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Switching From Tacrolimus to Cyclosporine A to Prevent Primary Biliary Cirrhosis Recurrence After Living-Donor Liver Transplantation

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Recurrence of primary biliary cirrhosis (PBC) after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A against PBC recurrence after liver transplantation have been reported. Participants were 4 patients who underwent living-donor liver transplantation (LDLT) for end-stage liver disease due to PBC. Tacrolimus was used for initial immunosuppression, and this was switched to cyclosporine A at least 3 months after liver transplantation. Targeted trough level of cyclosporine A was 20 times that of tacrolimus. We assessed liver and renal function, as well as antimitochondrial M2 antibody for recipients prior to LDLT, as well as before and after switching immunosuppressive agents. Patients were 1 man and 3 women, and they were ages 45 to 47 years at LDLT. Timing of switching from tacrolimus to cyclosporine A was 13, 3, 7, and 4 months respectively after liver transplantation, and all 4 patients have been on cyclosporine A without adverse effects at 20 to 46 months after transplantation. In 2 of 4 patients who had high titers of antimitochondrial M2 antibody before transplantation, antibody titer did not elevate after LDLT. In the other 2 patients without elevation of antimitochondrial M2 antibody, the titer did not turn positive. Switching from tacrolimus to cyclosporine A was possible without medical problems, and all patients exhibit no recurrence of PBC. Cyclosporine A may be useful for prevention of PBC recurrence after LDLT.

Key Words: Primary biliary cirrhosis – Living-donor liver transplantation – Immunosuppression – Recurrence

Primary biliary cirrhosis (PBC) has been one of the most common indications for liver transplantation in adults. Recurrence of PBC after liver transplantation has been shown to negatively affect graft and patient survival. Recently, protective effects of cyclosporine A (CyA) against PBC recurrence after liver transplantation have been reported.[1,2] Corticosteroids after liver transplantation may

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Table 1 Clinical variables before liver transplantation, and before and after switching from tacrolimus to cyclosporine A

	Patient 1			Patient 2			Patient 3			Patient 4		
	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After	Pre-LT	Before	After
Anti-M2 antibody, U/mL	<5	<5	<5	<5	<5	<5	149	66	66	155	47	94
AST, U/mL	167	15	13	112	15	18	112	103	20	132	19	21
ALT, U/mL	51	9	6	78	9	8	43	163	15	83	22	15
Total bilirubin, mg/dL	12.0	0.8	0.6	2.2	0.4	0.3	19.6	2.1	0.9	19.0	0.6	0.6
Albumin, g/dL	2.8	3.8	4.5	3.0	3.3	3.9	2.7	3.5	4.0	2.3	3.7	4.1
PT-INR	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0	1.2	1.0	1.0
Creatinine, mg/dL	0.4	0.74	0.76	0.48	0.65	0.78	0.5	0.62	1.02	0.68	1.19	1.37

ALT, alanine aminotransferase; AST, aspartate aminotransferase; pre-LT, before liver transplantation; PT-INR, prothrombin time–international normalized ratio.

be important to prevent recurrence of PBC.[3] We retrospectively assessed the outcome of switching from tacrolimus to CyA in patients who underwent living-donor liver transplantation (LDLT) for PBC.

Patients and Methods

Participants were 4 patients who underwent LDLT for end-stage liver disease due to PBC at Jikei University Hospital from 2008 to 2009. Tacrolimus and steroids were used for initial immunosuppression, and these were switched to CyA, steroids, and/or mycophenolate mofetil at least 3 months after liver transplantation. The targeted trough level of CyA was 20 times that of tacrolimus. We assessed liver function, renal function, antimitochondrial M2 antibody, and PBC recurrence among recipients before LDLT, and before and after switching immunosuppressive agents.

Results

Patient 1

The recipient was a woman age 45 years at LDLT who had received a diagnosis of PBC at age 36 years. The donor was the woman's 45-year-old husband. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's Model for End-Stage Liver Disease (MELD) score was 18, and her Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 22 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT. After LDLT, the patient was treated with insulin for diabetes mellitus due to adverse effects of tacrolimus.

Patient 2

The recipient was a woman age 44 years at LDLT who had received a diagnosis of PBC at age 30 years. The donor was the woman's 48-year-old older brother. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the recipient's MELD score was 11, and her Child-Pugh score was 9. Immunosuppressive agent was switched from tacrolimus to CyA at 3 months after LDLT without medical problems or PBC recurrence (Table 1). Antimitochondrial M2 antibody remained negative after LDLT.

Patient 3

The recipient was a woman age 47 years at LDLT who had received a diagnosis of PBC at age 38 years. The donor was an 18-year-old daughter. ABO blood type–identical LDLT was performed using the extended left lobe graft. At LDLT, the MELD score was 20, and the Child-Pugh score was 10. Immunosuppressive agent was switched from tacrolimus to CyA at 7 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 20 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection [rejection activity index (RAI) = 2; P1 B1 V0] without PBC recurrence (Fig. 1A).

Patient 4

The recipient was a man age 46 years at LDLT who had received a diagnosis of PBC at age 43 years. The donor was the man's 43-year-old younger sister. ABO blood type–identical LDLT was performed

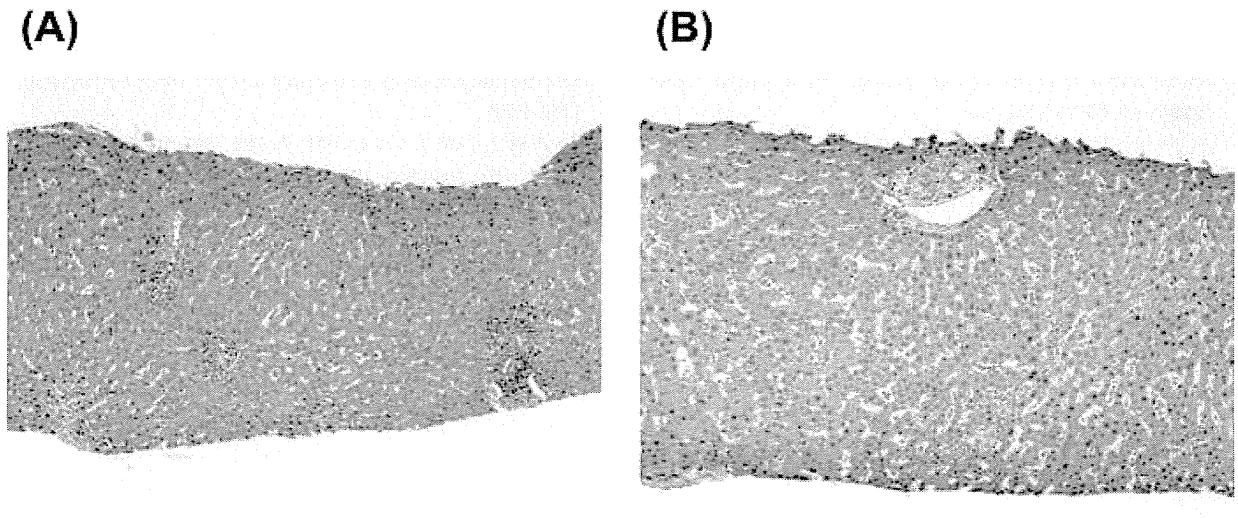

Fig. 1 (A) Liver biopsy specimen for liver dysfunction at 20 months after LDLT for patient 3 revealed moderate late cellular rejection (isolated central perivenulitis) and mild acute cellular rejection (RAI = 2; P1 B1 V0) without PBC recurrence. (B) Liver biopsy specimen for liver dysfunction at 8 months after LDLT for patient 4 revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence.

using the right lobe graft. At LDLT, the recipient's MELD score was 20, and his Child-Pugh score was 12. Immunosuppressive agent was switched from tacrolimus to CyA at 4 months after LDLT. Recipient had a high titer of antimitochondrial M2 antibody before LDLT; antibody titer did not elevate after LDLT (Table 1). At 8 months after LDLT, liver biopsy was performed for liver dysfunction. Liver biopsy specimen revealed moderate acute cellular rejection (RAI = 4; P1 B2 V1) without PBC recurrence (Fig. 1B).

