Original Article

Effects of eating frequency on respiratory quotient in patients with liver cirrhosis: a randomized controlled trial

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Background and Objectives: Respiratory quotient (RQ) is a good marker of substrate oxidation. Low RQ is frequently found in patients with liver cirrhosis and is associated with poor outcome. The purpose of this study was to demonstrate the effects of eating frequency on RQ in patients with cirrhosis. **Methods and Study Design:** We performed a randomized controlled trial to assess the effects of eating frequency on RQ in patients with cirrhosis. Seventy patients and 30 healthy controls were enrolled, and patients were further randomized to receive either normal eating frequency (NEF) meals at 08:00, 12:00 and 18:00 h, or high eating frequency (HEF) meals at 08:00, 10:00, 12:00, 15:00, 18:00 and 20:00 h. The two groups had equivalent energy intake. Fasting RQ was measured at 07:30 h and daytime RQ was measured at 11:30 and 17:30 h. Disease severity was evaluated using the Child–Turcotte–Pugh (CTP) classification. **Results:** Fasting RQ and daytime RQ were significantly lower in patients with cirrhosis than in healthy controls. Patients in the HEF group had a higher RQ than patients in the NEF group at three time points. In patients with CTP-A, no significant differences in daytime RQ were observed between the two groups. However, in CTP-C patients, daytime RQ was significantly higher in the HEF group than in the NEF group. Serum free fatty acid levels were significantly decreased and albumin was significantly increased after HEF intervention. **Conclusions:** HEF strategy is effective in improvement of RQ and is beneficial to patients with cirrhosis.

Key Words: cirrhosis, nutrition, meal frequency, respiratory quotient, indirect calorimetry

INTRODUCTION

Respiratory quotient (RQ), a ratio of oxygen consumption to carbon dioxide production, is considered to be a good marker of substrate oxidation to energy metabolism.[1] The metabolism of three major substrates produces different RQ values: 1.0 for glucose, 0.80 for protein and 0.71 for fat. Due to gluconeogenesis ability and glycogen storage capacity, patients with liver cirrhosis are prone to entering into a starvation state after a short fasting period.[2,3] In this situation, low RQ has been frequently reported, which means that lipid metabolism and protein catabolism are enhanced as alternate fuel sources.[4] It is reported that, after a short overnight fast, the rate of fat and protein catabolism in cirrhotic patients is similar to that of healthy individuals after 2–3 days of starvation.[2] Accordingly, free fatty acid (FFA) levels are elevated in cirrhosis patients. It has been proposed that high levels of FFA are caused by an increased rate of lipolysis in the fat tissue in the fasting state, and there is a significant correlation between FFA and fat oxidation rate in patients with cirrhosis.[5] Similarly, several studies in patients with cirrhosis have reported increased rates of whole body protein breakdown in the postabsorptive state, using isotopic tracer methods.[6-8] The altered metabolic status (as defined by the RQ values) contributes to the complications observed in patients with cirrhosis.[9,10] Moreover, it is reported that survival rate is significantly lower in cirrhosis patients with low RQ (<0.85) than in those with scores >0.85.[11]

To avoid low RQ, late evening snacks (LESs) are recommended in current European Society for Clinical Nutrition and Metabolism guidelines.[12] Previous studies have shown that LESs may improve fasting RQ in patients with cirrhosis.[13,14] However, LESs only improve RQ after an overnight fast, and do not improve fasting

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RQ in patients with severe chronic cirrhosis.[15,16] In fact, starvation. Therefore, in order to shorten episodes of patients with cirrhosis are often in a state of accelerated catabolism during the daytime, it is necessary to identify other useful interventions for improving daytime RQ in patients with cirrhosis.

The consumption of high frequency meals may shorten the interval between meals. Although glucose oxidation is retarded, patients with cirrhosis show increased carbohydrate oxidation after eating.[17] We hypothesize that a high eating frequency strategy of six meals per day, as compared to an equivalent energy intake with normal eating frequency of three meals per day, improves fasting and daytime RQ, and may improve nutritional status in cirrhosis patients. To date, there are few data about the effects of meal frequency on energy malnutrition in patients with cirrhosis. In the current randomized controlled study, we explored the effects of meal frequency on RQ in patients with cirrhosis, especially in those with severe cirrhosis.

