Resting Energy Expenditure and Substrate Metabolism in Chinese Patients with Acute or Chronic Hepatitis B or Liver Cirrhosis

Qing-Hua Meng¹, Jin-Huan Wang¹, Hong-Wei Yu¹, Juan Li¹, Yan-Mei Feng¹, Wei Hou¹, Jian Zhang¹, Qiang Zhang¹, Xin Wang¹, Xuan Wang¹ and Ya Liu²

Abstract

Objective  Patients with liver disease usually have an imbalanced nutrient and energy metabolism that leads to malnutrition and seriously affects their prognosis. Therefore, it is of great clinical interest to understand the resting energy expenditure (REE) and oxidation rates of glucose, fat, and protein in these patients.

Methods  A total of 315 patients with liver diseases caused by hepatitis B virus were categorized into three groups: 20 acute hepatitis patients, 142 chronic hepatitis patients and 153 liver cirrhosis patients. The REE and the oxidation rates of glucose, fat and protein were assessed by indirect heat measurement. Energy intake data were also collected which were compared with the REE results.

Results  The REE per kg (REE/kg) were 27.34 ± 5.46 kJ/kg, 21.67 ± 5.01 kJ/kg and 19.07 ± 4.45 kJ/kg in acute, chronic hepatitis and liver cirrhosis patients (p=0.000), respectively. Respiratory quotient (RQ) tended to be lower in patients with chronic hepatitis and liver cirrhosis than that in acute hepatitis patients (p=0.023). Energy, protein and carbohydrate intakes were lower in liver cirrhosis patients.

Conclusion  These data demonstrated that Chinese patients with chronic hepatitis B and liver cirrhosis had lower energy expenditure and abnormal substrate metabolism. Patients with chronic hepatitis and cirrhosis had a higher protein oxidation rate and a lower carbohydrate oxidation rate compared with acute hepatitis patients.

Key words: resting energy expenditure, energy metabolism, respiratory quotient, hepatitis B, liver cirrhosis

Introduction

The liver plays a pivotal role in energy metabolism. Several studies have shown that cirrhotic patients have imbalanced nutrient and energy metabolism that lead to malnutrition and seriously affect their prognosis (1, 2). Protein-energy malnutrition is a common finding in patients with liver cirrhosis (3, 4). Muller (5) found that 18% of cirrhotic patients have energy malnutrition with losses in body cell mass and fat mass, 20% have protein malnutrition with a predominant decrease in plasma protein concentration and normal or only minor change in body composition, 25% to 35% have a mixed type, and 35% have normal nutrition states. Energy expenditure and substrate metabolism in patients with liver disease is an important element of the complex process that leads to malnutrition in these people.

Some studies have reported an increased resting metabolic rate in cirrhotic patients (6-8), while others have described a normal (9, 10) or low rate (11). In part, this variation may be the result of different methods used for measuring and calculating energy expenditure. The resting metabolic rate is not a clear-cut phenomenon in cirrhotic patients. Increased energy expenditure has been reported in 16-34% of cirrhotic patients (12) in association with body weight loss (13). As a consequence, it has been suggested that hypermetabolism is...
of pathophysiologic importance in liver disease (14). However, whether increased resting energy expenditure (REE) is a constant feature of liver cirrhosis or not remains controversial (15). Selberg et al (16) have shown that hypermetabolism may predict a poor clinical outcome in patients undergoing liver transplantation, suggesting that nutritional assessment (i.e., measurement of energy expenditure) may be of clinical value in liver disease.

The incidence of acute and chronic viral hepatitis in China is very high and viral hepatitis B contributes 80% of liver cirrhosis. However, the previously published data is generally concerned with alcoholic cirrhosis patients. There is little data on the prevalence of energy expenditure and substrate metabolism in patients with viral hepatitis and cirrhosis, especially in patients with acute or chronic viral hepatitis B. Piche et al reported that chronic hepatitis C patients have a high energy metabolism related to their viral load and their high energy metabolism is resolved with antiviral treatment (17). Therefore, it is likely that high-energy metabolism is related to the presence of viral hepatitis.

The purpose of the present study was to assess energy expenditure and substrate metabolism in a large group of acute, chronic hepatitis and liver cirrhosis patients caused by hepatitis B virus.

