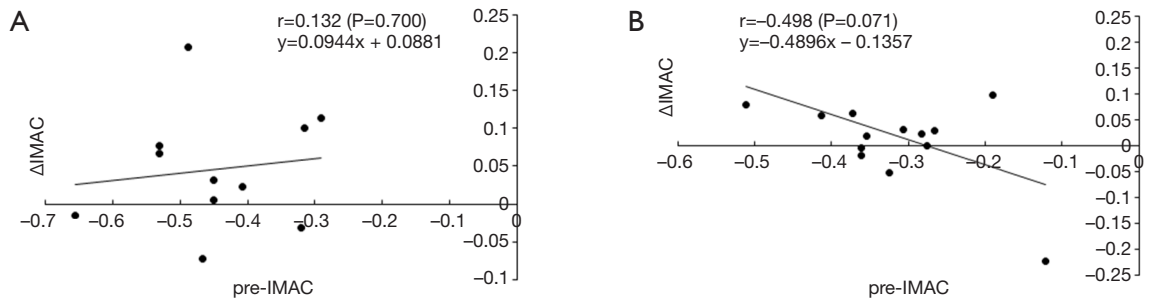

Figure 4 Relationship between pre-IMAC and ΔIMAC (A, males; B, females). pre-, pre-living donor liver transplantation; Δ, follow-up change (post-operative value minus pre-operative value); r, Pearson's correlation coefficient; x, pre-PMI; y, ΔPMI. PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content.

common, and it could not be attributed to pre-transplant characteristics including Child's score, Model for end-stage liver disease (MELD) score and nutritional status or the type or duration of post-orthotopic liver transplantation (OLT) immunosuppression (17). As our study included only recipients with favorable outcomes, future study with more recipients with severer sarcopenia might clarify the muscle condition required for favorable post-operative outcome.

There are several limitations in this study. First, this is a retrospective study with relatively small number of patients.

Table 4 The correlation between pre-values and Δ values for DMGMI, PMI, and IMAC

	Males		Females	
	r	P value	r	P value
Pre-DMGMI and ΔDMGMI (mm^2/m^2)	−0.675	0.008	−0.687	0.002
Pre-PMI and ΔPMI (mm^2/m^2)	−0.739	0.003	−0.641	0.006
Pre-IMAC and ΔIMAC*	0.132	0.700	−0.498	0.071

*, n=11 (males), n=14 (females). Pre-, pre-living donor liver transplantation; Δ, follow-up changes (post-operative values minus pre-operative values). DMGMI, dorsal muscle group mass index; PMI, psoas muscle mass index; IMAC, intramuscular adipose tissue content.

Second, ROI placement for muscle area and adiposity was evaluated by only one radiological technologist without reproducibility analysis. This was because ROI placement in the muscle was relatively straight-forward and there seemed to be no need to re-test the analysis. However, evaluation of intra- or inter-correlation coefficient may be needed for confirmation, when we consider that measurement with only a slice is likely to cause errors; the imaging slice may change according to the difference of posture and the change in body shape after LDLT. Third, although we measured muscle area rather than muscle volume (18), muscle volume measurement may be more sensitive to change.

In conclusion, improvement of sarcopenia in recipients after LDLT can be demonstrated regardless of sex using volumetric CT.

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None.

Footnote

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

Ethical Statement: This study obtained ethics approval from the ethics committee of Faculty of Health Sciences Hokkaido University (ID16-6). Written informed consent was obtained from the patient for the publication of this manuscript and any accompanying images.

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