



## Applied nutritional investigation

## Recovery of nutritional metabolism after liver transplantation



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## ABSTRACT

**Objective:** Perioperative nutritional assessment is critically important to reflect nutritional management because liver transplantation (LTx) often is undertaken in patients with poor nutritional status. The aim of this study was to evaluate nutritional status, including the non-protein respiratory quotient (npRQ), resting energy expenditure (REE), nitrogen balance, and blood biochemical parameters in patients before and after LTx.

**Methods:** Fourteen patients undergoing LTx and 10 healthy controls were enrolled in this study. The npRQ and REE were measured using indirect calorimetry before LTx and at 2, 3, and 4 wk after the procedure. Blood biochemistry and nitrogen balance calculated by 24-h urine collection were performed concurrently with indirect calorimetric measurement; the results were compared between the two groups.

**Results:** Before LTx, npRQ was significantly lower and serum non-esterified fatty acid levels were significantly higher in the patients than in the controls. Furthermore, a negative nitrogen balance was observed in the patients. These, however, improved significantly at 4 wk after LTx. REE did not significantly increase compared with the preoperative values in recipients. Blood biochemistry showed gradually increasing levels of serum cholinesterase and albumin. These failed to reach to normal levels by 4 wk post-transplant.

**Conclusions:** The findings revealed that improvement of nutritional metabolism after LTx may require 4 wk. Additional nutritional strategies, therefore, may be needed to minimize catabolic state during the early post-transplant period. Adequate, individualized nutritional guidance before and after LTx should be performed in these patients.

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## Introduction

It is well recognized that poor nutritional status is associated with increased morbidity and mortality rates after liver transplantation (LTx) [1,2]. Protein–energy malnutrition is highly prevalent in all forms of liver disease and is common in patients

with end-stage liver disease (ESLD) [3]. Therefore, perioperative nutritional management is critically important to maintain the nutritional status in patients undergoing LTx.

Patients with ESLD waiting for LTx may reflect altered carbohydrate, lipid, and protein metabolism. This leads to malnutrition and may cause a progressive deterioration of their clinical condition. Impaired glucose tolerance is frequently observed in patients with cirrhosis [4,5], resulting in reduced stimulation of nonoxidative glucose disposal (i.e., glycogen synthesis) in the liver and muscle [5–7]. After overnight fasting, enhanced lipid oxidation and reduced glucose oxidation were observed in patients with cirrhosis due to depleted glycogen store [8–10]. Several studies have reported a significant decrease in non-protein respiratory quotient (npRQ) after overnight fasting

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even in patients with moderate cirrhosis, and that npRQ is closely associated with severity of disease state and its prognosis [8–10]. Serum non-esterified fatty acid (NEFA) levels, after overnight fasting, are higher in patients with cirrhosis than in normal individuals. This is due to the increased rate of lipolysis in fat tissue [11]. It has been suggested that this increase in lipolysis may be a useful predictor of npRQ [10–12].

Some studies reported that LTx may effectively reverse cirrhosis-induced alterations in glucose metabolism [13,14]. Therefore, it is quite tempting to speculate that many metabolic disturbances may improve with the recovery of liver function after LTx. The long-term nutritional assessment and health-related quality of life after living donor LTx has been reported [15]. However, to our knowledge, few studies have evaluated nutritional metabolism, especially npRQ, in the early post-transplant period. Short-term nutritional assessment is also needed to monitor recovery of nutritional metabolism and to study the effectiveness of nutritional management instituted in the early post-transplant period. This study aimed to investigate recovery time of nutritional metabolism, including the npRQ, resting energy expenditure (REE), nitrogen balance, and blood biochemical parameters after LTx.

## Methods

### Patients

Patients who underwent living donor LTx and indirect calorimetric measurement at Tokushima University Hospital were studied. Healthy individuals who donated part of their liver were also recruited, making comparative analysis with recipients. This study was approved by the ethics committee of Tokushima University Hospital and conducted in accordance with the Declaration of Helsinki of 1996. The purpose and methodology of the study was explained in detail to all study participants, and their informed consent was obtained.