**Patients and Methods**

**Characteristics of patients**

This study was conducted between April 1, 2004 and April 30, 2009 in the Department of Hepatology, Capital University of Medical Science Affiliated Beijing You An Hospital, Beijing, China. Three hundred and fifteen (222 males, 93 females, with a mean age of 42.34 ± 12.76 years) consecutive hospitalized patients were enrolled in the study, including 20 patients (17 males, 3 females) with acute hepatitis, 142 patients (98 males, 44 females) with chronic hepatitis, and 153 patients (107 males, 46 females) with liver cirrhosis. All these diseases were caused by hepatitis B virus. The diagnosis of acute hepatitis generally rested upon the finding of hepatitis B surface antigen (HBsAg) in less than six months and IgM antibody to hepatitis B core antigen (anti-HBc) in the serum of a patient with clinical and biochemical evidence of acute hepatitis. Following laboratory confirmation, the acute illness stage was estimated according to jaundice or elevated serum aminotransferase levels; additionally some may have had clinical symptoms. The diagnostic criteria for chronic hepatitis included a minimum of 6 months HBsAg positivity and persistent or intermittent elevation of serum transaminase. They were admitted to our hospital because of severely elevated serum transaminase. The diagnosis of liver cirrhosis was based on clinical, laboratory, and ultrasonographic criteria and histological confirmation in 90 patients. The severity of liver cirrhosis was assessed by modified Child-Pugh criteria (18), with 46 patients were considered as Child’s grade A, 55 patients were grade B, and 52 patients were grade C at entry. None of the patients had a history of diabetes mellitus, thyroid dysfunction, or neoplasm. Also patients co-infected with human immunodeficiency virus or hepatitis C virus were excluded from the study. Informed consent was obtained from all subjects. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Human Research Committee of the Capital University of Medical Science.

**Nutritional measurements**

**Anthropometry**

Anthropometric evaluation included measurement of body weight, height, triceps skinfold thickness (TSF), midarm circumference (MAC), and midarm muscle circumference (MAMC). Body weight and height were measured by a height/weight scale (RGZ120, Wuxi Weigher Factory, Wuxi, Jiangsu, China) with a precision of 0.2 kg and 0.2 cm, respectively. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

TSF was measured to the nearest millimeter by an experienced observer with a skinfold caliper (Changshu Instrument Co. Ltd, Changshu, China) at the middle point between the acromion and the olecranon of the non-dominant arm. MAC (cm) was measured with a tape at the same site as TSF (19). To minimize practical variability, the average of three consecutive measurements was recorded. The MAMC was calculated by the following formula: MAMC (cm)=MAC-(π×TSF [cm]). Based on the Chinese Working Group for Obesity (20), Triceps skinfold thickness of 8.3 mm in males and 15.3 mm in females was considered as standard fat stores, while the standard values for MAMC was 24.8 cm in males and 21.0 cm in females. Observed values of TSF and MAMC were calculated as a percentage of the standard and less than 90% was considered as malnourished.

**Blood samples**

A fasting blood sample was obtained to measure albumin (ALB), prealbumin (PA), acetylcholine esterase (CHE) by a full automatic biochemical analyzer (OLYMPUS 5421, Olympus, Japan) at the hospital laboratory of the Beijing You An Hospital.

**REE and glucose, protein and fat oxidation rates**

The subjects were required to fast for at least 8 h prior to test. The REE and the carbohydrate, protein and fat oxidation rates were determined by indirect heat measurement. The REE was determined using the CCM-D nutrition metabolism investigation system (Medical Graphics Corporation, St. Paul, MN). The average O2 amount consumed and the CO2 amount produced per minute by the subjects were used to calculate the actual REE using the Weir formula REE (kcal) = 5.50VO2 + 1.76VCO2- 1.99TUN (21); subsequently, the respiratory quotient (RQ), the ratio of the average O2 amount consumed to the CO2 amount produced per
Table 1. Nutrition Status of Patients according to Disease