Discussion

With the recent improvements in surgical, anesthetic, and microbiological techniques; the development of immunosuppressive agents; and increasing experience and better patient selection, better outcomes for liver transplantation for end-stage liver disease have been achieved. Liver transplantation is the treatment choice for patients with end-stage liver disease due to PBC; however, the incidence of recurrent PBC increases progressively, and histologic recurrent PBC is reported in approximately one third of patients by 10 years after liver transplantation.[1–6] The pathogenesis of PBC remains uncertain, and the perioperative clinical variables associated with recurrence of PBC after liver transplantation are not completely elucidated.

Despite the era effect of immunosuppressive agents, a major conclusion of most reports in patients who underwent liver transplantation for PBC is that the use of CyA is associated with a lower incidence of PBC recurrence in comparison with tacrolimus.[1–6] However, mechanisms of CyA for prevention of PBC recurrence are unknown. Conversely, tacrolimus is considered as a potent immunosuppressive agent with regard to mortality and graft loss at 1 year, as well as acute rejection.[7] Switching from tacrolimus as the primary immunosuppressive agent for PBC after liver transplantation to CyA as a maintenance immunosuppressive agent may enable safe prevention of PBC recurrence, as well as better outcomes.

Conclusions

Switching from tacrolimus to CyA was possible without sequelae, and all patients exhibit no recurrence of PBC. CyA may be useful for prevention of PBC recurrence after LDLT.

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Original Article

Pre- and postoperative nutritional assessment and health-related quality of life in recipients of living donor liver transplantation

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Aim: The nutritional state of living donor liver transplantation (LDLT) recipients is one of the most important factors affecting postoperative outcome. Although the assessment of health-related quality of life (HRQOL) is of increasing importance, few studies have examined this in conjunction with LDLT recipient nutritional state.

Methods: Ten LDLT recipients with end-stage liver disease were recruited for this study. Measurements of energy expenditure, anthropometrics and laboratory data were performed before and 1, 6 and 12–24 months after LDLT. HRQOL was measured by using the 36-item Short-Form (SF-36) before and 1, 3, 6 and 12–24 months after LDLT.

Results: The preoperative value of non-protein respiratory quotient (npRQ) was 0.796 ± 0.026 and it increased significantly after the operation. Serum non-esterified fatty acid (NEFA) levels were high in the preoperative state, but had significantly decreased 1 month after the operation. A negative correlation between npRQ and NEFA was observed throughout the study period. Cholinesterase and albumin levels improved to normal levels within 6 and 12–24 months, respectively. The recovery of the physical component summary of the SF-36 was observed after the improvement of all domains of laboratory data and energy metabolism based on the nutritional state.

Conclusion: This study demonstrated that the recovery of metabolic function, laboratory data and HRQOL in LDLT recipients are variable, and it took more than 6 months to normalize the liver protein synthetic capacity and physical HRQOL score periods. Therefore, long-term nutritional support is required in LDLT recipients.

Key words: energy metabolism, living donor liver transplantation, non-protein respiratory quotient, nutritional assessment, quality of life

INTRODUCTION

LIVER TRANSPLANTATION IS the accepted treatment for patients with end-stage liver disease (ESLD). The outcome for liver transplantation patients has improved markedly in recent years as a result of advances in immunosuppressive protocols, preservation techniques and postoperative management.[1] In Japan, a total of 4292 living donor liver transplantations (LDLT) have been performed in 2006, and 2621 of these were adult-to-adult LDLT. The overall 3- and 5-year patient survival rates were 73.8% and 70.4%, respectively.[2]

Living donor liver transplantation recipients' malnutrition was found to be associated with increased length of stays in the intensive care unit (ICU), mortality and total hospital charges.[3,4] Therefore, adequate nutritional management and therapy are required to avoid malnutrition and the associated risks. However, there have been few studies which have performed nutritional assessment of LDLT patients.

The majority of patients with ESLD have decreased respiratory quotient (RQ) and increased resting energy expenditure (REE).[5,6] Low RQ is associated with decreased glucose oxidation and increased fat oxidation[7] and is indicative of starvation, such as which can

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occur after an overnight fast due to a lack of glycogen storage. For this reason, an increase in non-protein RQ (npRQ) values can be used as a marker of recovery in chronic liver disease patients.[8] Tajika *et al.*[9] also found that the npRQ represented an independent risk factor for survival in cirrhotic patients as individuals with a lower npRQ had a worse prognosis. Hypermetabolism may contribute to the protein energy malnutrition (PEM) associated with liver disease[10] as an increased REE has been reported in cirrhotic patients.[5] However, a definitive connection cannot be made as other reports have described normal or decreased REE.[7,11] In addition, a longitudinal study reported that postoperative hypermetabolism peaked on day 10 after transplantation, and continued to the hypermetabolic state over the following 6 months.[12] By 12 months post-transplant, there was no longer a difference between the measured and predicted basal metabolic rates.[13] Despite these studies, very little information is available which describes REE and RQ changes over the long term after LDLT.

The goal of transplantation is not only to ensure patient survival, but also to return a similar state of health as was enjoyed before the disease. This requires achieving a balance between the functional efficacy of the graft and the patient's physical and psychological integrity. The assessment of the health-related quality of life (HRQOL) is increasingly used as an outcome measure when evaluating medical procedures.[14] Although numerous studies have reported significantly improved HRQOL compared with the preoperative state,[15,16] the precise timing of the improvement is often debated. In addition, most studies that have investigated HRQOL following LDLT have not included measurements of energy metabolism, which is the basis of nutritional therapy, such as RQ.

In this study, we therefore performed nutritional assessment, including energy metabolism based on nutritional state, laboratory data and HRQOL, in both the pre- and postoperative states of LDLT recipients.

METHODS

Patients

THIS STUDY WAS conducted at Tokushima University Hospital. Ten recipients and eight control subjects were recruited for the study. The study design was approved by the ethical committee of Tokushima University Hospital. Written informed consent was obtained from each patient.

Anthropometric and food intake data

Bodyweight (BW) and body mass index (BMI) were measured under fasting conditions using a TBF-102 body composition meter (Tanita, Tokyo, Japan). Before LDLT, the dry weight was calculated by deducting an estimated weight for ascites in patients with ascites. Dieticians interviewed the amount of food eaten (meals + snacks), and asked the dietary intake by 24-h recall method and calculated energy intake. Under a dietitian's advice, a recommended energy intake of 30–35 kcal/kg was adjusted depending on their activity, with a protein intake of 1.0–1.2 g/kg and fat intake of below 50 g/day. Patients with inadequate food intake received supplemental enteral nutrient. A dietitian checked BW at every measurement day by indirect calorimetry and instructed on maintaining adequate BW.

Laboratory data

Serum biochemical parameters (white blood cells [WBC], red blood cells [RBC], hemoglobin [HGB], platelets [PLT], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [T-bil], direct bilirubin [D-bil], γ-glutamyltransferase [GGT], total protein [TP], albumin [Alb], cholinesterase [ChE], ammonia [NH_3] and C-reactive protein [CRP]) were measured prior to and 1, 6 and 12–24 months after LDLT. Blood samples were taken to determine the concentrations of fasting blood glucose (FBG) and non-esterified fatty acids (NEFA) at the indirect calorimetry measurements.