### Anthropometric measurements

Before indirect calorimetric measurement, anthropometric measurements were performed to determine body weight and body mass index (BMI) under overnight fasting conditions using bioelectrical impedance analysis (DC-320, Tanita Corp., Tokyo, Japan). Before LTx, the dry weight was calculated by deducing an estimated weight for ascites in patients with ascites.

### Indirect calorimetric measurements

REE and npRQ were measured using indirect calorimetry (the AE-300 S respiratory gas analyzer; Minato Medical Science Corp., Ltd., Osaka, Japan). Indirect calorimetric measurements were performed within 1 wk before LTx and at 2, 3, and 4 wk after the procedure. Patients were instructed to avoid eating or drinking anything except non-caloric water or tea from 19:00 the day before the indirect calorimetric measurements. Dietitians interviewed participants regarding the amount of food eaten (meals and snacks) and leftover food, if any, the day before the day of indirect calorimetric measurement. We calculated energy intake as described in a previous study [10]. Urinary urea nitrogen was measured using 24-h urine samples. Nitrogen balance was calculated by 24-h urinary urea nitrogen measurement, as previously described [16]. Indirect calorimetric measurements were performed at 7:30 after overnight fasting. Oxygen consumption and carbon dioxide production rates were measured for 15 min; mean values from the final 10 min were used for analysis. REE and npRQ for each patient were calculated using measured oxygen consumption, rates of carbon dioxide production, and urinary urea nitrogen.

### Perioperative nutritional management and immunosuppressive treatment

All patients registered for LTx were given general dietary advice based on their clinical condition and were provided with a standard hospital diet containing a daily caloric value of 30 to 35 kcal/kg and 1.2 g/kg protein, including branched-chain amino acid (BCAA)-enriched nutrients, according to the Japanese nutritional guideline of cirrhotic patients [17]. A nutrient mixture enriched with BCAA (Aminoleban EN®; Otsuka Pharmaceutical Corp., Tokyo, Japan) or BCAA nutrients (Livact®; Ajinomoto Pharma Corp., Tokyo, Japan) as late evening snack was used for nutritional therapy according to patients' clinical conditions. Dietitians calculated the daily amounts of energy and protein required for each

recipient and adjusted the amount of the enteral nutrition according to the oral intake. After LTx, early enteral nutrition using standard enteral nutrient (Racol®, Otsuka Pharmaceutical Corp., Tokyo, Japan) was initiated as soon as possible. Oral nutrition was started ~5 d after surgery and gradually increased to 30 to 35 kcal/kg caloric value daily and 1.2 g/kg of protein daily. Enteral feeding was discontinued when the patient could tolerate adequate oral intake containing solid diet three times a day.

For immunosuppressive therapy, two doses of basiliximab (on postoperative days 0 and 4) were administered. Standard immunosuppressive therapy at discharge consisted of corticosteroids and calcineurin inhibitors (either tacrolimus or cyclosporine) with mycophenolate mofetil.

### Blood biochemistry

Blood samples were collected when indirect calorimetric measurement. Serum NEFA levels were assayed using an Iatro tech NEFA kit (Mitsubishi Chemical Medicine Corp., Tokyo, Japan). Fasting blood glucose levels were measured by a glucose oxidase electrode method (Quick Auto Neo GLU-HK; Shino-Test Corp., Tokyo, Japan). Serum biochemical parameters such as the levels of white blood cells, C-reactive protein, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, total protein, albumin, cholinesterase, ammonia, and indocyanine green retention test at 15 min results were measured using standard methods.

### Statistical analysis

All data are expressed as mean  $\pm$  SEM. Statistical analyses were performed using SPSS for Windows, release 18.0 (SPSS Inc, Chicago, IL, USA). Baseline and 6-wk clinical data between recipient and healthy control were compared using unpaired *t* test. Changes of clinical data from baseline were evaluated using analysis of variance for repeated measures followed by the Bonferroni test. The significance threshold was  $P < 0.05$ .