<table>
<thead>
<tr>
<th></th>
<th>Normal value</th>
<th>Acute hepatitis (n=20)</th>
<th>Chronic hepatitis (n=142)</th>
<th>Liver cirrhosis (n=153)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex(Male/Female)</td>
<td>17/3</td>
<td>98/44</td>
<td>107/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>34.45±6.67</td>
<td>37.44±11.57</td>
<td>50.58±10.80***</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Height(cm)</td>
<td>171.95±5.49</td>
<td>168.06±9.22</td>
<td>167.27±6.67</td>
<td>0.754</td>
<td></td>
</tr>
<tr>
<td>Body weight(kg)</td>
<td>69.50±10.51</td>
<td>67.50±11.70</td>
<td>65.86±10.79</td>
<td>0.194</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>18.5-23.9</td>
<td>23.47±3.07</td>
<td>23.88±3.43</td>
<td>23.48±3.23</td>
<td>0.594</td>
</tr>
<tr>
<td>TSF(mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8.3</td>
<td>15.90±4.09</td>
<td>15.98±3.57</td>
<td>14.80±3.28*</td>
<td>0.048</td>
</tr>
<tr>
<td>Female</td>
<td>15.3</td>
<td>17.63±5.13</td>
<td>15.50±3.35</td>
<td>14.33±3.55</td>
<td>0.098</td>
</tr>
<tr>
<td>MAMC(cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24.8</td>
<td>21.64±2.80</td>
<td>21.20±3.05</td>
<td>16.74±4.95***</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>21.0</td>
<td>19.14±3.15</td>
<td>20.70±2.70</td>
<td>18.43±4.83**</td>
<td>0.027</td>
</tr>
<tr>
<td>ALB(g/L)</td>
<td>36-55</td>
<td>37.78±4.62</td>
<td>39.46±4.37</td>
<td>30.21±5.46***</td>
<td>0.000</td>
</tr>
<tr>
<td>PA(mg/L)</td>
<td>200-400</td>
<td>89.88±37.16**</td>
<td>155.61±67.60</td>
<td>91.05±57.32**</td>
<td>0.000</td>
</tr>
<tr>
<td>CHE(U/L)</td>
<td>4000-10000</td>
<td>4915.00±1423.17**</td>
<td>6371.59±1816.73</td>
<td>33765.71±1897.89***</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* p<0.05 compared with chronic hepatitis group; # p<0.05 compared with acute hepatitis group; ** p<0.01 compared with chronic hepatitis group; ## p<0.01 compared with acute hepatitis group.

Results

Dietary intake

Food intake was recorded by a dietitian immediately after each meal by inspecting food served and the amount left over for 5 days after admission. Intakes of energy and nutrients were calculated by means of nutritional analysis software devised by the General Hospital of the People’s Liberation Army.

Statistical analysis

The data was presented as mean ± SD. Means were compared by using one-way analysis of variance (ANOVA). SPSS 11.5 statistical software was used for all analysis. p<0.05 was considered statistically significant.

Anthropometric and laboratory data

The anthropometric characteristics and laboratory data of the three groups are shown in Table 1. The mean age of patients with acute and chronic hepatitis was significantly lower than the mean age of patients with liver cirrhosis (p<0.05, respectively). However, there was no significant difference among the three groups in height or body weight. Fat mass (mean triceps skinfold thickness) in the male cirrhotic group was significantly lower than in the male chronic hepatitis group (p<0.05). Muscle depletion (midarm muscle circumference) could also be seen in the cirrhotic group when compared with the acute or chronic hepatitis group (p<0.05, respectively). However, there was no significant difference between the acute hepatitis group and the chronic hepatitis group in TSF and MAMC. The albumin, proalbumin concentrations and cholinesterase activity were lower in the liver cirrhotic group than in the chronic hepatitis group (p=0.000). Proalbumin concentrations and cholinesterase activity were lower in the acute hepatitis patients than in the chronic hepatitis patients.
Table 2. Resting Energy Expenditure of Patients according to Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Acute hepatitis</th>
<th>Chronic hepatitis</th>
<th>Liver cirrhosis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>%REE(kcal/kg.d)</td>
<td>27.34±5.46</td>
<td>21.67±5.01</td>
<td>19.07±4.45</td>
<td>0.000</td>
</tr>
<tr>
<td>%pred(REE/kg.d)</td>
<td>23.18±3.79</td>
<td>23.51±2.52</td>
<td>21.91±1.97</td>
<td>0.000</td>
</tr>
<tr>
<td>%predREE</td>
<td>117.80±12.99</td>
<td>92.59±20.58</td>
<td>87.06±18.84</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypermetabolic</td>
<td>17/20(85%)</td>
<td>22/142(15.49%)</td>
<td>21/153(13.73%)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>3/20(15%)</td>
<td>67/142(47.18%)</td>
<td>52/153(33.99%)</td>
<td></td>
</tr>
<tr>
<td>Hypometabolic</td>
<td>0</td>
<td>53/142(37.12%)</td>
<td>80/153(52.29%)</td>
<td></td>
</tr>
<tr>
<td>RQ</td>
<td>0.88±0.07</td>
<td>0.84±0.06</td>
<td>0.83±0.06</td>
<td>0.023</td>
</tr>
</tbody>
</table>

%REE, resting energy expenditure; %pred, predicted REE. %predREE, REE as a percentage of predicted REE. %predREE >110%. Normal, %predREE between 90%-110%. Hypometabolic, %predREE <90%. RQ, respiratory quotient.

