Original Article

Comparison of measured and predicted energy expenditure in patients with liver cirrhosis

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Obesity is a risk factor for the onset of liver cancer in patients with cirrhosis. To prevent overfeeding and obesity, estimation of energy requirement is important, but energy expenditure in patients with liver cirrhosis has not been fully elucidated. This study aimed to investigate resting energy expenditure (REE) and energy intake in patients with cirrhosis and determine adequate energy intake criteria. In this cross-sectional study, indirect calorimetry measurement was conducted in 488 Japanese inpatients with cirrhosis. We compared REE measured by indirect calorimetry (M-REE) with basal energy expenditure (BEE) predicted by the Harris-Benedict equation (H-BEE) and Dietary Reference Intakes (DRI) for Japanese (D-BEE). Mean M-REE (1256 kcal) was significantly lower than H-BEE (1279 kcal); however, it was not significantly different from D-BEE (1254 kcal). Mean M-REE expressed in relation to body weight (BW; REE/kg BW) was 21.7 kcal/kg BW. H-BEE was significantly higher than M-REE in patients in the first and second quartiles of BMI, and D-BEE was significantly different from M-REE in patients in the highest and lowest quartiles of BMI. Average energy intake was 30.5 kcal/kg BW, which was 1.4 times greater than REE/kg BW. Although DRI is a useful tool for the estimation of REE in patients in the second and third quartiles of BMI, M-REE is recommended to ensure the provision of adequate nutritional care to patients with cirrhosis, including those in the highest and lowest quartiles of BMI.

Key Words: indirect calorimetry, resting energy expenditure, Harris-Benedict, non-protein respiratory quotient, non-esterified fatty acids

INTRODUCTION

The liver plays a central role in nutritional metabolism. Most patients with liver cirrhosis show imbalance with regard to nutrient and energy metabolism, which contribute to protein-energy malnutrition and poor prognosis.[1,2] Although many studies have shown that patients with cirrhosis have decreased respiratory quotient (RQ) because of decreased glucose oxidation and increased fat oxidation,[3] resting energy expenditure (REE) in these patients remains to be clarified. Some studies have reported increased REE in patients with cirrhosis,[4,5] while others have described unchanged[6,7] or decreased REE.[3,8] On the other hand, the amount of daily energy intake in patients with cirrhosis remains unknown. Until 2000 in Japan, a high-energy and high-protein diet was recommended for patients with liver cirrhosis. This diet was established by applying European nutritional therapy advice for alcoholic hepatitis in heavy drinkers to Japanese.[9] However, the prevalence of obese patients with cirrhosis has recently increased in Japan.[10] In developed countries, because of the high prevalence of obesity and metabolic complications, approximately 20%-30% adults suffer from non-alcoholic fatty liver disease,[11,12] which induces steatohepatitis, fibrosis, and cirrhosis.[13] Obesity has also been reported to induce liver cancer and increase mortality in America[14] and Japan.[15]

This study aimed to investigate REE in a large group of Japanese patients with liver cirrhosis, determine adequate energy intake criteria, and calculate the required energy intake to prevent obesity in such patients.

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MATERIALS AND METHODS

Subjects

Four hundred and eighty-eight hospitalized Japanese patients with biopsy-proven liver cirrhosis admitted to the Department of Gastrointestinal Surgery at Tokushima University Hospital (Tokushima, Japan) were enrolled in this study. Etiologies included hepatitis B virus infection (n=138), hepatitis C virus infection (n=238), coexisting hepatitis B and C infection (n=14), excessive alcohol consumption (n=27), and others (n=71). The Child-Pugh classification[10] was used to assess the severity of cirrhosis. Child-Pugh score was calculated considering the degree of ascites and hepatic encephalopathy, serum bilirubin and albumin concentration, and prothrombin time. All patients were in a stable clinical condition at the time of the study. They had not been treated with chemotherapy, radiation, interferon and ribavirin at least 3 months prior to the study, and no patient had respiratory impairment, lung disease, renal dysfunction, acute phase of liver disease or elevated body temperature. Concomitant hepatocellular carcinoma was presented in 395 patients. The study design was approved by the ethical committee of Tokushima University Hospital. Written informed consent was obtained from all patients.