## Results

### Characteristics of patients

Sixteen patients were enrolled in this study, of which 2 were unable to complete the study: One had to be reoperated due to complications of hepatic artery dissection and retroperitoneal hemorrhage and the other developed an acute renal failure and had to be treated with continuous hemodiafiltration. These patients were excluded from the study because procedures were highly invasive and could influence nutritional metabolism. The results of the study, therefore, are based on data obtained from 14 patients (6 men, 8 women; mean age  $51.4 \pm 2.7$  y). Etiologies of liver disease varied: hepatitis B (5 patients), hepatitis C (4 patients), primary biliary cirrhosis (1 patient), autoimmune hepatitis (1 patient), Wilson's disease (1 patient), and others (2 patients). Concomitant hepatocellular carcinoma was present in 9 patients. The reported severity of cirrhosis was Child-Pugh class A or B (3 patients) and Child-Pugh class C (11 patients). The mean Model for End-Stage Liver Disease score was  $16.6 \pm 1.6$ . Liver reserve function assessed using retention rate of indocyanine green in 15 min was  $42.1 \pm 3.4\%$ . Living donor LTx was performed using the left and caudate lobe for all patients. The ratio of graft volume to standard liver volume was  $37.6\% \pm 1.4\%$ . No patient suffered from any severe postoperative complications (Clavien-Dindo classification [18] Grade III or higher) or acute graft rejection during the study period. Ten healthy individuals who donated parts of their liver were also included in this study (9 men, 1 woman; mean age  $45 \pm 4.7$  y). There were no significant differences in age and BMI between recipients and controls.

### Anthropometry and dietary intake

Data for anthropometric parameters and food intake before and after LTx are presented in Table 1. Body weight and BMI progressively decreased after LTx. Before LTx, adequate energy

**Table 1**

Anthropometric parameters, dietary intake, and nitrogen balance before and after LTx

	Control	Recipient				P value
		Before	2 wk	3 wk	4 wk	
Body weight (kg)	59.5 ± 2.2	60.7 ± 3.0	57.4 ± 2.9*	56.9 ± 2.9*	55.6 ± 2.8*	<0.001
BMI (kg/m <sup>2</sup> )	21.2 ± 0.8	22.7 ± 0.8	21.2 ± 0.9*	21.2 ± 0.8*	20.5 ± 0.8*	<0.001
Energy intake (kcal/d)	1930 ± 87	1787 ± 123	1565 ± 134	1827 ± 119	1665 ± 139	0.282
Energy intake (kcal/kg/d)	32.7 ± 1.7	29.8 ± 1.8	27.9 ± 2.5	32.7 ± 2.1	30.5 ± 2.5	0.308
Protein intake (g/d)	66.8 ± 2.8	55.1 ± 4.7	53.5 ± 6.7	59.3 ± 5.7	61.1 ± 4.4	0.561
Protein intake (g/kg/d)	1.13 ± 0.05	0.93 ± 0.09	0.96 ± 0.12	1.05 ± 0.10	1.13 ± 0.08	0.218
UUN (g/d)	6.7 ± 0.8	6.8 ± 1.4	6.7 ± 0.9	5.5 ± 0.7	5.3 ± 0.6	0.334
Nitrogen balance (g/d)	0.0 ± 0.9	−1.8 ± 1.6	−2.2 ± 1.1	0.0 ± 1.2	0.5 ± 0.6	0.148

BMI, body mass index; LTx, liver transplantation; UUN, urinary urea nitrogen

Data are expressed as means ± SEM

\* Significant difference from the preoperative value ( $P < 0.05$ ; one-way repeated measures analysis of variance with the Bonferroni post hoc test).

and protein intake was observed in the recipients and controls. Preoperative energy and protein intake were maintained after LTx, although a slight decrease did occur at 2 wk post-LTx.

