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Effects of pretransplant sarcopenia and sequential changes in sarcopenic parameters after living donor liver transplantation

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ABSTRACT

Objective: Sarcopenia is characterized by muscle mass depletion and decrease in muscle power or physical activity. We previously reported that low skeletal muscle mass (SMM) is closely involved with posttransplant mortality in patients undergoing living donor liver transplantation (LDLT). The aim of this study was to prospectively investigate the effects of pretransplant sarcopenia on survival and examine sequential changes in sarcopenic parameters after LDLT.
Methods: Sarcopenia was defined by measuring SMM using a multifrequency body composition analyzer and assessing grip strength (GS) in 72 adults who underwent LDLT at Kyoto University Hospital between January 2013 and October 2015. The effects of pretransplant sarcopenia on short-term survival and sequential changes in SMM and GS were prospectively analyzed.
Results: Of 72 patients, 10 (14%) were defined as having pretransplant sarcopenia. Overall survival rates were significantly lower in patients with sarcopenia ($n = 10$) than those without sarcopenia ($n = 62$; $P < 0.001$). SMM worsened after LDLT and did not return to preoperative levels until 1 y after LDLT. In contrast, GS returned to preoperative levels at 6 mo after LDLT, following sharp decrease at 1 mo after LDLT.
Conclusions: This prospective study confirmed that pretransplant sarcopenia is closely associated with short-term survival after LDLT and that GS recovers before SMM.

Introduction

Sarcopenia is characterized by muscle mass depletion and a decrease in muscle power or physical activity and is classified according to cause as primary when no cause is evident other than aging and secondary sarcopenia [1,2]. As for secondary sarcopenia, disease-related sarcopenia is associated with advanced organ failure including that of the liver and heart. Nutrition-related sarcopenia results from insufficient dietary intake of energy or protein. Patients with end-stage liver diseases requiring liver transplantation (LT) usually have liver failure and poor nutrition. Therefore, most patients undergoing LT meet the criteria of secondary sarcopenia. With LT, the impaired liver is replaced by normal liver. Consequently, the metabolic state dramatically changes after LT. However, the recovery of body composition including skeletal muscle mass (SMM) and muscle power after LT, especially living donor LT (LDLT), is not fully understood.

A previous retrospective study found that preoperative low SMM is an independent risk factor for death after LDLT and that appropriate perioperative nutritional status is useful for patients with low SMM [3]. According to the finding, we have incorporated the sarcopenia-related factor of being able to walk unaided into the selection criteria for LT to exclude patients with severe

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sarcopenia since January 2013. We also clarified that the quality of skeletal muscle was an independent risk factor for death after LDLT [4]. A previous study measured the size of the psoas muscle using computed tomography (CT) and found that central sarcopenia closely correlates with post-LT mortality [5]. However, that study examined only the effect of pretransplant quality and quantity of muscle mass on outcomes after LT. As previously mentioned, sarcopenia is defined as muscle mass depletion and a decrease in muscle power or physical activity [1,2]. The effects of sarcopenia based on this definition on outcomes after LT, especially LDLT, are thus unclear.

The present study prospectively determined the relevance of the new criteria and examined the effect of pretransplant sarcopenia, defined by these guidelines, on outcomes after LDLT. We also investigated sequential changes in sarcopenic parameters including SMM and muscle power after LDLT.

Patients and methods

Patients

Eighty-three patients aged ≥18 y underwent LT at Kyoto University Hospital between January 2013 and October 2015. We excluded nine patients who underwent deceased donor LT (DDLT) and two who underwent LDLT for acute liver failure because body composition as well as grip strength (GS) on admission could not be measured due to an emergency situation or hepatic coma. Therefore, 72 patients were enrolled in this study. The Ethics Committee at Kyoto University approved the study, which proceeded in accordance with the Declaration of Helsinki, 1996.

The median patient age was 55 y (range 21–68 y), and 38 (53%) were men. The median Model for End-stage Liver Disease score was 18 (range 6–41). Orthotopic LDLT proceeded using right lobe, left lobe, and posterior segment grafts for 42, 27, and 3 patients, respectively. The median graft-to-recipient body weight ratio was 0.87 (range 0.56–1.49). Fifteen and 57 patients were ABO incompatible, and identical or compatible, respectively. The Child-Pugh classifications were C, B, and A for 52, 16, and 4 patients, respectively. The indications for LT were hepatocellular diseases such as hepatitis B or C virus-associated liver cirrhosis (n = 16), hepatocellular carcinoma (n = 16), and progressive intrahepatic cholestatic diseases including primary biliary cholangitis and primary sclerosing cholangitis (n = 16), followed by alcoholic liver cirrhosis (n = 7), biliary atresia (n = 6), nonalcoholic steatohepatitis-associated liver cirrhosis (n = 3), and other causes including Budd-Chiari syndrome, polycystic liver, and autoimmune hepatitis (n = 8).

Surgical procedures and immunosuppressive therapy

The selection criteria for the recipients as well as surgical techniques for the donor and recipient are described in detail elsewhere [6–9]. We included the new criterion of being able to walk unaided, which can be assessed without devices at the time of admission and on the day of LT surgery, to exclude patients with severe sarcopenia since January 2013. Patients who were unable to walk were reevaluated after intensive rehabilitation and nutritional therapy.

Current immunosuppressive therapy essentially consisted of tacrolimus and mycophenolate mofetil for ABO-compatible patients [10], and systemic steroid therapy was added for those who were ABO-incompatible until 3 mo after LT as described [11,12]. All patients received intravenous prophylaxis with ampicillin (0.5 g) and cefotaxime (0.5 g) twice daily for 3 d starting 30 min before surgery.