Energy metabolism

Indirect calorimetric measurements were performed at 8:00 after overnight fasting using an AE-300S respiratory gas analyzer (Minato Medical Science Co, Ltd, Osaka, Japan). After overnight fasting, patients were asked to remain in bed for 30 min prior to calorimetric measurement and maintain a supine position throughout the measurement period. Oxygen consumption and carbon dioxide production rates were calculated, and once a steady state of equilibrium was achieved, these values were used for analysis. Mean values obtained during the last 10 min of the measurement period were used for calculation. Non-protein respiratory quotient (npRQ) and REE for each patient were then calculated on the basis of measured oxygen consumption rate, carbon dioxide production rate, and urinary nitrogen excretion assessed by 24 h urine collection. To avoid the potential bias and effects of outliers, npRQ values of 0.700-1.000 was used as inclusion criteria. REE was calculated using Elwyn equation[17] and basal energy expenditure (BEE) was estimated according to the equation reported by Harris-Benedict[18] and the Dietary Reference Intakes (DRI) for Japanese.[19] Patients were identified as hypermetabolic when REE measured by indirect calorimetry (M-REE) exceeded the predicted values by >20%, while they were identified as hypometabolic when M-REE was >20% below the predicted values.

Anthropometry

Before measuring energy metabolism, anthropometry was conducted under fasting conditions. Body weight (BW) was measured using a DC-320 body composition meter (Tanita Corp., Tokyo, Japan). BMI was calculated as BW in kilogram divided by height in meters squared (kg/m^2). We evaluated measured REE and predicted BEE among patients stratified by quartiles of BMI.

Nutritional assessment

All patients received dietary advice based on their medical condition and were provided with standard hospital diet containing 30-35 kcal/kg BW·day and 1.0-1.2 g/kg BW·day of protein. No restrictions were enforced regarding snacking between meals until 20:00 on the previous day of energy metabolism measurement.

Dieticians interviewed the patients regarding the amount of food eaten (meals + snacks), and checked leftover food. We calculated energy intake on the basis of Standard Tables of Food Composition in Japan (5th revised and enlarged edition).[20]

Laboratory data

Blood samples were collected concomitantly with the measurement of energy metabolism and analyzed to determine the following parameters: white blood cell count, red blood cell count, platelet count, and levels of NEFA, hemoglobin, prothrombin time, asparate aminotransferase, alanine aminotransferase, total bilirubin, gamma-glutamyl transpeptidase, total cholesterol, triglyceride, total protein, albumin, cholinesterase, and ammonia.

Statistical analyses

Statistical analyses were performed using SPSS for Windows, release 16.0 (SPSS, Chicago, IL, USA). Statistical analyses were conducted in complete cases. Comparison of data between measured and predicted values was performed with repeated-measure ANOVA and Bonferroni's post hoc test. Comparison among Child-Pugh groups A, B, and C was performed by one-way ANOVA and Tukey's post hoc test. When npRQ was compared among Child-Pugh groups, ANCOVA with age as a covariate and Bonferroni's post hoc test were performed to eliminate the confounding factor. The significance threshold was p<0.05.

RESULTS

Subjects

A total of 537 patients with liver cirrhosis were enrolled in this study. Forty-nine patients were excluded because the npRQ values were out of the range of 0.7-1.0. Characteristics of the 488 patients are shown in Table 1.

Resting energy expenditure

Mean M-REE was 1249 kcal, 1254 kcal, and 1363 kcal in Child-Pugh groups A, B, and C, respectively, and it showed no significant differences among groups. Mean M-REE, basal energy expenditure predicted by the Harris-Benedict equation (H-BEE), and basal energy expenditure predicted by DRI (D-BEE) were 1256 kcal, 1279 kcal, and 1254 kcal, respectively, with M-REE and D-BEE being significantly lower than H-BEE.

Hypermetabolism and hypometabolism were seen in 26 (5.3%) and 25(5.1%) patients, respectively, as determined by H-BEE. In turn, 47(9.6%) and 27(5.5%) patients were hypermetabolic and hypometabolic, respectively, as determined by D-BEE (Table 2).

Mean M-REE in relation to BW (REE/kg) was 21.7 kcal/kg, 21.7 kcal/kg, 21.5 kcal/kg, and 22.2 kcal/kg in all patients and Child-Pugh groups A, B, and C, respectively. These values did not increase with disease progression.