Energy measurements

Measurements of energy expenditure were made before and 1, 6, and 12–24 months after LDLT. Indirect calorimetry measurements were carried out at 07.30 hours after overnight fasting using an AE-300S respiratory gas analyzer (Minato Medical Science, Osaka, Japan). The O_2 consumption and CO_2 production rates were calculated, and once an equilibrium steady state was achieved, these values were used to calculate the REE. The basal energy expenditure (BEE) was estimated according to the equation reported by Harris and Benedict,[17] and the ratio of REE to BEE was expressed as the %REE. Urine was collected to assay the amount of nitrogen excretion. The npRQ was calculated from measurements of the daily urinary nitrogen excretion.

HRQOL

Questionnaires were completed prior to and 1, 3, 6 and 12–24 months after LDLT. HRQOL was assessed by the Short-Form Version 2 (SF-36v2)[18,19] which consists of

eight categories, including physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). It also includes two summary areas, with one representing a physical component summary (PCS) and the other a mental component summary (MCS). The raw scores were linearly transformed with standard scoring algorithms yielding scores that were then further adjusted using a Japanese norm-based scoring system to generate normalized scores with a mean (standard deviation) of 50 ± 10 (norm-based scores [NBS]).[20]

Statistical analysis

All data are expressed as mean ± standard error. Statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS, Chicago, IL, USA). Repeated measures ANOVA with subsequent Dunnett's test were used to assess postoperative changes from the preoperative state. Differences between recipients and control subjects were analyzed with the use of Student's *t*-test. QOL score of LDLT recipient before and after LDLT was compared with healthy control subjects at baseline using Student's *t*-test with Bonferroni correction. Pearson's correlation coefficient analysis and simple regression were used to assess the relationship between npRQ and serum NEFA levels. *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Patients

THE CHARACTERISTICS OF the LDLT patients and control subjects are listed in Table 1. LDLT was performed using the left and caudate lobe for all patients. The severity of postoperative complications was graded according to the Clavien–Dindo classification. Continuous hemodiafiltration was performed in case 7 at 13 days after LDLT, because the patient was complicated with acute renal failure (grade IV-a). Case 1 suffered from supraventricular arrhythmia and case 3 suffered from hemophagocytic syndrome (grade II). Other patients did not have severe complications after LDLT (grade I). None of the patients required reoperation for complications arising from the transplant operation. No patients suffered long-term complications associated with LDLT, such as biliary tract stricture and chronic rejection. The control group consisted of eight healthy individuals who donated part of the liver.

Table 1 Characteristics of LDLT recipients and control subjects

Case	Sex	Age (years)	Bodyweight (kg)	Body mass index (kg/m²)	MELD score	Child–Pugh		Diagnosis	Period in ICU (days)	Period in hospital (days)	Graft	
						Grade	Score				(g)	GV/SLV (%)
1	M	55	54.5	20.8	16.0	C	13	LC (HCV)/HCC	7	46	396	34.2
2	M	55	67.9	24.3	24.5	C	10	LC (HBV)/FH	7	72	515	41.3
3	F	52	52.9	23.8	12.6	C	11	LC (HCV)/HCC	12	50	510	47.8
4	M	56	61.3	20.5	14.5	C	13	LC (HBV)	7	44	450	36.8
5	M	66	50.1	17.9	14.0	B	9	LC (HCV)/HCC	11	35	420	37.8
6	F	57	52.5	22.7	18.5	C	12	LC (non-B, non-C)	7	50	460	45.6
7	F	59	63.4	27.1	17.8	C	13	LC (HCV)	25	85	385	33.9
8	F	38	57.0	22.5	13.1	C	10	LC (HBV)/HCC	8	37	390	35.2
9	F	56	83.9	28.7	16.3	C	10	LC (HCV)/HCC	6	70	520	37.5
10	F	57	55.9	21.6	27.2	C	11	LF (autoimmune)	8	73	370	32.1
Recipient ($n = 10$)	M4/F6	55.1 ± 2.2	59.9 ± 3.2	23.0 ± 1.0	17.4 ± 1.5		11.4 ± 0.5		9.8 ± 1.8	56.2 ± 5.5	441.6 ± 20.5	38.2 ± 1.8
Control ($n = 8$)	M7/F1	48.8 ± 4.8	58.6 ± 1.9	20.9 ± 0.6								

Values are expressed as mean ± standard error.
FH, fulminant hepatitis; GV/SLV, graft volume/standard liver volume; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; LC, liver cirrhosis; LF, liver failure; MELD, model for end-stage liver disease.

Table 2 Body composition and energy intake

	Control	Before LDLT	After LDLT		
			1 month	6 months	12–24 months
Body composition					
BW (kg)	58.6 ± 1.9	59.9 ± 3.2	56.5 ± 3.6	56.0 ± 2.0	59.6 ± 3.9
BMI (kg/m^2)	20.9 ± 0.6	23.0 ± 1.0	21.7 ± 1.3	21.1 ± 0.6	22.8 ± 1.1
Energy intake					
Total (kcal/day)	1996 ± 71	1570 ± 102†	1736 ± 173	1823 ± 125	1873 ± 101
per kg of BW (kcal/kg per day)	34.3 ± 1.7	26.8 ± 4.0†	31.5 ± 1.4	33.2 ± 0.1	31.2 ± 0.1

Values are expressed as mean ± S.E.
$^\dagger P < 0.05$ vs control value (unpaired Student's *t*-test).
BMI, body mass index; BW, bodyweight; LDLT, living donor liver transplantation.

Body composition and dietary intake

Table 2 lists the measurement data for BW, BMI and dietary intake. The mean BW decreased 3.4 ± 1.4 kg in the first month after the operation. An identical trend was observed for BMI. However, there were no significant differences in BW and BMI among postoperative measurements compared with the preoperative values.

The patient preoperative dietary intake was 26.8 ± 4.0 kcal/kg per day, while the postoperative dietary intake was 31.5 ± 1.4, 33.2 ± 0.1 and 31.2 ± 0.1 kcal/kg per day at 1, 6 and 12–24 months, respectively, after LDLT. The postoperative values also did not significantly differ from those obtained before the transplant.

Laboratory data

The serum of LDLT recipients and control patients were subjected to various biochemical analyses (Table 3). The WBC count did not differ significantly at each postoperative time point compared with preoperative value. However, the RBC count and HGB levels had not returned to normal levels after 12–24 months, while the PLT numbers significantly increased in all periods after LDLT. Both T-bil and D-bil were higher in preoperative measurements compared with normal levels, but they had returned to normal levels after 6 months. Although GGT did not significantly differ at most postoperative time points compared with the preoperative value, it increased during the first 6 months after LDLT. After an initial decrease, TP returned to normal levels after 6 months. Alb was significantly higher in both the 1- and 6-month measurements after LDLT, but it returned to the lower limit of normal levels after 12–24 months. FBG did not significantly change at each postoperative point compared with the preoperative value. Although the amount of NH_3 was higher in the preoperative sample compared with normal levels, it significantly decreased in all periods after LDLT. ChE significantly increased after LDLT from its initially low level in the 6- and 12–24-month serum samples and had reached normal levels after 6 months. The preoperative levels of NEFA were higher than the normal levels and significantly decreased after the operation. In addition, simple regression analysis revealed a negative correlation between npRQ and serum NEFA concentrations for samples regardless of when they were collected ($r = -0.624$, $P < 0.001$; Fig. 1).

