Original Article

Effects of an individualized nutrition intervention on the respiratory quotient of patients with liver failure

Xing Liu MD[1,2], Ming Kong PhD[1,3], Xin Hua MSc[4], Yinchuan Yang BSc[1], Manman Xu MSc[1], Yanzhen Bi MD[1], Lu Li MD[1], Zhongping Duan PhD[1,3], Yu Chen PhD[1,3]

[1]*Difficult & Complicated Liver Diseases and Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University, Beijing, China*
[2]*Department of Infectious Disease, Linyi People's Hospital, Linyi, China*
[3]*Beijing Municipal Key Laboratory of Liver Failure and Artificial Liver Treatment Research, Beijing, China*
[4]*Department of Clinical Nutrition, Beijing YouAn Hospital, Capital Medical University, Beijing, China*

Background and Objectives: Malnutrition and energy metabolism disorders are characterized by a low respiratory quotient in patients with liver failure and often lead to poor prognosis. Therefore, early nutrition interventions are crucial for patients with liver failure to ameliorate abnormal metabolic status and malnutrition. This study explored the effect of an individualized nutrition intervention on the respiratory quotient of patients with liver failure. **Methods and Study Design:** An individualized 2-week nutrition intervention was conducted on patients with nutritional risk caused by liver failure according to patient resting energy expenditure. Patients were separated into two groups for further analysis according to whether their energy intake reached 1.2 times their resting energy expenditure. **Results:** Fifty-two patients with nutritional risk caused by liver failure were enrolled. Their average respiratory quotient was 0.79 (0.76–0.84) at the baseline. Patients with an energy intake of ≥1.2 times their resting energy expenditure had a higher respiratory quotient and lower scores on the model for end-stage liver disease and Child–Pugh test than those with an energy intake of <1.2 times their resting energy expenditure at weeks 1 and 2 after the intervention. Moreover, no significant differences were observed between the two groups at the baseline. Respiratory quotient was negatively correlated with the model for end-stage liver disease and Child–Pugh scores. **Conclusions:** Individualized nutrition interventions with an energy intake ≥1.2 times the patient's resting energy expenditure can effectively improve the respiratory quotient and reduce disease severity in patients with nutritional risk caused by liver failure.

Key Words: liver failure, energy metabolism, resting energy expenditure, respiratory quotient, individualized nutrition intervention

INTRODUCTION

The liver is a central regulator of energy metabolism and plays a critical role in the metabolism of nutrients. Extensive necrosis of hepatocytes can be observed when non-chronic liver failure occurs, which impairs liver function and leads to malnutrition and various energy metabolism disorders. Malnutrition is a serious complication of liver disease and is almost universal in patients with end-stage liver disease (ESLD).[1-5] The degree of malnutrition is correlated with the severity of hepatic disease regardless of the cause.[6-8] Malnutrition leads to increased morbidity and mortality rates[9-12] in patients with ESLD, both before and after liver transplantation.[2,13,14] Therefore, conducting nutritional intervention for patients with liver failure at an early stage is vital.

Respiratory quotient (RQ)[15,16] is considered an excellent indicator of substrate oxidation, which is the ratio of the amount of carbon dioxide produced to the amount of oxygen consumed. The metabolism substrate of patients with ESLD is similar to that of healthy individuals after 3 days of starvation.[17-19] Impaired glycogen storage and insulin resistance result in earlier and more excessive use of fats and proteins as fuel sources.[20] This leads to increased free fatty acid and ketone body production; moreover, a significant correlation has been reported between free fatty acid production and fat oxidation rate in cirrhotic patients.[21] Low RQ has been frequently observed in patients with ESLD. Furthermore, significantly lower RQ has been reported in patients with acute-on-chronic liver failure (ACLF) than in patients with cirrhosis or chronic hepatitis B. In patients with ACLF, the RQ of nonsurvivors is significantly lower than that of survivors.[22] Therefore, RQ is useful for monitoring changes in energy metabolism and may be related to the prognosis of patients with liver failure.