* p<0.05 compared with chronic hepatitis group; # p<0.05 compared with acute hepatitis group; ** p<0.01 compared with chronic hepatitis group; ## p<0.01 compared with acute hepatitis group.

Figure 1. The proportion of energy supplied by the three major substrates among the three groups. * p<0.05 compared with acute hepatitis group; ** p<0.01 compared with acute hepatitis group.

Resting energy expenditure and substrate metabolism

The energy profile for the three groups is summarized in Table 2. The REE per kg (REE/kg) was 27.34±5.46 kcal/kg in acute hepatitis patients, 21.67±5.01 kcal/kg in chronic hepatitis patients, and 19.07±4.45 kcal/kg in cirrhotic patients (p=0.000), respectively. %predREE refers to REE as a percentage of predicted REE. %predREE of more than 110% was considered as hypermetabolic, less than 90% was hypometabolic, while 90% to 110% was normal. The mean value of %predREE was 117.80±12.99% in acute hepatitis patients (85% hypermetabolic and 15% normal metabolic), 92.59±20.58% in chronic hepatitis patients (15.49% hypermetabolic, 47.18% normal metabolic, and 37.12% hypometabolic), and 87.06±18.84% in cirrhotic patients (13.73% hypermetabolic, 33.99% normal metabolic, and 53.29% hypometabolic) (p=0.000). RQ tended to be lower in chronic hepatitis and liver cirrhosis patients than in those with acute hepatitis (p=0.023). The proportion of energy supplied by the three major substrates (carbohydrate, fat, and protein) differed among the three groups (Fig. 1). Chronic hepatitis and liver cirrhosis groups had significantly higher protein oxidation rates and lower carbohydrate oxidation rates than those of acute hepatitis group (p<0.05, respectively), while no significantly difference was observed in fat oxidation rate among the three groups, which ranged from 24.01% to 28.73% (p=0.147).

Energy and the three major substrates intake and consumption

Table 3 shows the energy and three major substrates intake and consumption in the three groups. Patients with liver cirrhosis had the lowest energy intake and REE (p<0.01, respectively). Statistical analysis also showed that there was a positive correlation between the energy intake and the % pred REE in cirrhotic group (r=0.389, p<0.05). In patients with acute and chronic hepatitis, no significant difference was found in energy intake, but REE of chronic hepatitis patients was significantly lower than that of acute hepatitis patients (p<0.01). Patients with liver cirrhosis had a significantly lower protein intake and higher protein consumption than chronic hepatitis patients, with a significantly lower carbohydrate intake and lower carbohydrate consumption (p<0.05, respectively). There was no significant difference in the three major substrates (carbohydrate, fat, and protein) intake and consumption between acute and chronic hepatitis patients.

Resting energy expenditure and substrate metabolism in cirrhosis patients

From Child-Pugh group A to Child-Pugh group C, the REE tended to be lower, although there was no significant difference observed among the three groups. A comparison of energy metabolism between REE and predicted REE showed that REE was significantly lower than predicted REE in all three groups (p<0.01). There was no significant difference in RQ among three groups. Resting energy expenditure and RQ according to the progressive stages of cirrhosis are summarized in Table 4.

The proportion of energy supplied by the three major substrates (carbohydrate, fat, and protein) differed among the three groups according to the progressive stages of cirrhosis (Fig. 2). Protein oxidation rate of Child-Pugh group A was the lowest, while that of Child-Pugh group C was the highest. The carbohydrate oxidation rate of Child-Pugh group C tended to be lower than that of Child-Pugh group A and B but there was no significant difference. No significant difference in the fat oxidation rate was found among the three groups.
The proportion of energy supplied by the three major substrates among the three groups of cirrhotic patients.