Table 1. Characteristics of the patients

	Total (n = 488)	Child-Pugh A(n = 304)	Child-Pugh B(n = 158)	Child-Pugh C(n = 26)
Male/Female	361/127	230/74	117/41	12/14
Age (year)	60.0±0.5	60.8±0.6	59.8±0.9	50.9±2.8*,†
Height (cm)	163±0.4	162.6±0.5	163±0.8	163±2.0
BW (kg)	58.4±0.5	58.0±0.6	58.7±0.9	61.9±2.1
BMI (kg/m^2)	22.0±0.1	21.9±0.2	22.2±0.3	23.2±0.6
NEFA (μEq/L)	681±14	624±17	741±24*	957±80*
WBC (/μL)	5421±113	5556±145	5290±186	4712±586
RBC (×10^6/μL)	3.79±0.03	3.99±0.04	3.52±0.04*	3.25±0.10*
HGB (g/dL)	11.7±0.1	12.2±0.2	11.2±0.2*	11.1±0.3*
PLT (×10^4/μL)	18.1±0.6	18.2±0.7	19.3±1.2	9.2±1.2*,†
PT (sec)	13.5±0.2	12.4±0.1	14.0±0.4*	18.8±0.5*,†
AST (IU/L)	55±2	51±2	62±3*	59±10
ALT (IU/L)	56±3	55±3	57±4	58±30
T-Bil (mg/dL)	1.6±0.1	1.0±0.02	2.2±0.2*	4.5±0.6*,†
γ-GTP (IU/L)	103±6	109±7	103±12	32±5*,†
T-CHO (mg/dL)	141±2	153±3	125±4*	90±9*,†
TG (mg/dL)	85±2	91±3	73±5*	51±9*
TP (g/dL)	6.8±0.04	7.0±0.05	6.5±0.1*	6.4±0.2*
Alb (g/dL)	3.1±0.03	3.4±0.03	2.7±0.04*	2.5±0.1*
ChE (IU/L)	161±4	195±5	105±4*	73±7*,†
NH_3 (μg/dL)	59±2	49±2	69±3*	92±7*,†

Values are mean±SD.
*Mean value was significantly different from that for Child-Pugh A ($p < 0.05$).
†Mean value was significantly different from that for Child-Pugh B ($p < 0.05$).
Child classes: A, 5-6 points; B, 7-9 points; C, 10-15 points.
BW, body weight; WBC, white blood cell count; RBC, red blood cell count; HGB, hemoglobin; PLT, platelet count; PT, prothrombin time; AST, asparate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin; γ-GTP, gamma glutamyl transpeptidase; T-CHO, total cholesterol; TG, triglyceride; TP, total protein; Alb, albumin; ChE, cholinesterase; NH_3, ammonia.

Table 2. Rates of hypermetabolism and hypometabolism patients

	H-BEE		D-BEE	
	n	%	n	%
Hypermetabolism†				
Total (n = 488)	26	5.3	47	9.6
Child-Pugh A (n = 304)	19	6.3	29	9.5
Child-Pugh B (n = 158)	6	3.8	14	8.9
Child-Pugh C (n = 26)	1	3.8	4	15.4
Hypometabolism†				
Total (n = 488)	25	5.1	27	5.5
Child-Pugh A (n = 304)	14	4.6	19	6.3
Child-Pugh B (n = 158)	10	6.3	7	4.4
Child-Pugh C (n = 26)	1	3.8	1	3.8

H-BEE, basal energy expenditure predicted by Harris-Benedict equation; D-BEE, basal energy expenditure predicted by Dietary Reference Intakes in Japanese.
Child classes: A, 5-6 points; B, 7-9 points; C, 10-15 points.
†Hypermetabolism and hypometabolism were defined as measured REE which was >20% higher or >20% lower than the predicted BEE, respectively.

When M-REE and predicted BEE were calculated for patients in each quartile of BMI groups, mean M-REE values were 1099 kcal, 1209 kcal, 1314 kcal, and 1405 kcal, respectively, in patients in the first (Q1; 14.9-19.7), second (Q2; 19.7-21.8), third (Q3; 21.8-23.8), and fourth quartiles (Q4; 23.8-36.4), respectively. In all groups, M-REE did not exceed 120% above the predicted BEE (Table 3). In groups Q1 and Q2, H-BEE was significantly higher than M-REE. In groups Q1 and Q4, D-BEE was significantly different from M-REE (Figure 1).

Energy intake

Average overall energy intake was 30.5 kcal/kg BW (Table 4). Most patients had adequate energy intake, and no significant intergroup differences were found in relation to disease severity. The patients' BW was maintained by this level of intake during hospitalization. Average energy intake divided by REE/kg BW was 1.4. The daily energy requirement in inpatients with liver cirrhosis was derived from the following equation: Energy intake = M-REE × 1.4.