Corresponding Author: Dr Yu Chen, Difficult & Complicated Liver Diseases and Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University, No. 8 Xitoutiao, Fengtai District, Beijing 100069, China.
Tel: +86 010 839 97157; Fax: +86 010 632 95285
Email: chybeyond@163.com
Manuscript received 26 February 2019. Initial review completed 17 March 2019. Revision accepted 31 March 2019.
doi:

A late evening snack (LES) is recommended by both the European Society for Clinical Nutrition and Metabolism guidelines[23] and the American Society for Parenteral and Enteral Nutrition[24] for improving the catabolic state. Many studies[25-28] have discovered that LESs can improve fasting RQ and quality of life in patients with cirrhosis, moreover, one study reported that a high-frequency diet strategy is effective for improving RQ and is beneficial to patients with cirrhosis.[29] The fasting RQ of patients with ACLF also significantly improved after LES supplementation.[30]

However, no research has been conducted on improving RQ in patients with liver failure through individualized nutrition intervention. Therefore, we performed nutritional risk screening of patients with liver failure using nutritional risk screening 2002 (NRS-2002).[31] We also established a nutrition support team (NST) consisting of physicians, dietitians, pharmacists, and nurses who conducted an individualized nutrition intervention on the basis of comprehensive internal medicine treatment for patients with nutritional risk caused by liver failure. The purpose of this study was to explore the effect of an individualized nutrition intervention on RQ in patients with liver failure.

METHODS

Patients

This study was conducted from December 2016 to July 2018 at the Artificial Liver Center, Beijing YouAn Hospital, Capital Medical University. A total of 52 patients with nutritional risk caused by liver failure were enrolled in the study. Of these, 2 cases were acute liver failure (ALF), 1 case was sub-acute liver failure (SALF), 49 cases were ACLF. Of the ACLF cases, 42 cases were hepatitis B virus-related ACLF, six were caused by alcohol, and one had an unknown cause. The diagnosis of liver failure was based on the guidelines of the 13th Asia-Pacific Congress of Clinical Microbiology and Infection Consensus.32 None of the patients with liver failure had a history of thyroid dysfunction, neoplasia, diabetes mellitus, or other diseases that can potentially affect energy metabolism. None had hepatic encephalopathy, gastrointestinal bleeding, or fever during the study. None of the patients were administered drugs that could affect energy metabolism. Each participant signed an informed consent form. The study protocol was in accordance with the ethical guidelines of the Helsinki Declaration of 1975 and was authorized by the Institutional Review Board of Beijing YouAn Hospital, Capital Medical University, Beijing, China (Approval No. 2016-18). The clinical trial was registered at http://www.chictr.org.cn (registration number: ChiCTR1900020900).

Study design

We screened patients with liver failure for nutritional risk using the NRS-2002, and those with nutritional risk caused by liver failure were enrolled in the study. The energy intake of each patient was assessed based on 24-hour dietary records. The resting energy expenditure (REE) and fasting RQ of each patient was measured by indirect calorimetry at the baseline and once each week. The precise energy requirements of patients were determined according to their REE. The individualized nutrition intervention was conducted by NST and lasted for 2 weeks on the basis of comprehensive internal medicine treatment for patients with nutritional risk caused by liver failure. All patients were provided with six meals per day and snacks between breakfast, lunch, and dinner and before going to bed. The American Society for Parenteral and Enternal Nutrition suggests that patients with ESLD have an energy requirement of 1.2–1.4 times their REE.[33] Based on an energy intake of 1.2 times their REE, all patients were divided into two groups: one with an energy intake of no less than 1.2 times their REE (≥1.2REE) and one with an energy intake of less than 1.2 times their REE (<1.2REE). We then explored the effects of the individualized nutrition intervention on RQ in patients with liver failure.

Anthropometric variables

Body height and weight were measured using a height/weight scale (RGZ120, Wuxi Weighter Factory, Wuxi, China), and the precision of height and weight measurements were to 0.1 cm and 0.1 kg, respectively. Body mass index (BMI) was calculated as kg/m^2. Triceps skinfold thickness (TSF) was measured at the midpoint between the olecranon and acromion of the left arm with a skinfold caliper (Changshu Instrument Company, Changshu, China). Midarm circumference (MAC) was measured at the same site as TSF with a tape measure.[34] To reduce operational error, TSF and MAC were consecutively measured three times and then the average was recorded. Midarm muscle circumference (MAMC) was calculated using the following formula: MAMC (cm) = MAC (cm) - π x TSF (cm).

Laboratory variables

We collected patient demographics, clinical data, and laboratory parameters at the baseline and on a weekly basis. An Olympus Automatic Biochemical Analyzer AU5400 (Olympus, Tokyo, Japan) was used to measure serum biochemical parameters. The severity of liver failure was assessed according to the model for end-stage liver disease (MELD) and Child–Pugh scores.

Fasting RQ and REE

Before indirect calorimetry was performed, patients stayed in bed at least 30 minutes and fasted for at least 8 h in the morning. The humidity of the quiet room was maintained at 45%–60% with a temperature of 24°C–26°C. REE and fasting RQ were measured using the cardiorespiratory diagnostics investigation system for nutrition metabolism (Medgraphics corporation, Saint Paul, MN, USA), and the gas and volume were calibrated before performing tests. The Weir formula, REE (kcal) = 5.50 VO2 + 1.76 VCO2−1.99 TUN,[35] was used for calculating the actual REE, and the Harris–Benedict formula[36] was used for calculating the predicted REE. RQ was calculated as VCO2/VO2.