#### Indirect calorimetric measurement and nitrogen balance

Data for REE before and after LTx are presented in Figure 1. REE in recipients did not significantly change during the study period, and similar to that of the controls. In the recipients, npRQ was  $0.809 \pm 0.018$ ,  $0.823 \pm 0.027$ ,  $0.851 \pm 0.015$ , and  $0.879 \pm 0.014$  at baseline and at 2, 3, and 4 wk post-LTx, respectively (Fig. 2). In the controls, the calculated baseline npRQ was  $0.899 \pm 0.010$ . Before LTx, npRQ was significantly lower in recipients than in controls ( $P < 0.05$ ). However, it gradually increased after LTx. A significant improvement in npRQ was observed at 4 wk after LTx and it became similar to that of controls. Despite nutritional support, negative nitrogen balance was observed before and at 2 wk after LTx (Table 1); however, it improved by 4 wk post-transplant.

#### Blood biochemistry

Serum NEFA levels were significantly higher in recipients than in controls ( $P < 0.05$ ; Fig. 2). Similar to npRQ, serum NEFA levels gradually decreased after LTx. Although there was significant difference between recipients and controls, significant improvements in NEFA levels were observed at 4 wk post-LTx. There was a negative correlation between npRQ and NEFA

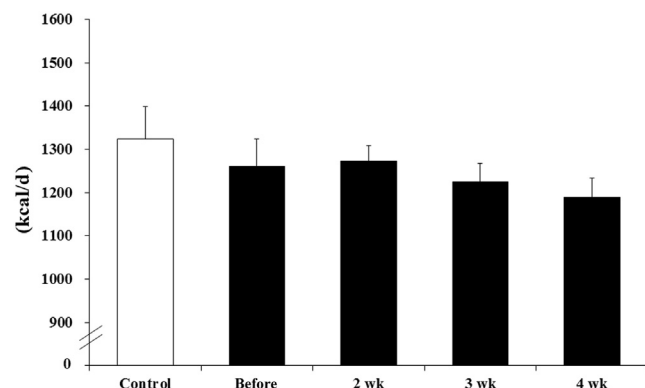
levels, as determined by Pearson's correlation coefficient analysis ( $r = -0.437$ ;  $P < 0.001$ ; Fig. 3). The results of biochemical analysis are shown in Table 2. White blood cells count and C-reactive protein levels normalized by 4 wk after LTx. Serum aspartate aminotransferase, alanine aminotransferase, total bilirubin and direct bilirubin levels normalized in most patients by 4 wk after LTx, although there were considerable interindividual variations. Serum albumin and cholinesterase levels, considered measures of protein synthetic ability in graft liver, gradually increased after LTx; however, they failed to normalize by 4 wk post-LTx.

#### Discussion

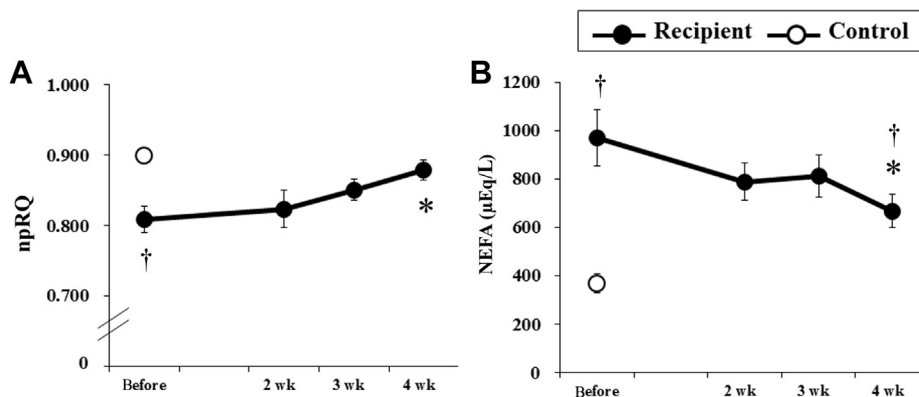
The present study demonstrated that poor nutritional status before LTx assessed by npRQ, serum NEFA levels, and nitrogen balance, improved drastically at 4 wk after transplantation. This finding suggests that the catabolic state, which is common in patients with ESLD, significantly improved after LTx.

