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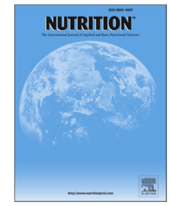

Applied nutritional investigation

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.

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 calorific 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 calorific 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 ± 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 ± 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 ± 1.6. Liver reserve function assessed using retention rate of indocyanine green in 15 min was 42.1 ± 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% ± 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 ± 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