Nutrition intake

The energy intake of carbohydrates, proteins and fats accounted for 74%, 10%, and 16%, respectively, in all enrolled patients. The precise energy requirements for

Table 1. Baseline characteristics of patients in the two groups

	<1.2REE group	≥1.2REE group	*p* value
Number	30	22	—
Women, n (%)	6 (20.0)	2 (9.1)	0.491
Age (y)	46.3±12.4†	41.6±11.4	0.168
BMI (kg/m^2)	23.9±3.7	23.6±3.7	0.813
Etiology, n (%)			0.113
HBV	27 (90.0)	16 (72.7)	
Alcohol	3 (10.0)	3 (13.6)	
Unknown reason	0 (0.0)	3 (13.6)	
Classification, n (%)			0.138
ALF and SALF	0 (0.0)	3 (13.6)	
ACLF	30 (100)	19 (86.4)	
Ascites, n (%)	24(80.0)	14 (63.6)	0.189
Child-Pugh score	11.0, 10.0-12.0‡	10.5, 10.0-12.0	0.823
MELD score	25.5, 20.5-28.3	22.0, 19.0-24.3	0.065
Energy intake (kcal/d)/REE	0.84, 0.64-0.93	0.87, 0.74-1.23	0.255
RQ	0.78, 0.75-0.82	0.79, 0.77-0.84	0.163
REE (kcal/d)	1576, 1268-1641	1528, 1338-1660	0.879
TSF (mm)	17.8, 10.5-27.8	14.0, 7.3-22.8	0.374
MAMC (cm)	21.9±3.0	22.5±2.7	0.435
ALT (IU/L)	98.1, 55.1-352	93.1, 41.8-157	0.578
AST (IU/L)	144, 87.7-227	189, 62.1-199	0.308
TBIL (μmol/L)	381±193	314±133	0.164
Albumin (g/L)	32.3, 30.7-33.2	31.8, 26.7-35.8	0.598
GLU (mmol/L)	4.8, 3.9-5.4	4.6, 4.0-4.8	0.578
eGFR (ml/min)	111±20.1	115±19.0	0.435

HBV: hepatitis B virus; ALF: acute liver failure; SALF: subacute liver failure; ACLF: acute-on-chronic liver failure; MELD: model for end-stage liver disease; REE: resting energy expenditure; RQ: respiratory quotient; TSF: triceps skinfold thickness; MAMC: midarm muscle circumference; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; GlU: fasting glucose; eGFR: estimated glomerular filtration rate

†Mean±standard deviation (all such values).

‡Median, interquartile range (all such values).

patients were determined on the basis of the REE. At the baseline and after exactly 2 weeks, food intake was recorded and analyzed by two dietitians. Energy and nutrient intakes were calculated according to the standardized Chinese Food Composition Tables.[37]

Statistical analysis

Mean ± standard deviation, median, or interquartile range was used to describe continuous variables, and frequency or percentage was used to describe categorical variables. The χ^2 test and Fisher's exact test were used to analyze categorical variables. The independent sample t test and Mann–Whitney U test were used to analyze continuous variables. Differences in fasting glucose, TSF, and MAMC were analyzed using the paired t test or Wilcoxon signed rank test in each group. Pearson's correlation coefficient was used to evaluate correlations of RQ with MELD and Child–Pugh scores. SPSS 19.0 (SPSS, Inc., an IBM Company, Chicago, IL) was used for analysis, and $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of patients in the two groups

No statistically significant differences were observed between the two groups at baseline with respect to demographics, etiology, energy intake, energy metabolism, disease severity, anthropometric variables, or laboratory data (Table 1).

Effects of individualized nutrition intervention on fasting RQ

At the baseline, the average RQ was 0.79 (0.76–0.84) and no significant difference in RQ was observed between the two groups (0.79, 0.77–0.84 vs 0.78, 0.75–0.82, p=0.163). The group with an energy intake of ≥1.2REE had a higher RQ than the group with an intake of <1.2REE at week 1 and week 2 after the individualized nutrition intervention (wk1: 0.87, 0.82–0.96 vs 0.79, 0.74–0.85, p=0.003; wk2: 0.83, 0.81–0.88 vs 0.78, 0.74–0.82, p=0.004) (Figure 1).