Nutritional metabolism

Although there was a great variability in the anthropometric and laboratory data between individuals, the preoperative mean of the npRQ value was consistently low (0.796 ± 0.026). However, it increased to 0.888 ±

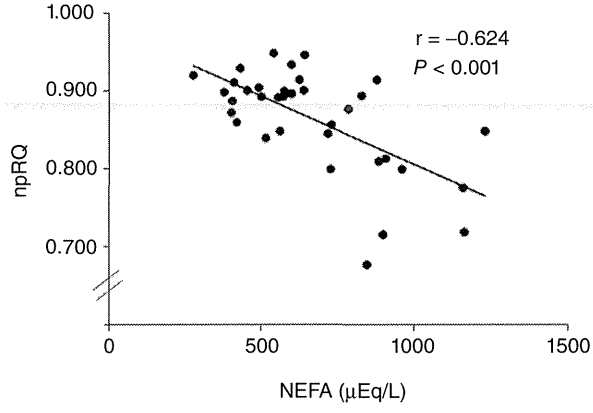

Figure 1 Relationship between npRQ and serum NEFA levels. ($P < 0.001$; Pearson's correlation coefficient analysis). NEFA, non-esterified fatty acids; npRQ, non-protein respiratory quotient.

Table 3 Laboratory data in LDLT recipients and control subjects

	Control	Before LDLT	After LDLT		
			1 month	6 months	12–24 months
WBC (/μL)	6163 ± 826	4440 ± 1217	6470 ± 1391	5478 ± 797	5544 ± 665
RBC ($\times 10^6$/μL)	4.28 ± 0.13	3.19 ± 0.18†	3.19 ± 0.15	3.89 ± 0.28*	4.10 ± 0.30*
HGB (g/dL)	12.5 ± 0.5	10.8 ± 0.5†	10.6 ± 0.5	12.0 ± 0.8	12.9 ± 0.9*
PLT ($\times 10^4$/μL)	25.6 ± 1.7	7.3 ± 1.6†	29.5 ± 4.2*	22.6 ± 2.9*	22.5 ± 1.7*
AST (IU/L)	17 ± 1	71 ± 18†	61 ± 26	30 ± 8	29 ± 7
ALT (IU/L)	17 ± 3	42 ± 12	62 ± 17	23 ± 6	16 ± 2
T-bil (mg/dL)	0.8 ± 0.1	9.5 ± 4.0	2.7 ± 1.4	0.9 ± 0.1*	1.0 ± 0.1*
D-bil (mg/dL)	0.1 ± 0.0	4.8 ± 2.8	1.4 ± 1.1	0.2 ± 0.1	0.1 ± 0.0
GGT (IU/L)	25 ± 5	30 ± 5	105 ± 18	112 ± 66	74 ± 31
TP (g/dL)	6.8 ± 0.1	6.3 ± 0.3	5.7 ± 0.1*	6.6 ± 0.1	7.1 ± 0.1*
Alb (g/dL)	3.9 ± 0.1	2.4 ± 0.1†	3.4 ± 0.1*	3.7 ± 0.2*	4.0 ± 0.1*
ChE (IU/L)	292 ± 22	77 ± 14†	132 ± 12*	299 ± 6*	309 ± 21*
NH_3 (μg/dL)	39 ± 4	91 ± 12†	43 ± 2*	41 ± 5*	35 ± 4*
CRP (mg/dL)	0.15 ± 0.08	0.64 ± 0.19†	0.74 ± 0.17	0.22 ± 0.08	0.29 ± 0.15
ICG15R (%)	5.1 0.9	45.4 ± 3.2†			
FBG (mg/dL)	94 ± 3	106 ± 9	89 ± 4	106 ± 8	113 ± 6
NEFA (μEq/L)	402 ± 42	1002 ± 112†	630 ± 66*	602 ± 17*	501 ± 45*

Values are expressed as mean ± standard error.
*$P < 0.05$ vs preoperative value (Dunnett's multiple comparison test).
†$P < 0.05$ vs control value (unpaired Student's *t*-test).
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; CRP, C-reactive protein; D-bil, direct bilirubin; FBG, fasting blood glucose; GGT, γ-glutamyltransferase; HGB, hemoglobin; ICGR15, retention rate of indocyanine green in 15 min; LDLT, living donor liver transplantation; NEFA, non-esterified fatty acids; NH_3, ammonia; PLT, platelet; RBC, red blood cell; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

0.011, 0.895 ± 0.009 and 0.892 ± 0.010 at 1, 6 and 12–24 months, respectively, after the operation, which represented a significant difference when compared to the preoperative value (Fig. 2). In addition, although the npRQ was lower in the recipient group than the control group prior to LDLT, there was no significant difference between these groups after LDLT.

In this study, the %REE (86.4 ± 4.3) in the preoperative state was similar with the values determined for the control group. After LDLT, the %REE increased to 92.3 ± 2.8% during the first month, and significantly increased to 98.7 ± 3.1% and 98.3 ± 2.6% at 6 and 12–24 months, respectively, after the operation.

HRQOL

During the preoperative period, the mean HRQOL scores for all of the represented scales were below the control group and Japanese NBS. One physical (PF) and two psychological (VT and SF) components were significantly improved after 12–24 months compared with the preoperative values (Fig. 3). Although the PCS was also significantly improved after 12–24 months, this score remained lower than the control group and Japanese NBS. In contrast, the MCS did not differ at each time point compared with the control group and Japanese NBS.

DISCUSSION

AS THE LIVER plays a central role in fuel and energy metabolism, protein-energy malnutrition is common in patients with liver cirrhosis due to abnormal fuel metabolism. Energy metabolism is unbalanced in patients with a poor nutritional status, as demonstrated by increased and decreased rates of lipid and glucose oxidation, respectively. In this study, the npRQ of the patients prior to LDLT was initially low; however, it significantly increased after the operation. Thus, patients had more calories derived from fat and fewer calories derived from carbohydrates before LDLT due to decreased glycogen storage as a result of liver disorder and is consistent with a previous report.[10] Moreover, a decreased npRQ in the fasting state in cirrhotic patients would induce an elevation of serum NEFA concentra-

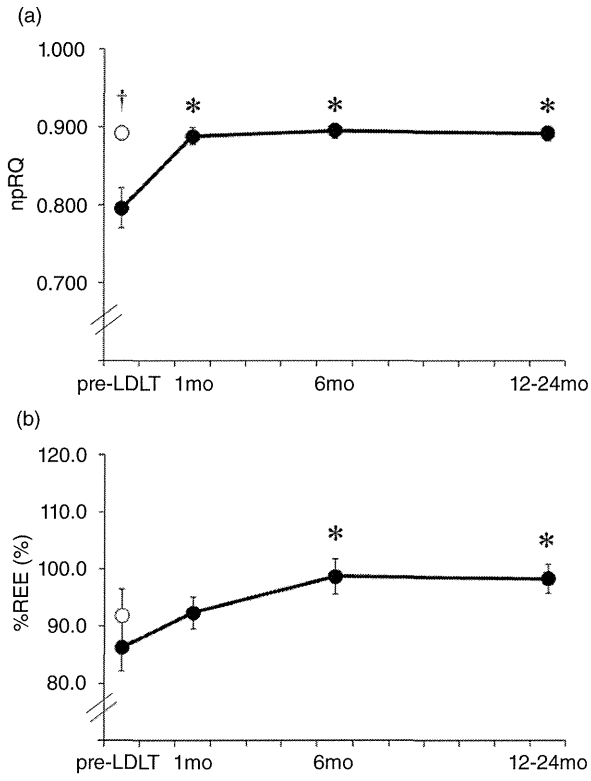

Figure 2 (a) npRQ and (b) %REE before and after LDLT. Open squares indicate control; filled squares indicate LDLT recipients. Values are expressed as mean ± standard error. $*P < 0.05$ vs preoperative value (Dunnett's multiple comparison test). $\dagger P < 0.05$ vs control value (unpaired Student's *t*-test). %REE, resting energy expenditure/basal energy expenditure; LDLT, living donor liver transplantation; npRQ, non-protein respiratory quotient. -○-, control: -●-, LDLT recipients.

tions by diminishing glucose oxidation and decrease glycogen stores in the liver and skeletal muscle.[5] Although the mean NEFA value was high before LDLT, it was significantly lower at all postoperative time points compared with the preoperative value. Moreover, a negative correlation was observed between npRQ and NEFA. For the diagnosis of npRQ, however, indirect calorimetry is required so that in daily practice most clinicians cannot use this approach. Taken together, these results suggest that the assessment of serum NEFA concentrations is a useful predictor of npRQ values, without the need for time-consuming indirect calorimetry measurements.