Non-protein respiratory quotient

Mean npRQ values were 0.847, 0.853, 0.841, and 0.818 in all patients and Child-Pugh groups A, B, and C, respectively (Figure 2). These values decreased with disease progression.

After adjustment by age, npRQ values were 0.854 (95% CI 0.847, 0.861), 0.841 (95% CI 0.832, 0.850), and 0.811 (95% CI 0.788, 0.834) in Child-Pugh groups A, B, and C, respectively. The results of analyses of covariance and a multiple comparison test with age as the dependent variable showed that npRQ was significantly lower in Child-Pugh group C than in Child-Pugh group A.

Non-esterified fatty acid levels

Mean NEFA concentrations were 681, 624, 741, and 957 μEq/L in all patients and Child-Pugh groups A, B, and C, respectively (Figure 2). Serum NEFA concentrations in Child-Pugh group C were significantly higher than those in Child-Pugh groups A and B.

Table 3. Energy metabolism in patients stratified by quartiles of BMI

	Q1	Q2	Q3	Q4
BMI (kg/m^2)	14.9-19.7	19.7-21.8	21.8-23.8	23.8-36.4
M-REE/H-BEE (%)	97.3±1.1	97.3±1.1	99.6±1.2	99.4±1.1
M-REE/D-BEE (%)	107±1.2	102±1.1	101±1.2	95.0±1.1

M-REE, resting energy expenditure measured by indirect calorimetry; H-BEE, basal energy expenditure predicted by Harris-Benedict equation; D-BEE, basal energy expenditure predicted by Dietary Reference Intakes in Japanese.

Table 4. Dietary intake and measured REE in relation to BW

	Total (n = 488)	Child-Pugh A (n = 304)	Child-Pugh B (n = 158)	Child-Pugh C (n = 26)
Dietary intake (kcal)	1759±19	1772±23	1745±37	1698±87
Intake (kcal/kg BW)	30.5±0.4	31.0±0.4	29.9±0.7	27.9±1.5
REE (kcal/kg BW)	21.7±0.1	21.7±0.2	21.5±0.5	22.2±0.7
Intake(REE/kg BW)	1.4±0.02	1.4±0.02	1.4±0.03	1.3±0.07

Child classes: A, 5-6 points; B, 7-9 points; C, 10-15 points.
REE, resting energy expenditure; BW, body weight

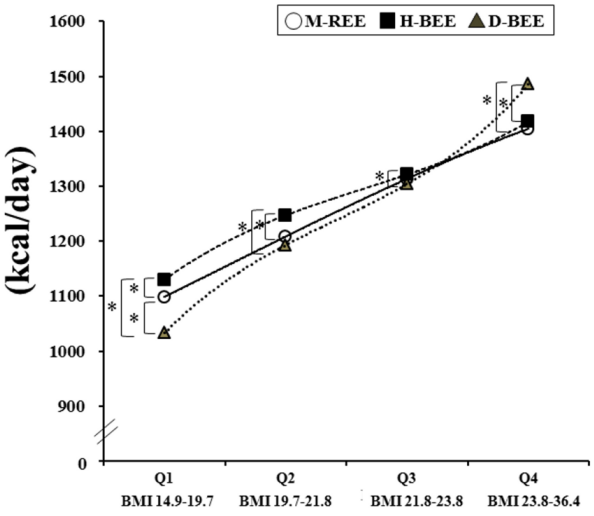

Figure 1. The comparison between measured REE and predicted BEE in quartiles of BMI. M-REE, resting energy expenditure measured by indirect calorimetry; H-BEE, basal energy expenditure predicted by Harris-Benedict equation; D-BEE, basal energy expenditure predicted by Dietary Reference Intakes for Japanese. *p < 0.05.