Effects of individualized nutrition intervention on MELD and Child–Pugh scores

No significant difference was observed between the two groups in terms of MELD score or Child–Pugh score at the baseline (22.0, 19.0–24.3 vs 25.5, 20.5–28.3, p=0.065; 10.5, 10.0–12.0 vs 11.0, 10.0–12.0, p=0.823). The ≥1.2REE group had lower MELD and Child–Pugh scores than the <1.2REE group at week 1 and week 2 after the individualized nutrition intervention (wk1: 18.0, 16.5–21.5 vs 25.0, 17.0–29.0, p=0.01; 10.0, 9.0–11.0 vs 11.0, 10.0–11.0, p=0.045; wk2: 17.5, 15.3–21.8 vs 23.5, 14.8–28.5, p=0.033; 9.0, 7.3–10.0 vs 10.5, 10.0–11.0, p=0.007) (Figure 2).

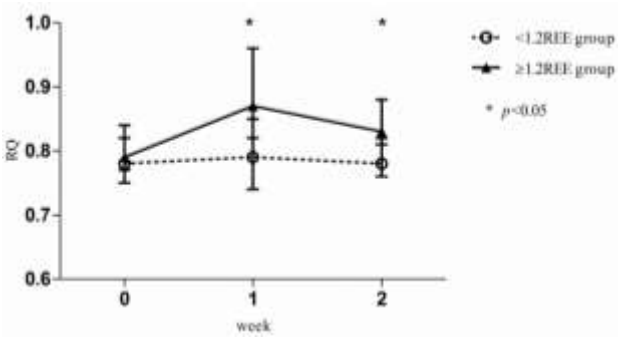

Figure 1. Effects of individualized nutrition intervention on fasting respiratory quotient (RQ) on patients in the group with an energy intake no less than 1.2 times their resting energy expenditure (REE; ≥1.2REE) and those in the group with less than 1.2 times their REE (<1.2REE).

Correlation analysis of RQ with MELD score and Child–Pugh score

For all patients, RQ was negatively correlated with MELD score and Child–Pugh score (r=−0.24, p=0.007; r=−0.35, p<0.001) (Table 2).

Effects of individualized nutrition intervention on anthropometric variables

In patients with liver failure, no significant difference was observed between the two groups with respect to TSF or MAMC at the baseline (Table 1). No significant difference was observed between 2 weeks after the individualized nutrition intervention and the baseline in either group in terms of TSF or MAMC (TSF: p=0.428, p=0.137; MAMC: p=0.071, p=0.363) (Table 3).

Side effects

No significant difference was noted between the two groups at the baseline with respect to fasting glucose level (Table 1) or in either group in terms of fasting glucose levels 2 weeks after the individualized nutrition intervention compared with the baseline (p=0.215, p=0.653) (Table 4). Moreover, no obvious side effects associated with individualized nutrition intervention were reported.

DISCUSSION

Malnutrition, which is partly caused by abnormal energy metabolism in patients with liver failure, is almost universal in patients with ESLD and worsens when liver failure occurs. Increased lipid oxidation rates and decreased glucose oxidation rates, which were associated with decreased RQ,[22] were observed in patients with ACLF. RQ is strongly associated with liver function and the severity of liver disease. Nonprotein RQ and malnutrition are both significant independent factors that determine the likelihood of survival in patients with liver cirrhosis.[12,38] Another study[22] discovered that RQ was significantly lower in patients with ACLF than in patients with liver cirrhosis and that in patients with ACLF, the nonsurvival group had a lower average RQ than did the survival group. According to these findings, RQ may be used as a factor for determining the prognosis of liver failure. Therefore, improving RQ, which is the equivalent of improving the catabolic state, is beneficial to patients with liver failure.

RQ values vary with the metabolism of different substrates: 0.7 for fat, 0.8 for protein, and 1.0 for glucose.[15,16] In the present study, we discovered that RQ was 0.79 (0.76–0.84) at the baseline in patients with liver failure, indicating an obvious metabolic abnormality. This result is consistent with the findings of other study.[22] If the abnormal metabolic status of patients is not corrected quickly enough, it is detrimental to their recovery. When the NST conducted an individualized nutrition intervention on patients with liver failure, we discovered that an energy intake of ≥1.2REE could improve patient RQ, MELD score, and Child–Pugh score and that RQ was negatively correlated with MELD score and Child–Pugh score. These results suggested that an individualized nutrition intervention with an energy intake of ≥1.2REE could improve the RQ of patients with liver failure and reduce the severity of liver failure. The findings and mechanisms of

