Original Article

Assessing current nutritional status of patients with HCV-related liver cirrhosis in the compensated stage

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Background/Aim: Nutritional states of Japanese patients with liver cirrhosis have recently shown great diversity, some show protein energy malnutrition and others excessive nutrition and obesity. For there to be adequate guidance regarding dietary treatment, it is important that a patient's current nutritional state be clarified. Methods: We assessed nutritive intake in Japanese cirrhotic patients and determined their nutritional problems. Subjects were non-hospitalized patients with hepatitis C virus (HCV)-related cirrhosis in the compensated stage (n=47), chronic hepatitis C (n=46) or healthy volunteers (n=32). A brief self-administered diet history questionnaire was conducted with assistance from a registered dietitian. Results: We categorized patients with cirrhosis according to daily intake of energy and protein; 10.6% had an energy and protein intake within a normal range, 72.4% showed excessive intake, and 17.0% showed insufficient intake of energy or protein. In cirrhotic patients with diabetic complications, the intake levels of energy, proteins, fat and carbohydrates were significantly higher than in patients without diabetes. Moreover, cirrhotic patients had significantly higher intake levels of energy, protein and fat than did chronic hepatitis C patients and healthy individuals. In patients with HCV-related liver cirrhosis, insufficient intake of energy and protein was shown in some, while many, especially those with diabetes, showed excessive intake. Conclusion: For nutritive management of cirrhotic patients, the intake of various nutrients should be appropriately assessed and effective nutritional education systems established.

Key Words: liver cirrhosis, HCV, nutrition, obesity, chronic hepatitis C

INTRODUCTION

It has been reported that protein energy malnutrition (PEM) is a frequent finding in patients with liver cirrhosis (LC); thus malnutrition may represent a risk factor influencing both short- and long-term survival, as well as quality of life (QOL), in these patients.[1-3] The mechanism responsible for malnutrition associated with LC is unclear. The clinical presentation of LC is heterogeneous and is not reflected by histological or biochemical parameters of liver disease. The pathophysiology of PEM in LC is complex and associated with many factors including malnutrition as a symptom in digestive organs and metabolic dysfunction of the liver. There have been various studies on energy and protein metabolism in cirrhotic patients. Characteristic changes of energy metabolism in LC include an acceleration of resting energy expenditure and downregulation of the non-protein respiratory quotient following increase in the combustion rate of fat.[4-6] These changes are explained by a depletion of stored glycogen caused by liver damage and insulin resistance resulting from cirrhosis. In protein metabolism, there is a reduction in branched-chain amino acids (BCAAs) in the blood of LC patients; this is because BCAAs are substances required for compensational ammonia metabolism and efficient energy production in skeletal muscles.[7,8]

The current and continuing increase in obesity and the metabolic syndrome is a serious problem in most advanced countries. Similarly, there appeared to be a remarkable increase in the incidence of obese patients with LC. In a large-scale study for LC patients in Japan, the

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percentage of lean patients with a BMI <18.5 kg/m^2, which may be considered as PEM, was only 5.5%, while a much higher percentage (28.3%) of patients was classified as being obese (BMI >25 kg/m^2).[9] This may be because nourishment therapies such as BCAA-enriched nutrients have been developed and dietary habits have recently changed to overeating with a rise in epicurism. Moreover, obesity is also a serious risk-factor for carcinogenesis in the liver.

Accordingly, LC patients now have a variety of dietary habits, from PEM to over-nourishment. As mentioned above, many studies have investigated energy and protein metabolism in cirrhotic patients; however, there are few studies regarding nutritional intake in patients with hepatitis C virus (HCV)-related LC (LC-C). Today's analyses should be examined based on current dietary habits. We aimed to provide a comprehensive assessment of nutritional status in patients with LC-C in the compensated stage, by using a brief self-administered diet history questionnaire (BDHQ),[10,11] and compared with that in chronic hepatitis C (CH-C) patients and healthy individuals.

MATERIALS AND METHODS

The study population included Japanese outpatients with LC-C (n=47) and those with CH-C (n=46), who were examined monthly at Kyushu Medical Center Hospital. They were enrolled in the study between February 2010 and May 2010. Liver cirrhosis was diagnosed by documented laboratory data and/or histology. Child-Pugh criteria were used to establish the severity of LC. All LC-C patients enrolled were in the compensated stage and cirrhotic patients with Child C, ascites and/or hypoalbuminemia (<3.5 g/dL) were excluded. Type 2 DM was diagnosed by fasting blood glucose >126 mg/dL, casual blood glucose >200 mg/dL, or HbA1c >6.5% before initiation of treatments. In this study population, daily alcohol consumption was <25 g. The study protocol was approved by the Ethics Committee of the Kyushu Medical Center and all patients provided written informed consent before entering the study. Healthy volunteers (n=32) were nutritionally assessed as the control group.