METHODS

Patients and healthy controls

We enrolled 79 consecutive patients with liver cirrhosis and 30 healthy controls. Nine patients were excluded as they fulfilled either one or more of the exclusion criteria. The diagnosis of cirrhosis was based on clinical, laboratory and radiological evidence or liver histological tests.[18] None of the cirrhosis patients had a history of neoplasia, diabetes mellitus, thyroid dysfunction, or other acute or chronic diseases. None had fever, hepatic encephalopathy, or gastrointestinal bleeding at the time of the study. Controls were recruited from healthy volunteers; most of who were hospital employees (Figure 1). Each participant gave signed informed consent at the beginning of the study. The study protocol was conducted in accordance with the provisions of the Declaration of Helsinki and approved by the Institutional Review Board of Beijing YouAn Hospital, Capital Medical University (Beijing, China) (ethical approval number: 2016-18).

Study design

This trial was conducted from December 2014 to May 2016 at the Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University (Beijing, China). Before intervention, the patients and healthy controls, who normally consumed 3 meals a day, were to evaluate energy intake based on a 24-h dietary recall and fasting RQ and daytime RQ at baseline. All patients were randomly divided into two groups: a normal eating frequency group (3 meals per day) and a high eating frequency group (6 meals per day). The assigned intervention was continued for 7 days. The primary outcomes of the study were to evaluate the effects of meal frequency on fasting RQ and daytime RQ in patients with cirrhosis.

The normal eating frequency consisted of 3 meals: breakfast at 08:00 h, lunch at 12:00 h, and dinner at 18:00 h. The high eating frequency group added 3 snacks at 10:00 h, 15:00 h and 20:00 h besides the normal diet. Fasting RQ and resting energy expenditure (REE) was measured at 07:30 h and daytime RQ at 11:30 h and 17:30 h. During the entire study period, all patients were provided with a standard hospital diet that included 25–30 kcal/kg daily, containing 60–65% carbohydrate, 20–25% fat and 10–15% protein. To provide a well-controlled and standardized antecedent diet for all study patients, each patient was required to follow a standardized meal plan for 3 days before initiation of the study.

RQ and REE

The REE was measured by the cardiorespiratory diagnostic system for nutrition metabolism (Medgraphics, Saint Paul, MN, USA). The test was performed in a silent, temperature-controlled room (24–26°C). The patients had 10 min bed rest before the beginning of the test. Before performing a test, the flow sensor and gas were calibrated. The volume of inspired oxygen (VO_2) and exhaled carbon dioxide (VCO_2) was collected by facemask for a total of 15 min, and only the last 5 min was used for analysis. RQ was calculated as VCO2/VO2. REE was calculated according to the Weir formula: REE (kcal/day) = REE (kcal/day) = (3.9 VO_2+1.1 VCO_2) × 1.44.[19] The predicted REE was calculated using the Harris and Benedict formula.[20]

Dietary intake

Dietary energy and macronutrient intake were assessed in each patient by two dietitians over the entire 1 week. Nutrient intake was calculated using standardized Chinese Food Composition Tables.[21]

Laboratory variables

At baseline, we collected data on patient demographics, clinical parameters, laboratory parameters, and severity of

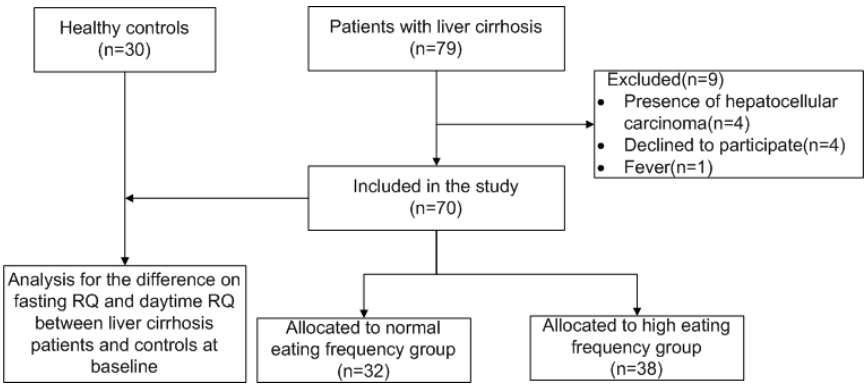

Figure 1. Flow chart of patients in the study

liver disease. All measurements were performed in the morning, under fasting conditions. Weight was measured to the nearest 0.1 kg and height to the nearest 0.1 cm (RGZ120; Wuxi Weigher Factory, China). Serum biochemical profiles were measured using an Olympus Automatic Biochemical Analyzer AU5400 (Olympus, Tokyo, Japan). The severity of liver disease was assessed by the Child–Turcotte–Pugh (CTP) classification, which included ascites, hepatic encephalopathy, prothrombin time, total bilirubin, and albumin.[22] During the intervention period, daily nutritional data (dietary energy and macronutrient intake), daytime RQ at each testing point, and REE were obtained. At the end of the intervention period, data on nutrition-related laboratory parameters, fasting glucose, FFA, and albumin were collected.