We also assessed changes in the laboratory data of blood serum associated with LDLT. The parameters of liver detoxification capacity, such as NH_3 and T-bil levels, immediately improved after transplantation. However, the length of time for the ChE and Alb levels, which indicate hepatic protein synthetic capacity, to improve to normal levels required 6 and 12–24 months, respectively. In a previous study, measuring the ChE activity showed liver function, which was useful for determining the prognosis of patients during the post-transplantation[21] and recovery period, which also agreed with past reports.[22] Although the mean npRQ was lower in the recipient group than the control group before LDLT, there was no significant difference between these groups 1 month after the transplantation. These results

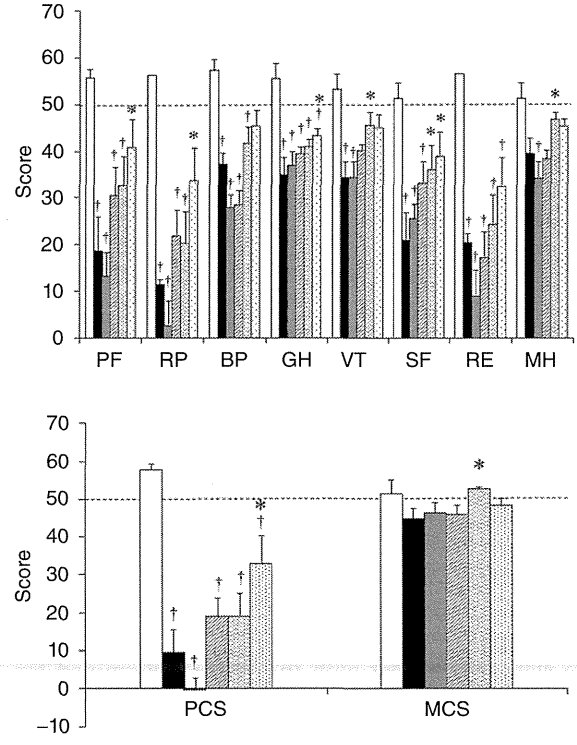

Figure 3 Normalized SF-36 scores at pre- and post-LDLT. Values are expressed as mean ± standard error. $*P < 0.05$ vs preoperative value (Dunnett's multiple comparison test). $\dagger P < 0.05$ vs control value (unpaired Student's *t*-test with Bonferroni correction). Fifty is the reference score of the general population. BP, bodily pain; GH, general health; LDLT, living donor liver transplantation; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-36, 36-item Short-Form; VT, vitality. □, control: ■, pre-LDLT; ▩, 1 month; ▨, 3 months; ▧, 6 months; ⬚, 12–24 months.

indicate that the patients' glycogen storage capacity improved to a comparable level with healthy subjects quite quickly after LDLT. Thus, although the liver detoxification and glycogen storage capacities were improved at an early postoperative period, a much longer recovery period is required to improve the hepatic protein synthetic capacity, as indicated by serum ChE and Alb levels. Therefore, these results strongly suggest that long-term nutritional management of at least 24 months is necessary in LDLT recipients.

As patients with cirrhosis have been reported to have either increased,[10] normal[7,11] or decreased[7] resting metabolic rates, this issue remains controversial. Although we have previously reported that the measured energy expenditure in Child–Pugh class A patients was typically higher than control subjects,[6] in the present study, a clear conclusion could not be reached because both hypo- and normal metabolism were observed in the liver cirrhosis patients. The variability observed in the results between these studies may have originated from differences in the degree of severity, individual variation and primary disease etiology. Thus, based on these existing variables, it would be appropriate to extend the metabolic analyses to include more cases in future studies to resolve this issue.

We also evaluated the progression of HRQOL effects before and after LDLT with the use of the Short-Form health survey, known as the SF-36, which is currently the principal tool used for reporting HRQOL changes by managed-care plans. It is also the most frequently used survey in clinical trials for a variety of interventions in a number of disorders.[19] The HRQOL of patients with severe liver cirrhosis (Child–Pugh class C) as assessed using the SF-36 were lower than those of patients with mild to moderate liver cirrhosis (Child–Pugh class A and B), as previously reported.[23–25] In this study, most patients were of Child–Pugh class C before LDLT. During the preoperative period, the patient scores for all eight scales were below the Japanese NBS, with the PCS representing the lowest value (Fig. 3). Although the HRQOL scores improved after LDLT, they tended to score below the general population in most areas even after 12–24 months, which is a trend that has been reported previously.[26] Although the PCS remained lower than the Japanese NBS, it displayed remarkable recovery within 12–24 months after LDLT. Among the factors that can affect the perception of HRQOL after LDLT, recurrent hepatitis C virus (HCV) infections and post-transplant complications were reported in previous studies to be of importance.[27,28] However, HCV did not recur in our patients after LDLT and helps explain why all HRQOL scores improved after LDLT. Our patients did not display remarkable depression on the MCS though the pre- and postoperative periods, and this may be attributed to the feeling of rebirth these patients experienced by having survived a serious illness and the greater well-being that might have accompanied this change. In addition, the recovery of PCS was observed only after all domains of laboratory data and energy metabolism based on the nutrition state were also improved. Therefore, the improvement of HRQOL encompasses a comprehensive index of progress after LDLT.

In conclusion, this study has demonstrated differences in the recovery time of nutritional metabolism function, serum biochemical data and HRQOL in LDLT patients. In particular, hepatic protein synthesis capacity and the physical score in HRQOL were shown to require a long recovery period. Therefore, it is proposed that long-term, adequate and careful nutritional care for a minimum of 2 years is required in LDLT patients. In the present study, the observed npRQ values of LDLT patients in the preoperative state were lower than the control group. As the RQ decreases after overnight fasting due to glycogen depletion in patients with liver cirrhosis, it is recommended that frequent meals and a late evening snack be consumed to correct fasting starvation in the morning.[29] The observed decrease in the npRQ in the preoperative state was thought to be due to insufficient glycogen storage in the liver. In addition, a long recovery time after LDLT is needed to improve the hepatic protein synthesis capacity. As current research indicates that branched-chain amino acid (BCAA) supplementation after hepatectomy promotes rapid improvement of protein metabolism,[30] the administration of BCAA after LDLT may be beneficial for patients' nutritional state.