A survey of nutritional variables was assessed by the BDHQ, which evaluates nutrient intake;[10,11] patients were assisted by a registered dietitian. The BDHQ is modified from a self-administered diet history questionnaire containing 80 important foods and its validity for estimating the habitual dietary intake for the past 1 month was verified. The BDHQ was easy for the patients to complete since it is designed to be completed within approximately 15 min. Unclear parts of the questionnaires were addressed and corrected by experienced dietitians acting as interviewers. Nutrient intakes were calculated using a special computer program developed to analyze the questionnaire by the DHQ Support Center, Gender Medical Research, Tokyo, Japan. Dietary intakes of energy, protein, fat and carbohydrates were normalized to dry weight and ideal body weight (IBW).

To determine nutritional status, cirrhotic patients were categorized according to Japanese standard intake levels. Three classes were established according to the levels of protein intake: an excessive level (>1.5 g/IBW kg/day), a normal level (1.0-1.5 g/IBW kg/day), and an insufficient level (<1.0 g/IBW kg/day). Additionally, three classes were established according to the levels of energy intake: an excessive level (> 35 kcal/IBW kg/day), a normal level (30-35 kcal/IBW kg/day), and an insufficient level (<30 kcal/IBW kg/day). For patients with diabetes, different cut-off values were set for energy intake: excessive, normal, and insufficient levels were >30, 25-30, and <25 kcal/IBW kg/day, respectively.

Data analysis was performed using JMP version 8.0 (SAS Institute, Cary, NA). All data are presented as mean ±SD. The differences between two groups were analyzed by the Mann-Whitney U test or chi-square test, and Tukey's HSD test was employed for multiple comparisons. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics are shown in Tables 1 and 2. Patients with decompensated cirrhosis (Child C), ascites and/or serum albumin <3.5 g/dL were not included in this study. The compensated LC-C patients were classified into nine classes according to the intake levels of energy and protein (see MATERIALS AND METHODS). The number of patients in each class is shown in Table 3. Many patients (72.4%) showed excessive daily intake levels of energy and/or protein, while energy and/or protein intake was insufficient in only 17.0% of patients. Moreover, the percentage of patients in whom both energy and protein intakes were within the normal range was also low (10.6%). These findings were irrespective of sex, age and disease severity (data not shown).

The nutritional intakes in LC-C patients with diabetes were compared with those without diabetes. No significant differences were found in age, sex, anthropometry, blood biochemistry, and the history of BCAA administration between the patient groups (Table 2). None of patients received late evening snacks (LES). However, higher intake levels of energy, protein, fat and carbohy-

Table 1. Characteristics of patients and healthy volunteers

	HCV-related cirrhosis	Chronic hepatitis C	Healthy volunteers
Patient number (M/F)	47 (32/15)	46 (21/25)	32 (19/14)
Age (years)	69.0 ± 7.5	58.5 ± 11.0*	61.8 ± 6.7*
Height (cm)	159 ± 9.0	161 ± 9.5	161 ± 7.8
Weight (kg)	60.3 ± 10.8	56.1 ± 10.1	58.8 ± 8.7
BMI (kg/m^2)	23.8 ± 4.3	21.7 ± 3.2	22.7 ± 3.4

*p < 0.01 compared with HCV-related cirrhosis

Table 2. Characteristics of patients with HCV-related liver cirrhosis

	Total	Diabetes (–)	Diabetes (+)
Patient number (M/F)	47 (32/15)	36 (23/13)	11 (9/2)
Age (years)	69.0 ± 7.5	69.4 ± 7.8	67.7 ± 6.6
Height (cm)	159 ± 9.0	159 ± 9.5	161 ± 7.2
Weight (kg)	60.3 ± 10.8	59.0 ± 8.4	64.6 ± 16.1
Child-Pugh score (A/B/C)	29/18/0	7/4/0	22/14/0
BCAA-enriched nutrients	21 (44.7%)	17 (47.2%)	4 (36.4%)
Albumin (g/dL)	4.0 ± 0.5	4.1 ± 0.5	4.0 ± 0.6
Total bilirubin (g/dL)	0.9 ± 0.5	0.9 ± 0.5	0.7 ± 0.4
NH_3 (µg/mL)	51 ± 38	47 ± 28	66 ± 65
Prothrombin Time (%)	82.1 ± 22.4	82.1 ± 21.4	81.9 ± 26.6
Hyaluronic acid (ng/mL)	267 ± 254	270 ± 249	257 ± 283