Assessment and definition of sarcopenia

Muscle mass in all patients was assessed at admission by multifrequency bioelectrical impedance analysis (BIA) using an InBody 720 (InBody, Tokyo, Japan) instrument with eight tactile electrodes. GS was tested to determine muscle power. We assessed hepatic encephalopathy by clinical symptoms including psychological and neurologic disorder on the day of GS assessment. We measured GS after confirming that each patient had no encephalopathy.

BIA devices used frequencies of 1, 5, 50, 250, 500, and 1000 kHz and produced 30 impedance values for five body segments. In preparation for BIA, patients fasted for ≥3 h and voided immediately before starting the analysis. The InBody 720 can automatically and simultaneously measure body mass index, intra- and extracellular water, body fat mass, and SMM within 2 min. The SMM is shown as an absolute value and as a ratio (%) compared with a standard SMM calculated based on the sex and height of each patient. The normal SMM obtained using the InBody 720 ranges from 90% to 110% of the standard SMM. Here, we defined low SMM as being <90% of the lower limit of the standard as previously described [3]. Normal or high SMM was defined as being within the normal limit or above the upper limit, respectively. Low GS was defined as <26 kg for men and <18 kg for women according to the consensus report of the Asian Working Group for Sarcopenia [2]. Therefore, we defined patients with sarcopenia as having both low SMM and low GS.

Perioperative nutritional and rehabilitation therapy

Preoperative nutritional therapy was administered for 1 to 2 wk before LDLT as previously described [13]. Nutrient therapy usually consisted of the nutrient mixture Aminoleban EN (Otsuka Pharmaceutical Co., Tokyo, Japan) enriched with branched-chain amino acids (BCAA) or Livact BCAA nutrients (Ajinomoto Pharma Co., Tokyo, Japan) as a late evening snack, GFO synbiotic supplement enriched with glutamine, dietary fiber, and oligosaccharide (Otsuka Pharmaceutical Factory, Tokushima, Japan) three times daily. Yakult 400 (Yakult Honsha Co., Tokyo, Japan), a fermented lactic beverage containing 5×10^8/mL of *Lactobacillus casei* Shirota strain, was given once a day, and patients with low serum zinc levels received 1 g/d of Polaprezinc (Promac D; Zeria Pharmaceutical Co., Tokyo, Japan). Dietitians adjusted the type and amount of food for each patient to maintain a total caloric intake of 30 to 35 kcal/kg and a protein intake of 1.2 to 1.5 g/kg including BCAA nutrients according to the guidelines of the European Society of Parenteral and Enteral Nutrition [14].

A tube jejunostomy for enteral nutrition was placed in the proximal jejunum using a 9-French enteral tube in all recipients at the time of surgery. Postoperative early enteral nutrition was started within the first 24 h after surgery through the tube jejunostomy. We gradually increased the total daily caloric intake until postoperative day (POD) 3, from 10 to 15 kcal/kg to 25 to 35 kcal/kg. As an enteral nutrient, we preferred a new immunomodulating diet, MEIN, which is a protein complex derived from milk and enriched with hydrolyzed whey peptide (Meiji Dairies Co., Tokyo, Japan). The initial infusion rate was 20 mL/h. If well tolerated, the enteral infusion rate was increased to 40 mL/h by POD 5. Oral nutrition was started after confirming the ability to swallow, usually around POD 3. Dietitians calculated the daily amounts of protein and carbohydrate required for each recipient and adjusted the speed of the enteral nutrition according to the oral intake. Enteral feeding was stopped when the patients could tolerate adequate oral intake containing solid food. All patients were supplemented with both GFO and Yakult 400 three times and once a day, respectively, via the feeding tube or orally until patients could consume a sufficient diet.

All patients underwent preoperative rehabilitation including pulmonary rehabilitation, evaluation of swallowing function, and physical therapy. All patients routinely underwent postoperative rehabilitation delivered by physical therapists at bedside in the intensive care unit, usually from POD 2 or 3 until they were able to walk.

Analyzed parameters

We initially assessed the relationship between SMM and GS at admission. Overall survival (OS) rates after LDLT were investigated in all patients and compared between those with and without preoperative sarcopenia. Postoperative sequential changes in SMM and GS (shown as ratios [%] of pretransplant levels) were compared at 1, 2, 3, 6, and 12 mo after LDLT. Patients who underwent LDLT up to June 2015 and December 2014 were analyzed at 6 and 12 mo after LDLT, respectively.

Statistical analysis

Continuous variables are presented as means ± SD and were nonparametrically analyzed using the Mann–Whitney U test. Correlations between two variables were analyzed using Spearman's rank correlation coefficient. Cumulative OS rates were calculated using Kaplan–Meier methods, and differences between curves were evaluated using the log-rank test. $P < 0.05$ was considered significant. All statistical data were generated using Prism 5 (GraphPad Software Inc., La Jolla, CA, USA).

Results

The median ratio of preoperative SMM at admission was 99% (range 72–127%) of the standard mass, and that of preoperative GS at admission was 32.2 kg (range 16.9–43.8 kg) for men and 17 kg (range 8.1–34.6 kg) for women. At this time, SMM positively correlated with GS ($r = 0.8326$; $P < 0.001$; Fig. 1).

Figure 2 shows the distribution of SMM and GS in all patients at admission using a Venn diagram. Thirteen and 29 patients had low SMM and low GS at admission, respectively. Therefore,

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