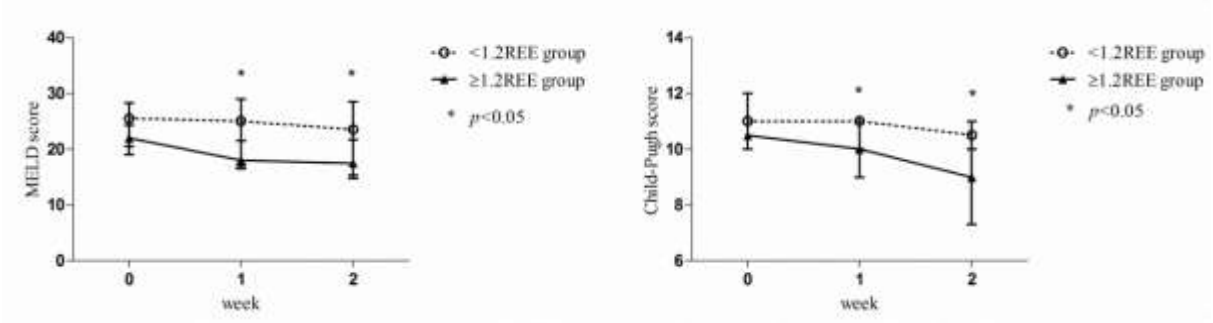

Figure 2. Effects of individualized nutrition intervention on the model for end-stage liver disease (MELD) score and Child–Pugh score in patients with an energy intake of no less than 1.2 times their resting energy expenditure (REE; ≥1.2REE) and in those with an energy intake of less than 1.2 times their REE (<1.2REE).

Table 2. Correlation analysis of RQ with MELD score and Child–Pugh score

	RQ	
	r	p value
MELD score	-0.24	0.007
Child-Pugh score	-0.35	<0.001

MELD: model for end-stage liver disease; RQ: respiratory quotient.

Table 3. Effects of individualized nutrition intervention on TSF and MAMC

	TSF (mm)		*p* value	MAMC (cm)		*p* value
	Baseline	Week 2		Baseline	Week 2	
<1.2REE group	17.8, 10.5-27.8[†]	16.5, 10.0-25.8	0.137	21.9±3.0[‡]	21.9±3.6	0.363
≥1.2REE group	14.0, 7.3-22.8	14.5, 8.0-20.0	0.428	22.5±2.7	22.0±2.4	0.071

REE: resting energy expenditure; TSF: triceps skinfold thickness; MAMC: midarm muscle circumference.
[†]Mean±standard deviation (all such values).
[‡]Median, interquartile range (all such values).

Table 4. Effects of individualized nutrition intervention on fasting glucose levels

	Fasting glucose (mmol/L)		*p* value
	Baseline	Week 2	
<1.2REE group	4.8, 3.9-5.4	4.2, 3.6-6.2	0.653
≥1.2REE group	4.6, 4.0-4.8	4.5, 4.1-5.3	0.215

REE: resting energy expenditure.
Values are expressed as a median, interquartile range

the study are shown in Figure 3.

Serum albumin and prealbumin are synthesized by the liver and are key indicators for evaluating the liver function and nutritional status of patients with hepatopathy. Extensive necrosis of hepatocytes can be observed when nonchronic liver failure occurs and the function of liver synthesis is severely impaired. In the absence of malnutrition in patients with liver failure, albumin and prealbumin levels also decrease significantly. However, patients with liver failure often receive exogenous albumin supplementation. Therefore, serum albumin and prealbumin are not ideal indicators for evaluating the nutritional status of patients with liver failure. Anthropometric variables such as TSF, MAC, and MAMC are primarily used to analyze lean body mass and fat mass and are not affected by ascites or lower limb edemas. Anthropometry is recognized as a basic indicator for evaluating of the nutritional status of patients with liver disease and is recommended by the European Society for Clinical Nutrition and Metabolism guidelines.[23] Studies[39,40] in which adult patients with chronic liver disease were administered LESs with different amounts of energy (700 kcal vs 200 kcal) over the course of a year reported a significant increase in the accumulation of lean body mass. In our study on patients with liver failure, no significant difference in terms of TSF or MAMC was observed before and after the indi-