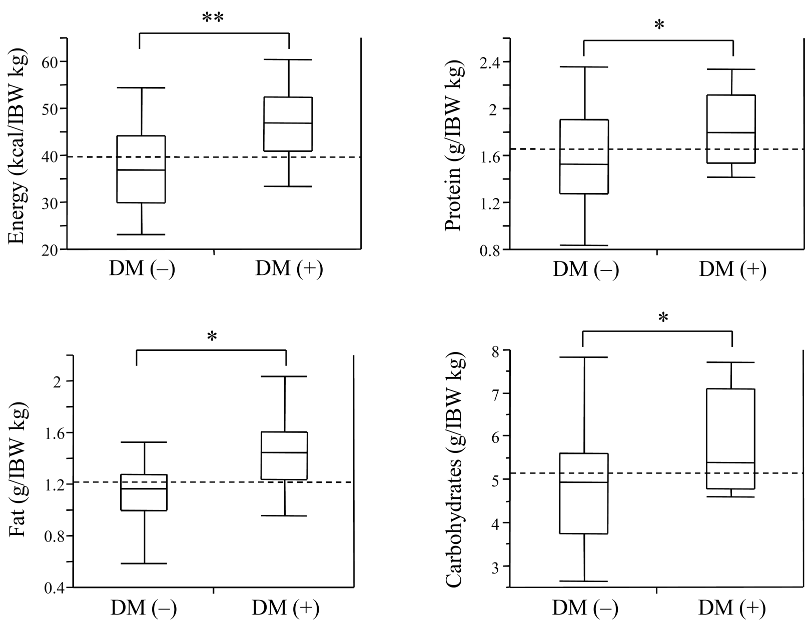

Figure 1. Comparison of daily intake levels of energy, protein, fat and carbohydrates between cirrhotic patients with and without diabetes. Dotted lines indicate mean levels from all patients. *$p < 0.05$, ** $p < 0.01$.

drates were significantly more prevalent in patients with diabetes than those in patients without diabetes (Figure 1).

As shown in Table 1, no difference was found in patient characteristics, except for age among the groups of compensated LC-C, CH-C and healthy controls. As shown by the dietary survey, the intake levels of energy, protein and fat were significantly higher in the LC-C group than those in the CH-C and control groups, while no significant difference was shown in carbohydrate intake among the groups (Figure 2). These findings were irrespective of sex, and were also unchanged when the intake of BCAA-enriched nutrients was excluded from the dietary lists (data not shown).

DISCUSSION

Through cross-sectional nutritional analysis we obtained three important findings: 1) In patients with LC-C, an excessive intake of energy and/or protein was much more prevalent than was an insufficient intake of energy and/or protein (Table 3); 2) LC-C patients with diabetes had higher intake levels of energy, protein, fat and carbohydrates than patients without diabetes; and 3) LC-C patients had higher intake levels of energy, protein and fat than did CH-C patients and healthy volunteers. These findings indicate that the dietary habits in most LC-C patients are not controlled well perhaps due to lack of effective nutritional education, and that this nutritional disorder does not appear related to the degree of liver injury. Interestingly, the percentage of an insufficient intake of energy and protein, which might be considered as a nutritional feature (PEM) in LC patients, was remarkably low, while there was a high proportion of overnourished patients accompanied by an increase of obesity. A high prevalence of overweight and obesity in patients with LC has been reported in some recent studies in Japan.[9] Accordingly, PEM may not be seen as a common complication of LC, especially in the compensated stage. Recent studies demonstrate that BCAA-enriched nutrients and LES improve hypoalbuminemia, event-free survival rate, QOL and energy metabolism,[12-16] and BCAAs and LES have been actively applied in clinical settings.