The npRQ was considered a nutritional parameter in this study, reflecting the status of energy metabolism in the whole body. Indirect calorimetric measurements allowed a more comprehensive view of energy metabolism in patients undergoing LTx. Before LTx, npRQ was significantly lower and serum NEFA levels were significantly higher in recipients than in controls, thereby suggesting a pronounced catabolic state. These results were consistent with previous studies [8–12]. It was recently reported that the overall survival rate was significantly lower in patients with low skeletal muscle mass than in patients with a normal or high skeletal muscle mass [19]. It also was reported that perioperative nutritional support, including preoperative supplementation of BCAA-enriched nutrients as a late evening snack, immunonutrition and early enteral nutrition, significantly improved overall survival after LTx in patients with low skeletal muscle mass [19]. Therefore, the prevention and improvement of the preoperative catabolic state of recipients is crucial. Aggressive pre-transplant nutritional support should be provided to improve not only patients' nutritional status but also their prognosis after LTx.

LTx causes significant improvement of metabolic disturbances in patients with ESLD. However, several factors, such as preoperative malnutrition, surgical stress, and pharmaceutical therapy can inhibit this improvement in metabolic disturbances. A need for nutritional management following LTx is, thus, warranted. Previous studies have shown that early enteral nutrition, immunonutrition, and provision of BCAA-enriched nutrients effectively reduce postoperative infections and induce an early recovery of nutritional metabolism [16,20,21]. This study demonstrated that recovery of nutritional



**Fig. 1.** Alteration of REE before and after LTx in recipients and controls. Data are expressed as means ± SEM. LTx, liver transplantation; REE, resting energy expenditure.



**Fig. 2.** Alteration of (A) npRQ and (B) serum NEFA levels before and after LTx in recipients and controls. Data are expressed as means  $\pm$  SEM. \*Significant difference from preoperative value ( $P < 0.05$ ; one-way repeated measures analysis of variance with the Bonferroni post hoc test). †Significant difference from the control ( $P < 0.05$ ; unpaired  $t$  test). LTx, liver transplantation; NEFA, non-esterified fatty acid; npRQ, non-protein respiratory quotient.

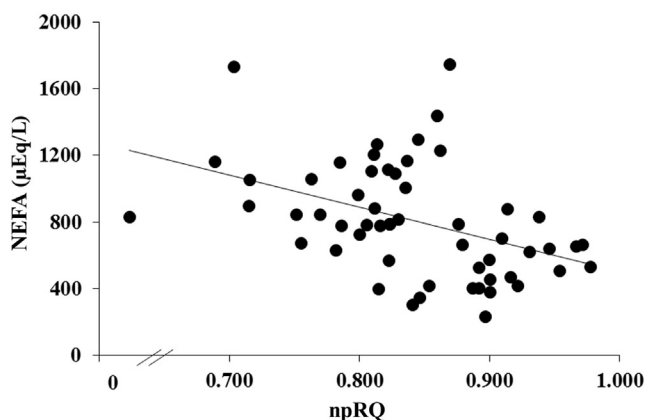
metabolism took approximately 4 wk after LTx. Another study [22] reported that maximum protein loss occurred during the first 10 d post-LTx, and that the restoration of body protein stores was gradual and incomplete even 1 y after LTx. Thus, additional nutritional strategies for the early post-transplant period are needed to minimize the catabolic state, which leads to loss of body protein. In the present study, continuous parenteral or enteral feeding was stopped when patients could tolerate an adequate solid diet three times a day. After initiation of solid food, an overnight fasting period was prolonged. Early onset of gluconeogenesis from amino acids may have occurred through the night leading to an additional loss of body protein. Because early satiety and taste changes due to medication side effects are common patient complaints after LTx, small and frequent meals may help not only to achieve adequate food intakes [23] but also to maintain a healthy nutritional metabolism. Therefore, to prevent a catabolic state, we recommended this strategy for 1 mo after LTx.