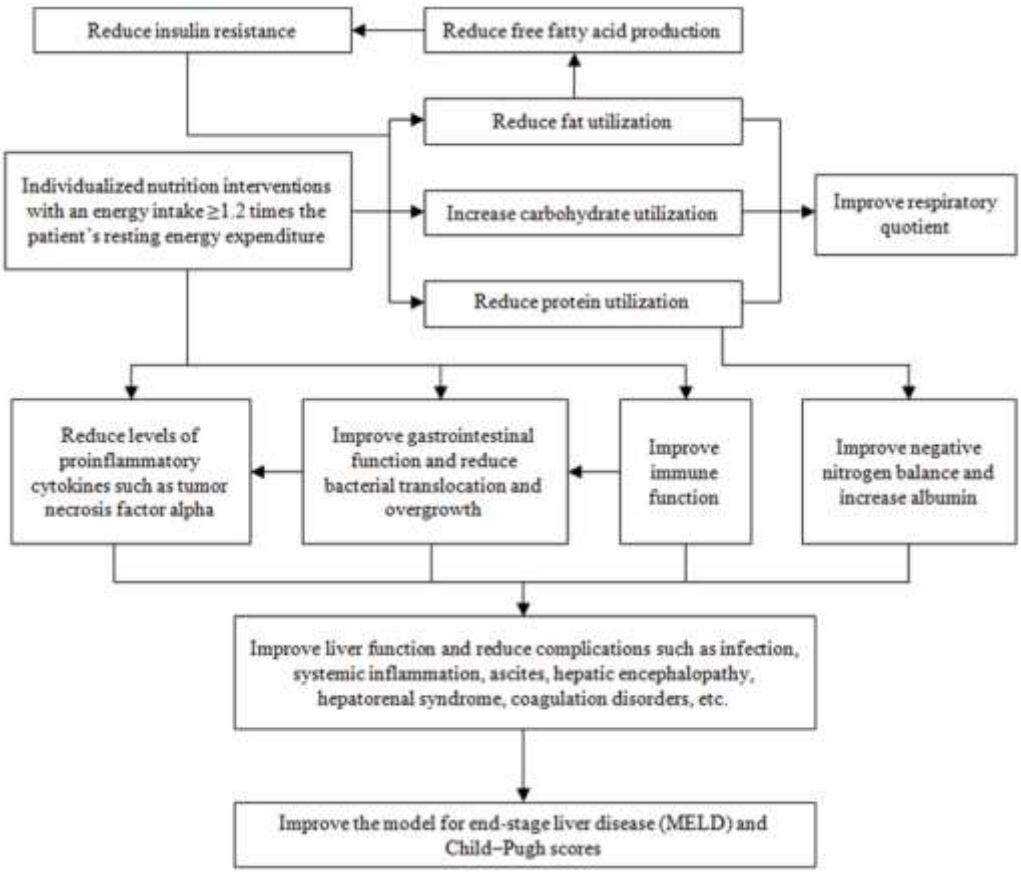

Figure 3. Conceptual diagram of the findings and mechanisms of individualized nutrition intervention in patients with liver failure.

vidualized nutrition intervention in the two groups. The individualized nutrition intervention in this study had a duration of only 2 weeks, which was insufficient for improving the TSF and MAMC of patients with liver failure. The duration of the individualized nutrition intervention should be extended to evaluate the effect on the nutritional status of patients.

Several studies have reported that glucose disturbances, especially hyperglycemia, are related to the progression of liver disease and increased mortality rate in patients with liver cirrhosis.[41-43] Moreover, hypoglycemia was also discovered to increase the mortality rate in patients with acute decompensation of liver cirrhosis.[44] In our study, we discovered that an individual nutrition intervention with an energy intake of ≥1.2REE had no significant effect on the blood glucose of patients with liver failure. No obvious side effects associated with individualized nutrition intervention were reported. Therefore, the individualized nutrition intervention is a safe treatment method.

In conclusion, an individualized nutrition intervention with an energy intake of ≥1.2REE can effectively and safely improve the RQ of patients with liver failure and reduce the severity of liver failure. Therefore, clinicians must formulate and implement individualized nutrition interventions as early as possible for patients with nutritional risk caused by liver failure and ensure that their energy intake is ≥1.2REE to improve the abnormal metabolic status and even prognosis of patients. The sample size of our study was small and the follow-up time was short; therefore, the sample size must be expanded and the follow-up time must be extended to further explore the effect of individualized nutrition interventions on the prognosis of patients with liver failure.

ACKNOWLEDGEMENTS

The authors thank all participants in the study.

AUTHOR DISCLOSURES

All authors declare no conflict of interest. This work was supported by the National Science and Technology Key Project on "Major Infectious Diseases such as HIV/AIDS, Viral Hepatitis Prevention and Treatment" (Nos. 2017ZX10203201-005, 2012ZX10002004-006, 2017ZX10202203-006-001, 2017ZX10201201 and 2017ZX10302201-004-002); National Key R&D Program of China(No.2017YFA0103000); Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No.ZYLX201806); "Beijing Municipal Administration of Hospitals" Ascent Plan (No. DFL20151601); and Capital Nursing Research Special Funding Support (No.17HL24).