Statistical analysis

The primary analytical goal was to assess differences in RQ between the normal eating and high eating frequency in patients with cirrhosis. Eligible patients were randomly assigned by computer to the normal or high eating frequency group. Our preliminary experiment showed the average difference of RQ was 0.07±0.04, 0.06±0.03 and 0.06±0.03 among the normal and high eating frequency groups at three time points, respectively. To show these differences at 1 week in the normal and high eating frequency groups, at least 6 patients needed to be randomly allocated to each group (α=0.05, power=0.8) according to PASS version 11 (NCSS,LLC, USA). In order to eliminate the influence of disease severity, we stratified the data by CTP classification. In each CTP subgroup, the sample size was at least 6 patients in the normal and high eating frequency groups.

Continuous variables are presented as mean ± standard deviation (SD) or median (range) and categorical variables as frequency and percentage. Depending on the data distribution, differences in continuous variables between the two groups were analyzed using the Mann–Whitney U test or the independent-samples t test. Categorical variables were analyzed by Pearson's χ^2 test. A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline data of patients with cirrhosis and healthy controls

A total of 70 patients and 30 healthy controls completed the whole study. There were no significant differences in age, sex, BMI and energy intake among the patients and healthy controls (Table 1). All patients were randomly divided into two groups: a normal eating frequency group (3 meals per day, n=32) and a high eating frequency group (6 meals per day, n=38). At baseline, the two groups were similar with respect to demography, etiology, severity of liver disease, energy intake and energy metabolism (Table 2).

Fasting RQ and daytime RQ in healthy controls and patients with cirrhosis

In order to analyze the change in RQ in patients with cirrhosis, we compared 30 healthy controls with 70 patients. The healthy controls and patients were well matched by age, sex and BMI, and there were no significant differences between the groups for energy intake (Table 1). The fasting RQ and daytime RQ were significantly lower in patients with cirrhosis compared to the healthy controls (0.86±0.04 vs 0.74±0.03, p=0.003; 0.87±0.03 vs 0.76±0.05, p=0.003; 0.86±0.04 vs 0.75±0.04, p=0.006). When stratifying the data by CTP classification, the fasting RQ still was significantly lower in patients with cirrhosis compared to the healthy controls (0.86±0.04 vs 0.78±0.03, p=0.016; 0.86±0.04 vs 0.76±0.04, p=0.008; 0.86±0.04 vs 0.72±0.04, p=0.003). However, in patients with CTP-A/B, the daytime RQ did not differ significantly from that in the healthy controls (0.87±0.03 vs 0.85±0.04, p=0.439, 0.86±0.04 vs 0.85±0.02, p=0.608; 0.87±0.03 vs 0.83±0.03, p=0.176, 0.86±0.04 vs 0.82±0.04, p=0.111). In patients with CTP-C, the daytime RQ was significantly lower than in the healthy controls (0.87±0.03 vs 0.76±0.05, p=0.008; 0.86±0.04 vs 0.75±0.04, p=0.006) (Figure 2).

Effects of eating frequency on fasting RQ and daytime RQ in patients with cirrhosis

Throughout the intervention period, patients in the high eating frequency group had a higher RQ than patients in the normal eating frequency group at the three testing time points (0.82±0.04 vs 0.75±0.03, p=0.030; 0.86±0.03 vs 0.80±0.05, p=0.023; 0.85±0.03 vs 0.79±0.04, p=0.021). When stratifying the data by CTP classification, the fasting RQ was significantly higher in the high eating frequency group compared to the normal eating frequency group (0.86±0.03 vs 0.79±0.03, p=0.011; 0.81±0.04 vs 0.74±0.03, p=0.02; 0.78±0.03 vs 0.71±0.04, p=0.03). In the CTP-A group, no major difference in the daytime RQ was observed in patients in the high eating frequency group and normal eating frequency group at 11:30 h and 17:30 h, respectively (0.87±0.02 vs 0.83±0.04, p=0.111; 0.86±0.03 vs 0.83±0.02, p=0.192). However, in the CTP-