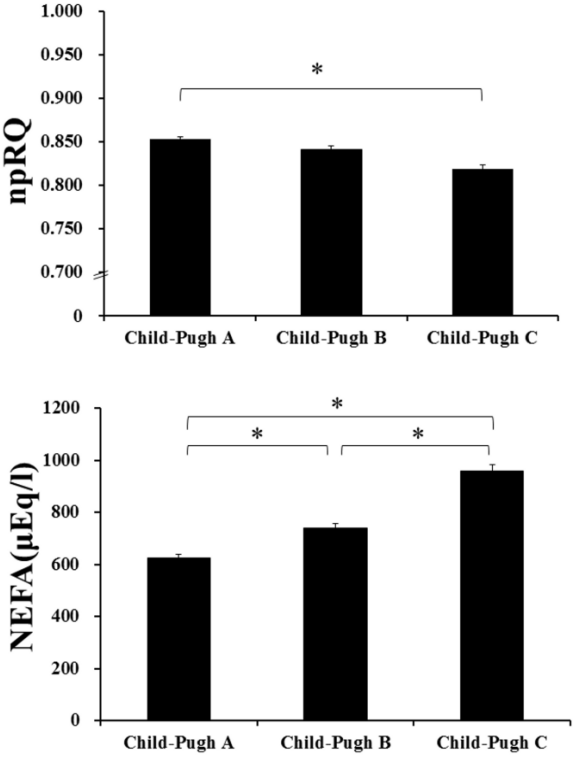

Figure 2. NpRQ values and in serum NEFA levels Child-Pugh groups A, B, and C.npRQ, non-protein respiratory quotient; NEFA, non-esterified fatty acids. *p < 0.05

DISCUSSION

Various reports have focused on the metabolism of patients with liver cirrhosis,[3-7] and it is unclear whether REE is elevated in these individuals. Elevation of plasma catecholamines[21] and activation of the sympathetic nervous system[22] induce hypermetabolism, while ascites,[23] hepatocellular carcinoma,[24] and portal hypertension[25] are reported to increase REE. On the other hand, decreased physical activity[7] may decrease REE. In addition to such variations in patient status and complications, differences related to race, setting of control groups, and method of adjustment of energy expenditure are further reasons for the inconsistencies in observations. Moreover, some reports have shown that most patients have normal REE, whereas others have hyper- or hypometabolism.[7,21,26,27] The criteria used to identify hyper- or hypometabolism vary widely among these studies; therefore, they are not comparable.

In all severity groups in the present study, M-REE was comparable to D-BEE and was significantly lower than H-BEE. Moreover, M-REE did not increase even in Child-Pugh group C. These data are inconsistent with previous findings of hypermetabolism in patients with cirrhosis.[4,5] In addition, in Q4 (the obesity group), M-REE did not indicate hyper- or hypometabolism. Therefore, excess energy intake should be avoided in patients with liver cirrhosis.

Although our findings showed no increase in measured REE values when compared with predicted REE values, only 5.1%-9.6% patients were hyper- or hypometabolic. While indirect calorimetry is recommended for metabolically abnormal patients, it is expensive and not widely

available; therefore, REE is usually calculated from the prediction equation in the clinical setting.

DRI for Japanese provides standard BEE values according to sex and age, with data derived from a BEE database of healthy Japanese individuals.[20] Although the Harris-Benedict equation is usually used to estimate BEE, this equation is based on data from healthy Caucasian individuals, and previous studies have shown that this equation tends to overestimate BEE in Japanese[28,29] and Asian populations.[30] In the present study, H-BEE was significantly higher than M-REE in low-BMI groups, which may be attributable to differences in body size between Japanese and Caucasian individuals. Because M-REE in our patients was found to be similar to that of a healthy population, the Japanese DRI is recommended for the estimation of REE in Japanese patients with cirrhosis. However, D-BEE was significantly different from M-REE in patients in the highest and lowest quartiles of BMI. Since the Japanese DRI is simple multiples of BW, it overestimates individual BEE in obese subjects and underestimates in lean subjects. Therefore predictive values cannot be applied to these patients.

The guidelines of the European Society of Parenteral and Enteral Nutrition recommend an energy intake of 35-40 kcal/kg BW·day.[31] In Caucasian studies, REE of liver cirrhosis patients was reported to be 22-27 kcal/kg BW.[3,4,32] The 24 h total energy requirement of liver cirrhosis patients is reported to amount to about 1.3 × measured REE.[32] On the other hand, in Japan, 25-35 kcal/kg ideal BW/day is recommended as daily energy intake in patients with liver cirrhosis on the basis of DRI;[33] however, there is little supporting evidence for this. In this study, the mean unrestricted and spontaneous energy intake until 20:00 on the previous day of indirect calorimetric measurement was 30.5 kcal/kg BW. Because REE of outpatients is reported to be higher than that of inpatients,[34] our patients with cirrhosis may have required more calories after discharge. Average energy intake divided by REE/kg BW was 1.4, a baseline value that is multiplied by REE to derive individual energy requirements for maintaining BW. The daily energy requirement in inpatients with liver cirrhosis was derived from the equation REE × 1.4.