REFERENCES

1. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: results of a prospective study. Nutrition. 2003;19: 515-21.
2. Merli M, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O et al. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. Liver Int. 2010;30: 208-14. doi: 10.1111/j.1478-3231.2009.02135.x.
3. Carvalho L, Parise ER. Evaluation of nutritional status of nonhospitalized patients with liver cirrhosis. Arq Gastroenterol. 2006;43:269-74.
4. Qin H, Li H, Xing M, Wu C, Li G, Song J. Nutritional support treatment for severe chronic hepatitis and posthepatitic cirrhosis. J Huazhong Univ Sci Technolog Med Sci. 2006;26:217-20.
5. Kalaitzakis E, Simrén M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, Björnsson E. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. Scand J Gastroenterol. 2006;41:1464-72. doi: 10.1080/00365520600825117.
6. Tai ML, Goh KL, Mohd-Taib SH, Rampal S, Mahadeva S. Anthropometric, biochemical and clinical assessment of malnutrition in Malaysian patients with advanced cirrhosis. Nutr J. 2010;9:27. doi: 10.1186/1475-2891-9-27.
7. Mccullough AJ, Bugianesi E. Protein-calorie malnutrition and the etiology of cirrhosis. Am J Gastroenterol. 1997;92: 734-8.
8. Merli M, Riggio O, Dally L. Does malnutrition affect survival in cirrhosis? PINC (Policentrica Italiana Nutrizione Cirrosi). Hepatology. 2010;23:1041-6.
9. Alvares-Da-Silva MR, Reverbel dST. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. Nutrition. 2005;21:113-7. doi: 10.1016/j.nut.2004.02.002.
10. Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. Liver Int. 2009;29:1396-402. doi: 10.1111/j.1478-3231.2009.02077.x.
11. Gunsar F, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, Sabin C, Burroughs AK. Nutritional status and prognosis in cirrhotic patients. Aliment Pharmacol Ther. 2006;24:563-72. doi: 10.1111/j.1365-2036.2006.03003.x.
12. Alberino F, Gatta A, Amodio P, Merkel C, Di PL, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis . Nutrition. 2001;17:445-50.
13. Selberg O, Böttcher J, Tusch G, Pichlmayr R, Henkel E, Müller MJ. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. Hepatology. 1997;25:652-7. doi: 10.1002/hep.510250327.
14. Stephenson GR, Moretti EW, Elmoalem H, Clavien PA, Tuttlenewhall JE. Malnutrition in liver transplant patients: preoperative subjective global assessment is predictive of outcome after liver transplantation. Transplantation. 2001;72: 666-70.
15. Livesey G, Elia M. Estimation of energy expenditure, net carbohydrate utilization, and net fat oxidation and synthesis by indirect calorimetry: evaluation of errors with special reference to the detailed composition of fuels. Am J Clin Nutr. 1988;47:608-28. doi: 10.1093/ajcn/47.4.608.
16. Nakaya Y, Harada N, Kakui S, Okada K, Takahashi A, Inoi J, Ito S. Severe catabolic state after prolonged fasting in cirrhotic patients: effect of oral branched-chain amino-acid-enriched nutrient mixture. J Gastroenterol. 2002;37:531-6. doi: 10.1007/s005350200082.
17. Chang WK, Chao YC, Tang HS, Lang HF, Hsu CT. Effects of extra-carbohydrate supplementation in the late evening on energy expenditure and substrate oxidation in patients with liver cirrhosis. JPEN J Parenter Enteral Nutr. 1997;21:96-9. doi: 10.1177/014860719702100296.
18. Owen OE, Reichle FA, Mozzoli MA, Kreulen T, Patel MS, Elfenbein IB et al. Hepatic, gut, and renal substrate flux rates in patients with hepatic cirrhosis. J Clin Invest. 1981; 68:240-52.