The mechanism through which LTx may normalize nutritional metabolism is unclear. Postoperative food intake was maintained at the preoperative value, although it slightly decreased at 2 wk after LTx. Thus, the recovery of nutritional metabolism may not be entirely due to adequate food intake but may involve improvements of endogenous metabolism. Several studies reported that impaired glucose tolerance is frequently

observed in patients with cirrhosis [4,5], resulting in reduced stimulation of nonoxidative glucose disposal in the liver and muscle [5–7]. After an overnight fast, npRQ was decreased more in cirrhotic patients than in healthy controls due to depleted glycogen stores [8–10]. Thus, it is speculated that recovery of npRQ is associated with improvement of the abnormal metabolism. In a previous study, it was reported that despite the associated immunosuppressive therapy, LTx may reverse many alterations of glucose metabolism that are typically present with cirrhosis [13]. Additionally, the study demonstrated that the main factor contributing to the normalization of glucose utilization was a strongly increased nonoxidative glucose disposal. Furthermore, another study reported that hepatic glycogen synthesis, assessed by monitoring hepatic uridine diphosphoglucose turnover with  $^{13}\text{C}$  galactose and acetaminophen, was normalized at 3 wk post-LTx [24]. Therefore, a possible explanation for the improvement of npRQ after LTx could be the normalization of glucose utilization leading to adequate glycogen stores. However, we could not evaluate these glucose metabolisms, which was one limitation of our study.

With respect to REE, studies have reported different results. Our results showed that REE did not significantly change and it was continuously lower than BEE, thereby indicating that energy requirements are not significantly elevated in patients after LTx. These findings are similar to those reported in a previous study that measured REE for duration of 28 d after LTx [25]. However, some studies reported that REE significantly increased during the early post-transplant period, although the method of adjustment of energy expenditure varied [16,22,26]. The variability observed in these studies may have originated from differences in individual variation, the degree of surgical stress, and primary disease etiology. As a result, we suggest that, whenever available, indirect calorimetry should be used to measure REE after LTx, and an individualized nutritional program should be provided.

Blood biochemical parameters reflected a negative correlation between serum NEFA levels and npRQ. This finding has clinical applications because indirect calorimetry is required for evaluation of npRQ and is not always available in the hospital. It has been previously reported that serum NEFA levels were relevant biomarkers for determining npRQ and were useful in determining effectiveness of nutritional therapy in patients with cirrhotic and undergoing hepatic resection [12,27]. Deranged serum NEFA levels may, therefore, be a useful indication for nutritional intervention after LTx.



**Fig. 3.** Correlation between npRQ and serum NEFA levels ( $r = -0.437$ ,  $P < 0.001$ ; Pearson's correlation coefficient analysis). NEFA, non-esterified fatty acid; npRQ, non-protein respiratory quotient.



**Table 2**

Blood biochemical parameters before and after LTx

	Control	Recipient				P value
		Before	2 wk	3 wk	4 wk	
WBC (/μL)	6140 ± 659	4471 ± 848	10036 ± 1392*	7579 ± 940	6979 ± 1085	0.002
CRP (mg/dL)	0.18 ± 0.07	1.39 ± 0.58	1.37 ± 0.21	1.13 ± 0.28	0.78 ± 0.15†	0.459
AST (IU/L)	16 ± 1	68 ± 13†	76 ± 16	65 ± 14	61 ± 20	0.801
ALT (IU/L)	16 ± 2	39 ± 9†	151 ± 34*	108 ± 23	69 ± 13†	0.010
T-Bil (mg/dL)	0.9 ± 0.1	9.5 ± 3.2†	3.3 ± 0.9*	3.0 ± 1.5*	2.8 ± 1.6*	0.037
D-Bil (mg/dL)	0.1 ± 0.0	4.3 ± 2.2	1.4 ± 0.6	1.4 ± 1.1	1.5 ± 1.3	0.175
TP (g/dL)	6.8 ± 0.1	6.3 ± 0.2	5.6 ± 0.2*	5.5 ± 0.2*	5.9 ± 0.1†	0.004
Alb (g/dL)	3.9 ± 0.1	2.6 ± 0.1†	3.5 ± 0.1*	3.4 ± 0.1*	3.4 ± 0.1*,†	<0.001
ChE (mg/dL)	296 ± 18	114 ± 23†	90 ± 9	111 ± 9	142 ± 7†	0.071
FBG (μg/dL)	94 ± 2	99 ± 8	123 ± 13	98 ± 9	93 ± 5	0.030
NH <sub>3</sub> (IU/L)	44 ± 5	84 ± 10†	43 ± 4*	47 ± 4*	48 ± 4*	0.006