Table 1. Characteristics of patients and healthy controls

Characteristics	Controls	Patients	p value
No. of patients	30	70	–
Age (yr)	53±6.2	56.1±5.1	0.199
Female, n (%)	14 (46.7)	31 (44.3)	0.826
BMI (kg/ m^2)	24.8±3.4	24.5±3.7	0.413
Energy intake (kcal/day)	2143±473	2064±642	0.281
Carbohydrate (g/day)	339±104	309 ±154	0.643
Fat (g/day)	56±23	50±27	0.722
Protein (g/day)	82±31	92±34	0.521

Table 2. Baseline characteristics of patients in the two groups

Characteristics	Normal eating frequency group (3 meals/day)	High eating frequency group (6 meals/day)	*p* value†
No. of patients	32	38	–
Age (yr)	54.8±4.9	57.3±4.7	0.173
Female, n (%)	13 (40.6)	18 (47.4)	0.458
BMI (kg/ m^2)	24.7±2.3	24.3±3.5	0.611
Etiology, n (%)			0.922
HBV	21 (65.6)	26 (68.4)	
HCV	3 (9.4)	4 (10.5)	
Alcohol	8 (25.0)	8 (21.1)	
ALT (IU/L)	72.3±64.7	89.6±73.5	0.586
AST (IU/L)	99.0±113	136±260	0.690
Albumi (g/L)	35.6±6.8	35.1±6.5	0.824
Total bilirubin (μmol/L)	129±196	121±164	0.886
PT (s)	16.8±7.4	15.5±6.1	0.572
INR	1.48±0.6	1.37±0.5	0.578
Urea (mmol/L)	8.0±12.3	6.0±2.1	0.520
Creatinine (μmol/L)	56.9±11.3	59.9±15.1	0.509
Presence of ascites, n (%)	24 (75.0)	27 (71.1)	0.711
CTP class, n (%)			0.998
A	5 (15.6)	6 (15.8)	
B	12 (37.5)	14 (36.8)	
C	15 (46.9)	18 (47.4)	
Energy intake (kcal/d)	2095±217	2133±263	0.394
Carbohydrate (g/d)	299±96	319±89	0.418
Fat (g/d)	51±25	49±31	0.475
Protein (g/d)	82±32	102±37	0.581
REE	1477±275	1413±242	0.319
RQ	0.75±0.08	0.74±0.06	0.567

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTP: Child-Turcotte-Pugh; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: international normalized ratio; PT: prothrombin time; RQ: Respiratory quotient.
Reference ranges are: ALT: 9–50 IU/L; AST: 15–40 IU/L; Albumin: 35–50 g/L; total bilirubin: 5–21 μmol/L; PT: 11–13 s; INR: 0.9–1.2; urea: 2.9–7.1 mmol/L; creatinine: 58–96 μmol/L.
†Normal eating frequency group vs high eating frequency group.

C group, a significant increase in daytime RQ was observed in patients in the high eating frequency group and normal eating frequency group at 11:30 h and 17:30 h, respectively (0.85±0.04 vs 0.78±0.06, p=0.029, 0.84±0.04 vs 0.77±0.05, p=0.027). In the CTP-B group, a significant increase in daytime RQ was observed in patients in the high eating frequency group at 17:30 h (0.85±0.03 vs 0.78±0.04, p=0.032) and no major difference in daytime RQ was observed in the two groups at 11:30 h (0.85±0.08 vs 0.79±0.07, p=0.062) (Figure 3).

Effects of eating frequency on fasting glucose, FFA and albumin in patients with cirrhosis

RQ is considered to be a good marker for substrate oxidation to energy metabolism. To analyze further the impact of increased frequency of meals on health outcomes in this population, fasting glucose, FFA and albumin were selected. These markers are closely related to changes in substrate oxidation. Table 3 shows the changes in fasting glucose, FFA and albumin in cirrhosis patients before and after changing eating frequency. There were no significant differences in fasting glucose, FFA and albumin between the two groups at baseline. After 1 week, the high eating frequency group experienced significant decreases in FFA (p=0.021) and significant increases in albumin (p=0.023). However, there were no significant changes in FFA and albumin in the normal eating frequency group (p=0.925, p=0.656).