In this study, there was a higher prevalence of overnutrition in LC-C patients with diabetes than in those without diabetes (Figure 1). An increased risk of liver cancer incidence has been observed in Japanese patients with a history of diabetes; the hazard risk of liver cancer

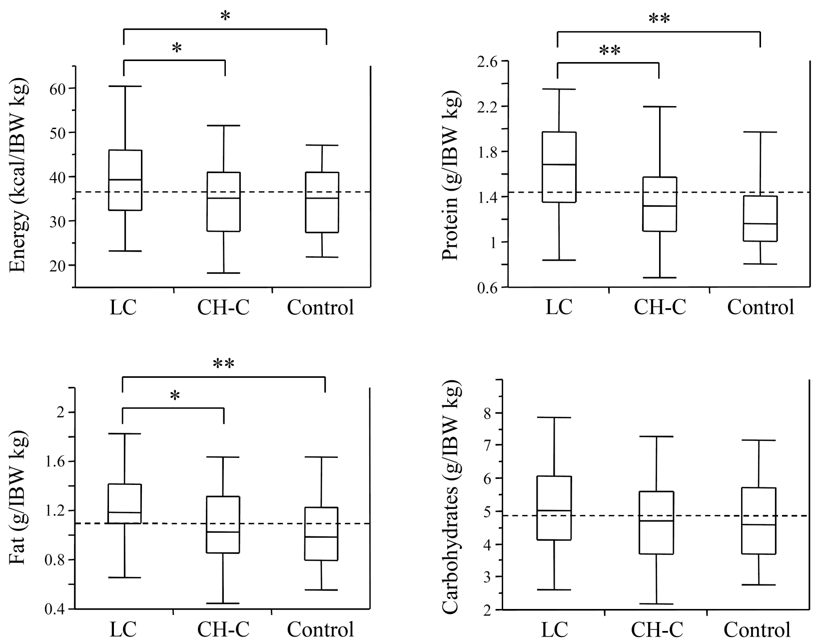

Figure 2. Comparison of daily intake levels of energy, protein, fat and carbohydrates among cirrhotic patients, chronic hepatitis patients and controls. Dotted lines indicate mean levels from all subjects. $*p < 0.05$, $** p < 0.01$ vs. cirrhotic patients.

Table 3. Categorization of cirrhotic patients according to daily intake levels of energy and protein

	Protein intake			Total
	excessive	normal	insufficient	
Energy intake				
excessive	27 (57.5%)	6 (12.8%)	0 (0%)	33 (70.3%)
normal	1 (2.1%)	5 (10.6%)	7 (14.9%)	13 (27.6%)
insufficient	0 (0%)	0 (0%)	1 (2.1%)	1 (2.1%)
Total	28 (59.6%)	11 (23.4%)	8 (17.0%)	47 (100%)

is 2.24 in males and 1.94 in females.[17] Therefore, strict nutrition management is needed for glucose tolerance and obesity in LC patients; however, effective methods for nutritional control or practical education programs have nutritional control or practical education programs have not been established for such patients.

Among the compensated LC-C, CH-C and control groups, nutritional intake levels were highest in the LC-C group, although mean age was significantly higher than those in the CH-C and control groups. This result was also present when BCAA-enriched nutrients were excluded from dietary intake. This may be because granulated BCAAs with low energy (only 48 kcal/day) were given to most patients (19/21). Richardson *et al*, in a study of 11 LC patients, reported that carbohydrates and energy intakes were lower than those in healthy controls.[18] However, that study was conducted in 1999, and the LC of these patients was at a more severe stage (Child-Pugh score: 9.2±2.3) than that in the present study. The reason why over-nutrition was common in the currently studied patients with LC-C is unknown. We investigated a small population and the BDHQ method employed as a dietary survey did not directly reflect the dietary intake of patients. Therefore, our results should be interpreted with caution, but we consider that our method is an appropriate tool because the BDHQ is a simple and easy method, and its validity was verified for estimating dietary habits for the past 1 month. Similar but larger-scale studies are required in the future.

The current nutritional status of LC-C patients in the compensated stage was investigated in this study. Our results indicated that, while some LC-C patients were likely to have PEM, there was a high prevalence of over-nutrition, especially in patients with diabetes. Malnutrition leads to deterioration of the natural history of the disease and QOL. Over-nutrition increases the risk of hepatic carcinogenesis associated with obesity and diabetes. Therefore, for nutritional management of LC patients, it is important to precisely assess the patients' nutritional intake and to establish effective nutritional education programs.

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AUTHOR DISCLOSURES

The authors have no conflicts of interest.