ALT, alanine aminotransferase; Alb, albumin; AST, aspartate aminotransferase; ChE, cholinesterase; CRP, C-reactive protein; D-Bil, direct bilirubin; FBG, fasting blood glucose; NH<sub>3</sub>, ammonia; T-Bil, total bilirubin; TP, total protein; WBC, white blood cell

Data are expressed as means ± SEM

\* Significant difference from the preoperative value ( $P < 0.05$ ; one-way repeated measures analysis of variance with the Bonferroni post hoc test).

† Significant difference from the control ( $P < 0.05$ ; unpaired *t* test).

Depending on the pathophysiological condition of each patient, perioperative nutritional management after LTx may be necessary. The guidelines of the European Society of Parenteral and Enteral Nutrition recommend a daily energy intake of 35 to 40 kcal/kg in these patients [28]. Our study followed the Japanese guidelines on nutritional management in cirrhotic patients [17] because of the significant difference in body size between Japanese and white individuals. In the present study, nutritional metabolism recovered by 4 wk after LTx despite the daily energy intake being limited to 30 to 35 kcal/kg. Excessive energy intake may have resulted in overfeeding, leading to hyperglycemia and consequent increased propensity for sepsis [25]. Therefore, changing the time of the meal may be more effective than the high-energy infusion to prevent the post-transplant catabolic state.

The present study has several limitations. First, we could not evaluate sequential data from controls. The data for recipients and controls were compared only before LTx; ideally, comparison after LTx also should have been performed. Second, the sample size was small and we could not evaluate certain factors that may have influenced recovery of nutritional metabolism, such as primary disease etiology, liver graft volume, and donor's background; thus, the mechanisms through which nutritional metabolism was normalized remains unclear. Larger longitudinal studies are needed to investigate the underlying mechanisms causing the recovery of nutritional metabolism after LTx.

## Conclusion

The findings revealed that the improvement of nutritional metabolism after LTx may require 4 wk. Additional nutritional strategies may be needed to minimize the catabolic state in patients undergoing LTx. Adequate individualized nutritional guidance before and after LTx should be provided to these patients.