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ORIGINAL ARTICLE

Effects of a whey peptide-based enteral formula diet on liver dysfunction following living donor liver transplantation

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Abstract
Background and aims Whey protein, a protein complex derived from milk is well known as a functional food with a number of health benefits. MEIN® (Meiji Dairies Co., Tokyo Japan) is a functional liquid-type nutritional diet containing whey-hydrolyzed peptide. In this study, we examined the effects of MEIN® on postoperative liver dysfunction in patients who underwent living donor-related liver transplantation (LDLT).
Methods Sixteen adult patients transplanted between 2005 and 2011 at our institute were evaluated retrospectively. In MEIN group ($n = 8$), administration of MEIN® was started around 14 days after liver transplantation when serum liver enzymes were re-elevated, while MEIN® was not administered in the control group ($n = 8$) who did not have postoperative liver dysfunction.
Results In the preoperative clinical characteristics, the model for end-stage liver disease score in the MEIN group was significantly lower than that in the control group. The graft-to-recipient body weight ratio in the MEIN group was lower than that in the control group. Elevation of enzymes in the liver function tests such as alanine aminotransferase and total bilirubin, and C-reactive protein in the MEIN group had significantly improved, and became almost normal values which were the same as those in the control group.
Conclusion These findings suggest that administration of whey-hydrolyzed peptide attenuates the post-transplant liver dysfunction and may avoid an unnecessary liver biopsy.

Keywords Liver transplantation · Whey peptide · Acute cellular rejection · Enteral nutrition

Abbreviations

AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CRP	C-reactive protein
CT	Computed tomography
GRWR	Graft-to-recipient body weight ratio
HBV	Hepatitis B virus
HCV	Hepatitis C virus
LDLT	Living related donor liver transplantation
LPS	Lipopolysaccharide
MRCP	Magnetic resonance imaging
MELD	Model for end-stage liver disease
T-Bil	Total bilirubin

Introduction

After liver transplantation, the levels of liver enzymes, such as aspartate aminotransferase (AST), and alanine aminotransferase (ALT), are often elevated due to acute cellular rejection, the recurrence of virus hepatitis, portal vein thrombosis, hepatic artery thrombosis, hepatic vein obstruction, bile duct complications, drug-induced liver injury, and various types of infection [1, 2]. The presence of vessel thrombosis or obstruction and bile duct complications can be determined by imaging modalities, such as ultrasonography (US), dynamic computed tomography

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(CT) or magnetic resonance imaging (MRI). In the patients with rejection or recurrence of hepatitis, a liver biopsy may be required [3, 4]; however, there may be some serious risks associated with such biopsies, such as bleeding, bile leakage or other organ injury. When the etiology of the elevation of liver enzymes can be determined, the liver biopsy may be avoidable [5–8].

Careful perioperative management, including defined nutrition, should be considered for patients undergoing liver transplantation [9]. Several studies have shown that immune-modulating nutritional formulas may have a role in improving the preoperative nutritional status, hastening recovery after transplantation, and reducing postoperative infectious complications [10]. Therefore, we retrospectively evaluated the effects of immune-modulating formulas in recipients after living donor-related liver transplantation (LDLT). In this study, we used a whey-hydrolyzed peptide for the formula, which is a protein complex derived from milk. It has been reported to have antioxidant, antihypertensive, antitumor, antiviral, hypolipidemic, and antibacterial effects [11]. The whey proteins from milk include β-lactoglobulin, α-lactalbumin, glycomacropeptide, immunoglobulins, and lactoferrin, and are used as a functional food that is considered to provide a number of health benefits [11]. These proteins also have been reported to exert anti-inflammatory and hepatoprotective effects [12–15]. Whey-hydrolyzed peptide has hepatoprotective effects against hepatitis and is more easily absorbed than whey protein. A previous study showed that the serum lipid peroxide levels significantly decreased, and the interleukin (IL)-2 levels and natural killer (NK) activity significantly increased in patients with chronic hepatitis due to hepatitis B virus (HBV) and C virus (HCV) infection following consumption of whey-hydrolyzed peptide [16].

MEIN® (Meiji Dairies Co., Tokyo, Japan) contains an abundance of whey-hydrolyzed peptide, which is extracted from bovine milk. This nutritional formula, like other whey-derived proteins, has been reported to have antioxidant, antihypertensive, antitumor, antiviral, hypolipidemic, and antibacterial effects in vivo and in vitro [11, 14, 17–19]. Moreover, early enteral nutrition with MEIN® was useful to prevent post-LDLT bacteremia and shorten the postoperative hospital stay in transplant patients [20].

In the present study, we evaluated the usefulness of MEIN® including a whey-hydrolyzed peptide for patients with re-elevation of the liver enzyme levels after LDLT.

Patients and methods

Study design and enrolled patients

Eight adult patients who received transplants between 2005 and 2011 at Tokushima University Hospital were evaluated retrospectively. The indication for LDLT was HCC in three cases, HCV infection in three cases, HBV infection in one case and Wilson's disease in one case (Table 1). Eight patients who did not have postoperative liver dysfunction and did not receive the MEIN formula served as the control group.

Table 1 Patients characteristics

Background	MEIN ($n = 8$)	Control ($n = 8$)	p value
Age	49 ± 13	55 ± 3	0.21
Gender (F/M)	3/5	4/4	0.25
Indication for LDLT			
HCC	3	0	
HCV-related liver cirrhosis	3	1	
HBV-related liver cirrhosis	1	4	
Others	1	3	
Child-Pugh classification A/B or C	2/6	0/8	N.A
MELD score	10 ± 4	16 ± 6	0.04
ABO compatibility			
Identical/compatible	6	8	N.A
Incompatible	2	0	
Graft type (left lobe/right lobe)	7/1	6/2	0.41
Graft versus recipient weight (GRWR)	0.72 ± 0.12	0.89 ± 0.19	0.06

Perioperative management of LDLT

Liver transplantation was performed using a living related donor. The surgical procedures for the donor and recipient have been described previously [21]. For immunosuppressive therapy, induction consisted of two doses of basiliximab (Simulect®, NOVARTIS) on postoperative days 0 and 4. Standard immunosuppressive therapy at discharge consisted of corticosteroids and calcineurin inhibitors (either tacrolimus or cyclosporine) with mycophenolate mofetil (MMF). Prednisolone was discontinued on day 21 after the surgery. In ABO incompatible cases, we administered preoperative anti-CD20 antibodies (Rituximab®, 375 mg/m^2) and performed plasma exchange for 3 days.

MEIN® composition

A commercially available enteral nutrition, MEIN® (Meiji Dairies Corporation, Tokyo, Japan) was used in this study. It is a newly designed enteral formula, including whey peptide. In terms of its general composition, it has 1 kcal/ml, including 50 mg/ml of protein, 28 mg/ml of fat, 133 mg/ml of carbohydrate, 12 mg/ml of alimentary fiber, 6 mg/ml of

ash content, and is made using 84.4 g/100 ml of water. Moreover, it includes 2.25 g/100 ml of essential amino acids and 2.63 g/100 ml of nonessential amino acids. The Fischer ratio is 3.7. The protein sources used for MEIN® are whey-hydrolyzed peptide and fermented milk.

Administration of MEIN®

The administration of MEIN® was started 14.6 ± 2.4 days after liver transplantation in the patients ($n = 8$) who showed a re-elevation of liver enzyme levels (MEIN group). The patients were administered MEIN® three times a day either orally or through a tube jejunostomy (Fig. 1).

Blood biochemistry

All patients were monitored for the liver enzyme levels, including AST and ALT, alkaline phosphatase (ALP) and γ-glutamyl transpeptidase (γGTP), as well as the total bilirubin (T-Bil) and C-reactive protein (CRP) levels as parameters of liver dysfunction before the administration of MEIN, after 7 days of administration and 14 days after starting the administration of MEIN.

Statistical analysis

Statistical comparisons of the mean values were conducted using a one-way analysis of variance (ANOVA). All results are presented as the mean ± standard deviation (SD). A p value <0.05 was considered to be statistically significant. The statistical analysis was performed using the JMP® 7.0.2 statistical software program (SAS Institute, Cary, NC).