19. Muller MJ, Lautz HU, Plogmann B, Burger M, Korber J, Schmidt FW. Energy expenditure and substrate oxidation in patients with cirrhosis: the impact of cause, clinical staging and nutritional state. Hepatology. 1992;15:782-94.
20. Cheung K, Lee SS, Raman M. Prevalence and mechanisms of malnutrition in patients with advanced liver disease, and nutrition management strategies. Clin Gastroenterol Hepatol. 2012;10:117-25. doi: 10.1016/j.cgh.2011.08.016.
21. Kawaguchi T, Itou M, Taniguchi E, Sakata M, Abe M, Koga H et al. Serum level of free fatty acids is associated with nocturnal hypoglycemia in cirrhotic patients with HCV infection: a pilot study. Hepatogastroenterology. 2011;58: 103-8.
22. Meng QH, Hou W, Yu HW, Lu J, Li J, Wang JH et al. Resting energy expenditure and substrate metabolism in patients with acute-on-chronic hepatitis B liver failure. J Clin Gastroenterol. 2011;45:456-61. doi: 10.1097/MCG. 0b013e31820f7f02.
23. Plauth M, Cabré E, Riggio O, Assis-Camilo M, Pirlich M, Kondrup J et al. ESPEN Guidelines on Enteral Nutrition: Liver disease. Clin Nutr. 2006;25:285-94. doi: 10.1016/j. clnu.2006.01.018.
24. ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. JPEN J Parenter Enteral Nutr. 2002;17:1SA-138SA.
25. Tsien CD, McCullough AJ, Dasarathy S. Late evening snack: exploiting a period of anabolic opportunity in cirrhosis. J Gastroenterol Hepatol. 2012;27:430-41. doi: 10.1111/j. 1440-1746.2011.06951.x.
26. Okamoto M, Sakaida I, Tsuchiya M, Suzuki C, Okita K. Effect of a late evening snack on the blood glucose level and energy metabolism in patients with liver cirrhosis. Hepatol Res. 2003;27:45-50.
27. 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. doi: 10.1016/j.nut.2006. 10.008.
28. Tsuchiya M, Sakaida I, Okamoto M, Okita K. The effect of a late evening snack in patients with liver cirrhosis. Hepatol Res. 2005;31:95-103. doi: 10.1016/j.hepres.2004.11.009.
29. Yao J, Zhou X, Kong M, Li L, Hua X, Zhao Y, Yu S, Chen Y, Duan Z. Effects of eating frequency on respiratory quotient in patients with liver cirrhosis: a randomized controlled trial. Asia Pac J Clin Nutr. 2018;27:322-8. doi: 10. 6133/apjcn.062017.07.
30. Hou W, Li J, Lu J, Wang JH, Zhang FY, Yu HW et al. Effect of a carbohydrate-containing late-evening snack on energy metabolism and fasting substrate utilization in adults with acute-on-chronic liver failure due to Hepatitis B. Eur J Clin Nutr. 2013;67:1251-6. doi: 10.1038/ejcn.2013.163.
31. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Ad Hoc EWG. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22:321-36.
32. Organization Committee of 13th Asia-Pacific Congress of Clinical Microbiology and Infection. 13th Asia-Pacific Congress of Clinical Microbiology and Infection Consensus Guidelines for diagnosis and treatment of liver failure. Hepatobiliary Pancreat Dis Int. 2013;12:346-54.
33. Johnson TM, Overgard EB, Cohen AE, DiBaise JK. Nutrition assessment and management in advanced liver disease. Nutr Clin Pract. 2013;28:15-29. doi: 10.1177/ 0884533612469027.
34. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. 1981;34:2540-5. doi: 10.1093/ajcn/34.11.2540.
35. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol. 1949;109:1-9.
36. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl Acad Sci U S A. 1918;4:370-3.
37. Guangya W. China food composition tables. Beijing: Peking University Medical Press; 2009.
38. 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.
39. Yamanaka-Okumura H, Nakamura T, Takeuchi H, Miyake H, Katayama T, Arai H et al. Effect of late evening snack with rice ball on energy metabolism in liver cirrhosis. Eur J Clin Nutr. 2006;60:1067-72. doi: 10.1038/sj.ejcn.1602420.
40. Plank LD, Gane EJ, Peng S, Muthu C, Mathur S, Gillanders L, McIlroy K, Donaghy AJ, McCall JL. Nocturnal nutritional supplementation improves total body protein status of patients with liver cirrhosis: a randomized 12-month trial. Hepatology. 2008;48:557-66. doi: 10.1002/hep. 22367.
41. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. World J Gastroenterol. 2009;15:280-8.
42. Hagel S, Bruns T, Herrmann A, Stallmach A, Schmidt C. Abnormal glucose tolerance: a predictor of 30-day mortality in patients with decompensated liver cirrhosis. Z Gastroenterol. 2011;49:331-4. doi: 10.1055/s-0029-1245933.
43. Nishida T, Tsuji S, Tsujii M, Arimitsu S, Haruna Y, Imano E et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. Am J Gastroenterol. 2006;101: 70-5. doi: 10.1111/j.1572-0241.2005.00307.x.
44. Pfortmueller CA, Wiemann C, Funk GC, Leichtle AB, Fiedler GM, Exadaktylos AK, Lindner G. Hypoglycemia is associated with increased mortality in patients with acute decompensated liver cirrhosis. J Crit Care. 2014;29: 316.e7-12. doi: 10.1016/j.jcrc.2013.11.002.