In healthy individuals, sympathetic daytime activity is higher than night-time activity, suggesting that REE may increase during the daytime. In patients with cirrhosis, the circadian rhythm seems to disappear,[22] and spontaneous physical activity level was considerably lower;[35] therefore, it is thought that daytime activity does not increase in these patients as much as it does in healthy individuals. One limitation of this research is that we investigated REE entirely during daytime; therefore, the total energy expenditure could not be shown.

Most studies have reported that npRQ decreases significantly after overnight fasting even in patients with moderate cirrhosis. This is because of increased fat oxidation and decreased carbohydrate oxidation[2,3,36] with a concomitant increase in NEFA mobilization from adipose tissue. Therefore, patients with liver cirrhosis exhibit high NEFA concentrations and low npRQ values in the fasting state.[3] In this study, npRQ values decreased with disease progression while NEFA concentrations increased with increasing Child-Pugh grade. These findings are consistent with those of previous study.[37]

A late evening snack (LES) is recommended for patients with cirrhosis to prevent overnight starvation.[38,39] In our previous study involving LES (a rice ball) intake by patients with cirrhosis, NEFA concentrations and npRQ values improved after 1 week of administration, without definitive changes in other hematological data or REE.[40] RQ was found to be improved even after 1 day of LES intake;[41] however, REE remained unaltered in other studies involving LES intake by patients.[42,43] This suggests that RQ reflects depleted liver glycogen storage capacity after overnight fasting;[44] however, REE may reflect not only liver function. Hypermetabolism exists in patients with presinusoidal extrahepatic portal obstruction[25] and 1 year after liver transplantation,[45] who have normal liver function. Therefore, REE may be influenced mainly by extrahepatic factors.

RQ is reported to be lower in older subjects than in younger subjects.[46] In the present study, RQ was adjusted for age to eliminate the influence of this confounding factor.[46-49] Age-adjusted npRQ was significantly decreased with disease severity; therefore, a decrease in npRQ values with an increase in disease severity was independent of age difference.

In clinical practice, the appropriate estimation equation is useful for determining REE without the involvement of indirect calorimetry. From the findings of our study, Japanese DRI is recommended for the estimation of REE. However, hyper- and hypometabolism can be observed in some patients; therefore, in our opinion, the best strategy for the determination of adequate energy intake is indirect calorimetry.

In conclusion, although DRI is a useful tool for the estimation of REE in patients in the second and third BMI quartiles, M-REE is recommended to ensure the provision of adequate nutritional care to patients with cirrhosis, including those in the highest and lowest quartiles of BMI.

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AUTHOR DISCLOSURES

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Original Article

Comparison of measured and predicted energy expenditure in patients with liver cirrhosis

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肝硬化患者能量消耗的实际测定值与估计值的比较

肥胖是肝硬化患者引发肝癌的一个风险因子。为了预防过量饮食和肥胖，估计能量需求是不必可少的。但是对肝硬化患者能量消耗情况尚未充分了解。本研究旨在调查肝硬化患者的静息能量消耗(REE)以及能量摄取情况，从而制定能量摄取的标准。本横断面研究主要对日本 488 名肝硬化病人进行了间接热量测定，并将间接热量测定法(M-REE)测得的 REE 结果与 Harris-Benedict 方程计算的基础能量消耗(BEE)结果(H-BEE)以及日本膳食指南(DRI)推荐的标准(D-BEE)进行比较。M-REE 的平均值(1256 kcal)显著低于 H-BEE(1276 kcal)；但与 D-BEE(1254 kcal)相比差别不大。M-REE 的均值与体重(BW; REE/kg BW)的关系为 21.7 kcal/kg BW. BMI 在第一和第二四分位数的病人的 H-BEE 显著高于 M-REE，而且 BMI 在最高和最低四分位数病人的 D-BEE 都与 M-REE 有明显差别。平均能量摄取量为 30.5 kcal/kg BW，高于 REE/kg BW 1.4 倍。虽然 DRI 可以用来帮助估计 BMI 在第二和第三四分位数病人的 REE，但 M-REE 则能够保证肝硬化病人得到足够的营养供应，即使 BMI 在最高四分位数和最低四分位数的病人也不例外。

关键词：间接能量测定、静息能量消耗、Harris-Benedict、非蛋白呼吸商、非酯化脂肪酸