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## References

- [1] Selberg O, Bottcher J, Tusch G, Pichlmayr R, Henkel E, Muller MJ. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. *Hepatology* 1997;25:652–7.
- [2] Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, et al. Nutritional status: Its influence on the outcome of patients undergoing liver transplantation. *Liver Int* 2010;30:208–14.
- [3] McCullough AJ, Bugianesi E. Protein-calorie malnutrition and the etiology of cirrhosis. *Am J Gastroenterol* 1997;92:734–8.
- [4] Petrides AS, Vogt C, Schulze-Berge D, Matthews D, Strohmeyer G. Pathogenesis of glucose intolerance and diabetes mellitus in cirrhosis. *Hepatology* 1994;19:616–27.
- [5] Selberg O, Burchert W, vd Hoff J, Meyer GJ, Hundeshagen H, Radoch E, et al. Insulin resistance in liver cirrhosis. Positron-emission tomography scan analysis of skeletal muscle glucose metabolism. *J Clin Invest* 1993;91:1897–902.
- [6] Owen OE, Reichle FA, Mozzoli MA, Kreulen T, Patel MS, Elfenbein IB, et al. Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis. *J Clin Invest* 1981;68:240–52.
- [7] Krahenbuhl L, Lang C, Ludes S, Seiler C, Schafer M, Zimmermann A, et al. Reduced hepatic glycogen stores in patients with liver cirrhosis. *Liver Int* 2003;23:101–9.
- [8] Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. *Nutrition* 2002;18:229–34.
- [9] Merli M, Riggio O, Romiti A, Ariosto F, Mango L, Pinto G, et al. Basal energy production rate and substrate use in stable cirrhotic patients. *Hepatology* 1990;12:106–12.
- [10] Yamanaka H, Genjida K, Yokota K, Taketani Y, Morita K, Miyamoto KI, et al. Daily pattern of energy metabolism in cirrhosis. *Nutrition* 1999;15:749–54.
- [11] Riggio O, Merli M, Cantafora A, Di Biase A, Lalloni L, Leonetti F, et al. Total and individual free fatty acid concentrations in liver cirrhosis. *Metabolism* 1984;33:646–51.
- [12] Yamanaka-Okumura H, Nakamura-Kutsuzawa T, Teramoto A, Urano E, Katayama T, Miyake H, et al. Non-esterified fatty acid is being validated as a substitute measure for non-protein respiratory quotient in patients with cirrhosis. *ESPEN J* 2013;8:90–4.
- [13] Merli M, Leonetti F, Riggio O, Valeriano V, Ribaudo MC, Strati F, et al. Glucose intolerance and insulin resistance in cirrhosis are normalized after liver transplantation. *Hepatology* 1999;30:649–54.
- [14] Merli M, Giusto M, Riggio O, Gentili F, Molinaro A, Attali AF, et al. Improvement of nutritional status in malnourished cirrhotic patients 1 year after liver transplantation. *ESPEN J* 2011;6:142–7.
- [15] Urano E, Yamanaka-Okumura H, Teramoto A, Sugihara K, Morine Y, Imura S, et al. Pre- and postoperative nutritional assessment and health-related quality of life in recipients of living donor liver transplantation [e-pub ahead of print]. *Hepatol Res* 10.1111/hepr.12263, accessed August 6, 2014.
- [16] Hasse JM, Blue LS, Liepa GU, Goldstein RM, Jennings LW, Mor E, et al. Early enteral nutrition support in patients undergoing liver transplantation. *JPN J Parenter Enteral Nutr* 1995;19:437–43.
- [17] Suzuki K, Endo R, Kohgo Y, Ohtake T, Ueno Y, Kato A, et al. Guidelines on nutritional management in Japanese patients with liver cirrhosis from the perspective of preventing hepatocellular carcinoma. *Hepatol Res* 2012;42:621–6.

- [18] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
- [19] Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. *Am J Transplant* 2013;13:1549–56.
- [20] Kaido T, Ogura Y, Ogawa K, Hata K, Yoshizawa A, Yagi S, et al. Effects of posttransplant enteral nutrition with an immunomodulating diet containing hydrolyzed whey peptide after liver transplantation. *World J Surg* 2012;36:1666–71.
- [21] Yoshida R, Yagi T, Sadamori H, Matsuda H, Shinoura S, Umeda Y, et al. Branched-chain amino acid-enriched nutrients improve nutritional and metabolic abnormalities in the early posttransplant period after living donor liver transplantation. *J Hepatobiliary Pancreat Sci* 2012;19: 438–48.
- [22] Plank LD, Metzger DJ, McCall JL, Barclay KL, Gane EJ, Streat SJ, et al. Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. *Ann Surg* 2001;234:245–55.
- [23] Sanchez AJ, Aranda-Michel J. Nutrition for the liver transplant patient. *Liver Transpl* 2006;12:1310–6.
- [24] Schreiter P, Gillet M, Chiolo R, Wauters JP, Berger M, Tappy L. Postprandial hepatic glycogen synthesis in liver transplant recipients. *Transplantation* 2000;69:978–81.
- [25] Plevak DJ, DiCecco SR, Wiesner RH, Porayko MK, Wahlstrom HE, Janzow DJ, et al. Nutritional support for liver transplantation: identifying caloric and protein requirements. *Mayo Clin Proc* 1994;69:225–30.
- [26] Ferreira LG, Santos LF, Anastacio LR, Lima AS, Correia MI. Resting energy expenditure, body composition, and dietary intake: a longitudinal study before and after liver transplantation. *Transplantation* 2013;96: 579–85.
- [27] Sugihara K, Yamanaka-Okumura H, Teramoto A, Urano E, Katayama T, Mori H, et al. Recovery pattern of non-protein respiratory quotient and non-esterified fatty acid after liver resection. *Nutrition* 2014;30:443–8.
- [28] Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J, et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. *Clin Nutr* 2006;25: 285–94.