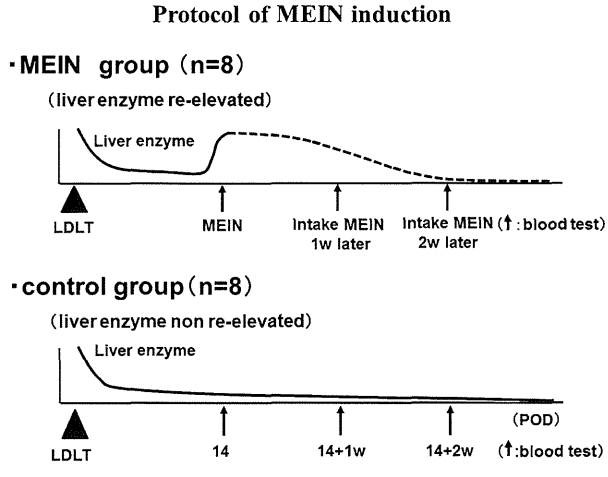

Fig. 1 The timing of the re-elevation of liver enzyme levels and the administration of MEIN

Results

Patient characteristics

The model for end-stage liver disease (MELD) score in the MEIN group was significantly lower than that in the control group (10 ± 4 vs. 16 ± 6, $p = 0.04$) (Table 1). In the control group, all of the patients categorized as having Child B/C status, while there were two Child A patients in the MEIN group. In the control group, there were no ABO incompatible cases, while there were two ABO incompatible cases in the MEIN group. The graft-to-recipient body weight ratio (GRWR) in the MEIN group was lower than that of the control group (0.72 ± 0.12 vs. 0.89 ± 0.19, $p = 0.06$). There were no significant differences in any of the other characteristics, including the patient age, gender or graft type.

Blood biochemistry

The serum levels of AST and ALT 1 and 2 weeks after starting the administration of MEIN® were significantly lower than those before MEIN® administration (AST: 101.4 ± 61.5 vs. 52.3 ± 31.4 vs. 45.8 ± 20.5, ALT: 201.1 ± 133.9 vs. 123.1 ± 104.2 vs. 79.9 ± 47.8, $p < 0.05$). The serum levels of T-Bil and CRP 2 weeks after starting the administration of MEIN® were significantly lower than those before MEIN® administration (T-Bil: 4.3 ± 4.9 vs. 2.5 ± 4.5, CRP: 1.7 ± 1.0 vs. 0.8 ± 0.7, $p < 0.05$) (Fig. 2a, b). After 2 weeks of MEIN, these values were almost identical to those values in the control group. The serum levels of ALP and γGTP did not differ significantly in the patients between before and after the administration of MEIN®.

Discussion

Patients often experience a re-elevation of liver enzyme levels around 2 weeks after LDLT, even after the early postoperative liver dysfunction is improved. In such cases, it is necessary to consider several possible etiologies, such as acute cellular rejection, recurrence of virus hepatitis, portal vein thrombosis, bile duct complication, and drug-induced liver injury, in order to optimize the treatment strategy. It is worth noting that the administration of an enteral formula (MEIN®), which contains whey-hydrolyzed peptide, significantly improved the re-elevated liver enzyme levels after LDLT in the present study. This is the first report demonstrating that whey-hydrolyzed peptide can ameliorate the liver dysfunction in patients after LDLT.

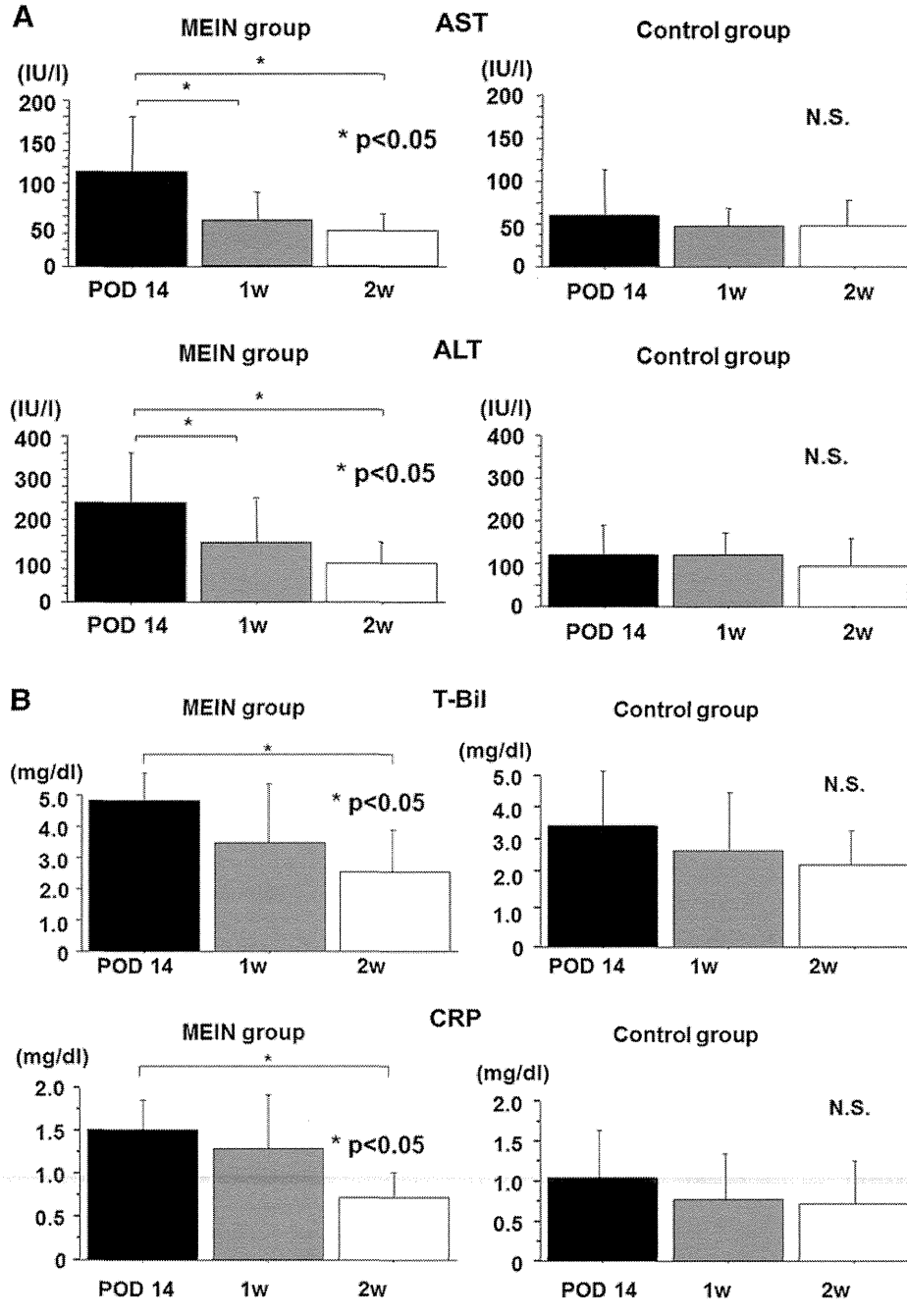

Fig. 2 The results of the biochemical analyses of the patients in the MEIN and control groups. **a** Aspartate aminotransferase (AST) and alanine aminotransferase (ALT), **b** total bilirubin (T-Bil) and C-reactive protein (CRP) levels

Kume et al. [13] previously reported that whey-hydrolyzed protein has hepatoprotective effects against D-galactosamine-induced hepatitis and liver fibrosis in rats by suppressing IL-6. In the burn rat model, whey-hydrolyzed peptide led to a significant increase in hepatic glutathione levels 4 h after burn injury. The hepatic and renal lipid peroxide levels were increased 4 h after burn injury in the rats fed a standard diet. Whey supplementation significantly suppressed the burn-induced increase in the hepatic and renal lipid peroxide levels. Whey-hydrolyzed peptide also suppressed the hepatic and renal oxidative stress after experimental burn injury [14]. Recently, it was reported that MEIN® demonstrated anti-inflammatory effects and protected against concanavalin-A induced hepatitis in mice by suppressing the production of inflammatory cytokines [22].