Adverse effects

There were no serious adverse events related to nutritional supplementation throughout the study.

DISCUSSION

In our study, a strategy of high eating frequency for patients with cirrhosis significantly improved daytime RQ, as compared with a strategy of a normal eating frequency, especially in patients with CTP-C cirrhosis. Malnutrition

Table 3. Effects of eating frequency on GLU, FFA and ALB in patients with cirrhosis

	Normal eating frequency group			High eating frequency group		
	Baseline	1 wk	*p* value	Baseline	1 wk	*p* value
GLU	6.4±3.1	6.6±4.2	0.937	6.5±2.1	6.9±2.9	0.843
FFA	1.25±0.8	1.21±0.9	0.925	1.15±0.7	0.73±0.6	0.021
ALB	32.6±6.8	33.3±6.8	0.656	31.1±6.8	36.6±6.8	0.023

GLU: fasting glucose: normal range, 3.9–6.1 mmol/L; FFA: free fatty acid: normal range, 0.1–0.9 mmol/L; ALB: albumin: normal range, 35–50 g/L.

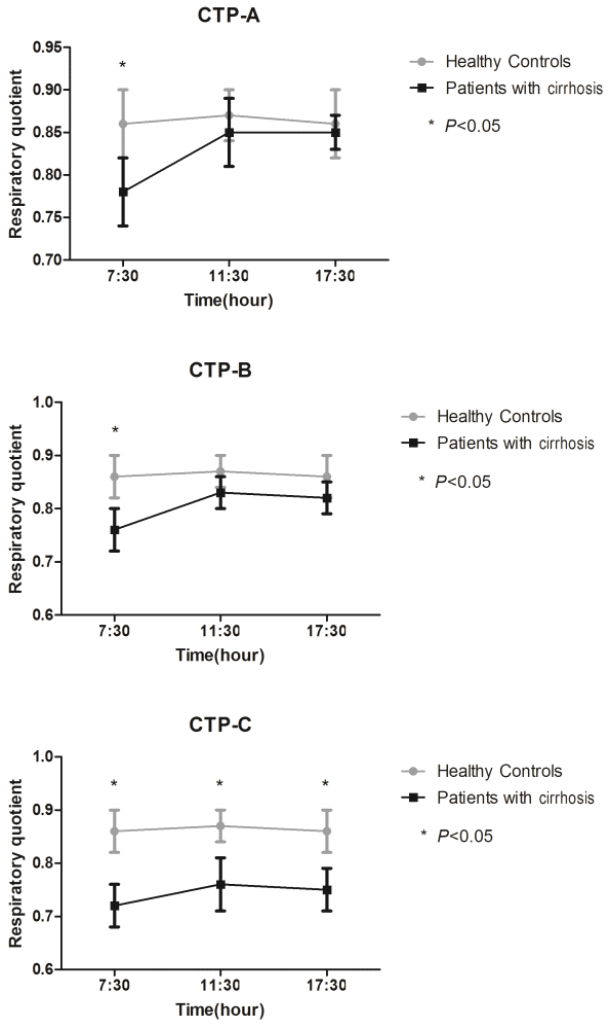

Figure 2. Difference in fasting RQ and daytime RQ among healthy controls and patients with cirrhosis according to disease severity (CTP classification).

is a risk factor influencing survival in patients with cirrhosis and can modify their prognosis. The malnutrition of these patients can be partly attributed to alterations of substrate oxidation. Therefore, these findings have important clinical implications for patients with cirrhosis.

Similar to previous studies, after an overnight fast, the fasting RQ in patients with cirrhosis was significantly lower than that in controls in the present study. Furthermore, there was no significant difference in daytime RQ among patients with CTP-A and controls. In the patients with CTP-C, however, daytime RQ was significantly lower than that in patients with CTP-A. The mean daytime RQ was <0.82, which inferred that non-carbohydrates were used as major substrates during the daytime in patients with CTP-C. This is similar to a previous study in which the RQ values correlated significantly with CTP classifications.[23] This suggests that patients with CTP-C are inclined to develop a catabolic state rapidly. Possible contributory reasons are that, with worsening severity of liver disease, the ability of hepatocytes to store, synthesize and break down glycogen is gradually reduced.[4]