REFERENCES

1. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. Nutritional status in cirrhosis. J Hepatol. 1994;21:

317-25.
2. Tajika M, Kato M, Mohri H, Miwa Y, Kato T, Ohnishi H, Moriwaki H. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition. 2002;18:229-34.
3. Alberino F, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. Nutrition. 2001;17:445-50.
4. Dolz C, Raurich JM, Ibáñez J, Obrador A, Marsé P, Gaya J. Ascites increases the resting energy expenditure in liver cirrhosis. Gastroenterology. 1991;100:738-44.
5. Lautz HU, Selberg O, Korber J, Bürger M, Müller MJ. Protein-calorie malnutrition in liver cirrhosis. Clin Investig. 1992;70:478-86.
6. Muller MJ, Boker KH, Selberg O. Are patients with liver cirrhosis hypermetabolic? Clin Nutr. 1994;13:131-44.
7. Kato M, Miwa Y, Tajika M, Hiraoka T, Muto Y, Moriwaki H. Preferential use of branched-chain amino acids as an energy substrate in patients with liver cirrhosis. Intern Med. 1998;37:429-34.
8. Shiraki M, Shimomura Y, Miwa Y, Fukushima H, Murakami T, Tamura T, Tamura N, Moriwaki H. Activation of hepatic branched-chain alpha-keto acid dehydrogenase complex by tumor necrosis factor-alpha in rats. Biochem Biophys Res Commun. 2005;328:973-8.
9. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res. 2006;35:204-14.
10. Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in woman. J Epidemiol. 1998;8:203-15.
11. Sasaki S, Ushio F, Amano K, Morihara M, Todoriki T, Uehara Y, Toyooka T. Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. J Nutr Sci Vitaminol. 2000;46:285-96.
12. Muto Y, Sato S, Watanabe A, Moriwaki H, Suzuki K, Kato A, et al. Effects of oral branched-chain amino acid granules on event-free survival in patients with liver cirrhosis. Clin Gastroenterol Hepatol. 2005;3:705-13.
13. Marchesini G, Bianchi G, Merli M, Amodio P, Panella C, Loguercio C, Rossi Fanelli F, Abbiati R. Nutritional supplementation with branched-chain amino acids in advanced cirrhosis: a double-blind, randomized trial. Gastroenterology. 2003;124:1792-801.
14. Nakaya Y, Okita K, Suzuki K, Moriwaki H, Kato A, Miwa Y, et al. BCAA-enriched snack improves nutritional state of cirrhosis. Nutrition. 2007;23:113-20.
15. Poon RT, Yu WC, Fan ST, Wong J. Long-term oral branched chain amino acids in patients undergoing chemoembolization for hepatocellular carcinoma: a randomized trial. Aliment Pharmacol Ther. 2004;19:779-88.
16. Aoyama K, Tsuchiya M, Mori K, Kubo Y, Shiraishi K, Sakaguchi E, Yamashita S, Sakaida I. Effect of a late evening snack on outpatients with liver cirrhosis. Hepatol Res. 2007;37:608-14.
17. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med. 2006;166:1871-7.
18. Richardson RA, Davidson HI, Hinds A, Cowan S, Rae P, Garden OJ. Influence of the metabolic sequelae of liver cirrhosis on nutritional intake. Am J Clin Nutr. 1999;69:331-7.

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評估 C 型肝炎導致肝硬化且處於代償期的患者之營養現況

背景與研究目的：最近研究顯示有肝硬化的日本病人其營養狀態有很大歧異性，有些人是蛋白質熱量營養不良，但有些則是營養過剩及肥胖。為了建立恰當的膳食療養指引，瞭解病人目前的營養狀況是很重要的。方法：評估日本肝硬化病人營養攝取情形以及確認他們的營養問題。受試者皆非住院病人，有 C 型肝炎相關的肝硬化且處於代償期的患者 47 人、慢性 C 型肝炎 46 人、健康自願者 32 人。由註冊營養師協助受試者自行填寫一份簡短的飲食史問卷。結果：肝硬化病人根據其每天攝取的熱量及蛋白質分組，熱量及蛋白質攝取量在正常範圍內者占 10.6%，攝取過多者占 72.4%，不足者占 17%。併發有糖尿病的肝硬化病人，其熱量、蛋白質、脂肪、醣類的攝取量顯著高於沒有糖尿病的病人。另外，肝硬化病人的熱量、蛋白質及脂肪的攝取量顯著高於慢性 C 型肝炎患者及健康受試者。在 C 型肝炎相關的肝硬化病人中，雖然有些人的熱量和蛋白質攝取有不足的情形，但大部分，尤其是同時患有糖尿病者，其攝取量是過多的。結論：對於肝硬化病人的營養管理，需適切地評估其各種營養素攝取情形及建立有效的營養教育系統。

關鍵字：肝硬化、C 型肝炎病毒、營養、肥胖、慢性 C 型肝炎