The mucosal secretion of lactoferrin, which is composed of whey-hydrolyzed peptide, a glycoprotein present in milk, contributes to the host defense. Harversen et al. [15] have previously shown that orally given milk lactoferrin

mediates anti-infectious and anti-inflammatory activities in vivo. They also showed that lactoferrin could down-regulate the lipopolysaccharide (LPS)-induced IL-6 secretion in a human monocytic cell line. Moreover, Hara et al. [12] reported that lactoferrin can also inhibit HCV and HBV infections in cultured human hepatocytes. Pre-incubation of the cells with bovine or human lactoferrin prevented the HBV infection of the cells. This report suggested that the interaction of lactoferrin with cells was important for its inhibitory effect, and that lactoferrin may be a candidate anti-HBV agent that could prove to be effective for the treatment of patients with chronic viral hepatitis.

In a recent clinical prospective study involving thirty adult patients, MEIN® was administered to ten patients who underwent LDLT and twenty patients (as controls) received a conventional enteral diet as the formula for early enteral nutrition. The incidence of bacteremia was significantly lower in the MEIN group than the control group (10 vs. 50 %, $p = 0.032$). The mean length of postoperative hospital stay after LDLT was significantly shorter in the MEIN group than that in the control group (45 ± 12 vs. 71 ± 34, $p = 0.018$) [23]. In a more recent study, it was shown that early administration of MEIN® could prevent post-transplant bacteremia in 76 consecutive patients [24].

Based on these previous studies and our current findings, we propose a flow chart for the management of patients with re-elevation of serum liver enzymes after LDLT, as shown in Fig. 3. If the patient shows re-elevation, diagnostic imaging, including US, CT or MRCP and blood tests should be performed to exclude blood flow disturbances, such as thrombosis or stenosis, bile duct complications or a recurrence of hepatitis virus infection. If the cause of the re-elevation is determined to be one of these etiologies, adequate management for such an etiology should be conducted. On the other hand, if the cause of the re-elevation cannot be clearly identified, then MEIN® should be administered. If the levels do not recover, a liver biopsy may be performed to rule out other etiologies, such as acute cellular rejection. However, since the number of patients included in this retrospective study was small, this flow chart should be confirmed in a prospective study involving a larger number of LDLT patients.

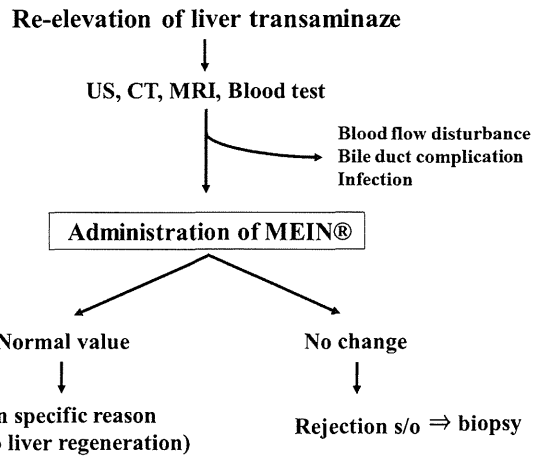

Fig. 3 A proposed flow chart of the postoperative management of patients who show a re-elevation of AST and ALT after LDLT

In conclusion, the administration of MEIN® can attenuate the re-elevation of liver enzyme levels after LDLT, and may help avoid the need for a liver biopsy.

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Article

Serial Changes of Serum Growth Factor Levels and Liver Regeneration after Partial Hepatectomy in Healthy Humans

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Abstract: This study aimed to investigate the associations of the serial changes of serum levels of various growth factors with liver regeneration after hepatectomy in healthy liver donors. Sixteen healthy liver donors who underwent conventional liver resection were included. Serum levels of various growth factors before hepatectomy and on postoperative day (POD) 1, 3, 5 and 7 were measured. Liver volume data calculated by multi-detector computed tomography using workstation. The ratio of remnant liver volume on POD 0 to liver volume before the operation was 51% ± 20%. The ratio of liver volume on POD 14 to liver volume on POD 0 were inversely correlated with remnant liver volume on POD 0 ($r = -0.91$). The ratio of liver volume on POD 14 to liver volume on POD 0 were significantly correlated with serum hepatocyte growth factor (HGF) levels on POD 1 ($r = 0.54$), serum leptin levels on POD 1 ($r = 0.54$), and serum macrophage colony-stimulating

factor (M-CSF) levels on POD 5 ($r = 0.76$) and POD 7 ($r = 0.80$). These results suggest that early-phase elevation of serum levels of HGF, leptin and M-CSF may be associated with the acceleration of liver regeneration after hepatectomy in humans.

Keywords: hepatectomy; hepatocyte growth factor; human; leptin; liver regeneration; macrophage colony-stimulating factor

1. Introduction

Liver transplantation is the only curative treatment for end-stage liver diseases. However, in a setting of the shortage of liver grafts, many patients deteriorate as a result of disease progression or develop complications because of the lack of a timely suitable donor while waiting for a liver graft [1,2]. Thus, in addition to liver transplantation, new therapeutic agents for promoting liver regeneration are desired.

In animal models, the mechanisms of liver regeneration have been investigated in detail. Hepatocytes are primed by tumor necrosis factor (TNF)-α and interleukin (IL)-6 mainly produced by Kupffer cells, and then proliferation and cell growth of hepatocytes are induced in response to transforming growth factor-α, hepatocyte growth factor (HGF), and epidermal growth factor [3]. In addition, vascular endothelial growth factor (VEGF) and thrombopoietin (TPO) are shown to promote liver regeneration [4,5].

In humans, *in vivo* investigations of liver regeneration have been mainly performed in patients undergoing surgical resection of liver cancers or liver transplant recipients; however, underlying diseases and immunosuppressant after liver transplantation may influence liver regeneration. Until now, a few studies have shown that serum HGF and IL-6 levels are elevated on postoperative day (POD) 1 [6–8]. In individuals without the appropriate elevation of serum HGF levels after partial hepatectomy, postoperative liver failure develops more frequently [9]. Serial changes of serum VEGF and TPO levels after partial hepatectomy have been also investigated in healthy liver donors [7,10]. However, associations of these growth factors with liver regeneration have not been fully revealed.

Recently, because of the shortage of liver grafts from deceased donors, the number of living donor liver transplantation has increased. In living donor liver transplantation, healthy liver donors undergo typical and anatomical hepatectomy. So, the mechanisms of liver regeneration in healthy humans, which may be different from those in patients undergoing surgical resection of liver cancers, liver transplant recipients, and animal models, may be revealed. In this study, we investigated the serial changes of serum levels of various growth factors after partial hepatectomy and the associations of these changes of various growth factors with liver regeneration after the operation in healthy liver donors.

2. Results

2.1. Clinical Characteristics of Study Population

Clinical characteristics of 16 healthy liver donors are shown in Table 1. Preoperative liver function tests were within normal limit in all patients. Each donor did not require perioperative transfusion or suffer from any major operative complications after surgery.