In order to improve the catabolic state, frequent meals or LESs have been recommended. The notion that LESs improve fasting RQ and quality of life in patients with cirrhosis has been confirmed in many studies. However, frequent meals are supported by limited experimental evidence. A previous study by W Verboeket-van de and colleagues,[24] who evaluated 8 patients with cirrhosis receiving 2 meals daily or 4–7 meals crossover intervention, showed that RQ was improved with 4–7 meals compared with 2 meals daily at the time of rising in the morning. However, there were no patients with CTP-C in their study. In fact, patients with CTP-C had a more severe catabolic state. Meng[15] and Sakaida[16] found that patients with severe liver disease (CTP-C or MELD >30) receiving LESs did not show improved RQ. In our study, under isoenergetic conditions, daytime RQ was significantly improved with high eating frequency compared with normal eating frequency, especially in patients with CTP-C cirrhosis. Therefore, it is possible that high eating frequency may be effective as a nutritional support approach to prevent abnormal substrate oxidation in patients with CTP-C. Corresponding to improvement of RQ, we found that the level of FFAs had significantly decreased in the high eating frequency group by the end of the study, but not in the normal eating frequency group. Previous studies have shown a significant correlation between fat oxidation rate and FFA level in cirrhosis patients.[25,26] In the starvation state, the level of FFAs increased with rate of

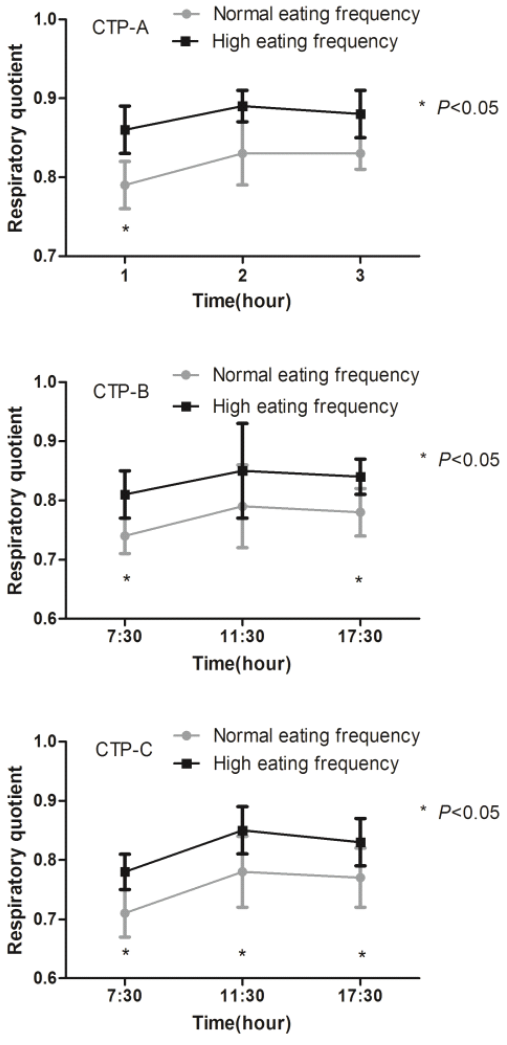

Figure 3. Difference in fasting RQ and daytime RQ among high and normal eating frequency groups according to disease severity (CTP classification).

lipolysis in fat tissue. High eating frequency can shorten episodes of catabolism during the day to decrease FFA level. In addition, since cirrhosis and insulin resistance are related, 4 patients with cirrhosis are prone to have high postprandial levels of glucose.[27] It has been reported that cirrhosis accompanied by high blood glucose presents a high risk of hepatic insufficiency.[27] In our study, there were no significant changes in fasting glucose in the high eating frequency group. This indicates that high eating frequency does not induce an increase in fasting glucose.

In the present study, the sample size was small. Although it may have limited the value of the study, the data showed clearly that at least some patients with severe liver disease developed a catabolic state in the daytime, and high eating frequency may help to improve the state. The long-term effect of high eating frequency on nutritional status is limited. Further studies, therefore, are required to evaluate the effects of high eating frequency on long-term prognosis and nutritional status in patients with cirrhosis.

In conclusion, fasting RQ and daytime RQ were significantly lower in patients with cirrhosis compared to healthy controls. A high eating frequency strategy improves RQ in patients with cirrhosis, and is beneficial to patients with cirrhosis. Further studies are required to evaluate the effects of eating frequency on long-term prognosis in patients with cirrhosis.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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