Table 3. Energy and the Three Major Substrates Intake and Consumption according to Disease

<table>
<thead>
<tr>
<th></th>
<th>Acute hepatitis</th>
<th>Chronic hepatitis</th>
<th>Liver cirrhosis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IE (kcal/kg.d)</td>
<td>26.18±9.72</td>
<td>27.94±9.64</td>
<td>23.12±7.13</td>
<td>0.001</td>
</tr>
<tr>
<td>REE (kcal/kg.d)</td>
<td>27.34±5.46</td>
<td>21.67±5.01**</td>
<td>19.07±4.45**</td>
<td>0.000</td>
</tr>
<tr>
<td>EI/REE</td>
<td>0.91±0.39</td>
<td>1.36±0.62**</td>
<td>1.30±0.58</td>
<td>0.076</td>
</tr>
<tr>
<td>PROI/g(kg.d)</td>
<td>0.82±0.22</td>
<td>0.96±0.39</td>
<td>0.84±0.33*</td>
<td>0.045</td>
</tr>
<tr>
<td>PROE/g(kg.d)</td>
<td>1.16±0.47</td>
<td>1.16±0.51</td>
<td>1.61±1.08**</td>
<td>0.001</td>
</tr>
<tr>
<td>PROI/PROE</td>
<td>0.83±0.38</td>
<td>0.94±0.47</td>
<td>0.85±1.19</td>
<td>0.797</td>
</tr>
<tr>
<td>FATI/g(kg.d)</td>
<td>1.07±0.28</td>
<td>0.76±0.33</td>
<td>0.73±0.70</td>
<td>0.783</td>
</tr>
<tr>
<td>FATE/g(kg.d)</td>
<td>1.26±3.46</td>
<td>0.62±2.04</td>
<td>0.56±1.92</td>
<td>0.484</td>
</tr>
<tr>
<td>FATI/FATE</td>
<td>1.13±4.68</td>
<td>1.47±0.82</td>
<td>1.86±1.52</td>
<td>0.207</td>
</tr>
<tr>
<td>CHOI/g(kg.d)</td>
<td>4.03±1.69</td>
<td>4.27±1.69</td>
<td>3.70±1.30**</td>
<td>0.032</td>
</tr>
<tr>
<td>CHOE(g/kg.d)</td>
<td>3.69±3.54</td>
<td>3.31±2.20</td>
<td>2.38±1.62**</td>
<td>0.003</td>
</tr>
<tr>
<td>CHOI/CHOE</td>
<td>1.09±2.90</td>
<td>1.76±2.71</td>
<td>1.92±2.76</td>
<td>0.244</td>
</tr>
</tbody>
</table>

*EI, energy intake. **REE, resting energy expenditure. PROI, protein intake. PROE, protein expenditure. FATI, fat intake. FATE, fat expenditure. CHOI, carbohydrate intake. CHOE, carbohydrate expenditure.

The present study showed that 53.29% patients with liver cirrhosis had reduced resting energy expenditure compared with the predicted REE according to the Harris-Benedict formula. This is different from the high-energy metabolism condition found in cirrhosis patients, which is widely acknowledged. In addition, our results also suggested that there was a positive correlation between energy intake and % predREE in patients with liver cirrhosis, which was proven by the fact that the lower energy intake and lower resting energy expenditure was found in liver cirrhosis patients. Therefore, we believe that the formation of low-energy metabolism in patients with liver cirrhosis is caused by the long-term deficiency of nutritional intake - semistarvation status. Yamanaka et al (26) concluded that because of the lack of glycogen reserves in liver cirrhosis patients, the metabolic state in the early morning is similar to the starvation status. Therefore, increasing the energy supplies at night may be able to correct metabolic abnormalities in patients with liver cirrhosis and prevent the development of malnutrition.

In this study, we found that chronic hepatitis and liver cirrhosis patients had significantly higher protein oxidation rates and lower carbohydrate oxidation rates than those of acute hepatitis group. Similar findings have also been reported by other studies. Miwa et al (27) indicated that the respiratory quotient in patients with liver cirrhosis was significantly lower than that of healthy controls, with a marked increase in fat oxidation rate and lower carbohydrate oxidation rate. The energy metabolism of these changes is similar to the starvation status, which may lead to malnutrition.

Our study also showed that from acute hepatitis, chronic hepatitis to liver cirrhosis patients, protein and fat oxidation rates gradually increase, with carbohydrate oxidation rate gradually reduce, which indicated that the more serious liver disease is, the more protein and fat be used. The mechanism needs further examination.

The problem of oral intake is frequently found in acute and chronic liver disease patients. In acute hepatitis and liver cirrhosis patients, the problem of oral intake is more...
serious than that in chronic hepatitis patients. The energy, protein and carbohydrate intakes in liver cirrhosis group were significantly lower than those in chronic hepatitis group. It may be stemming from multiple factors. First, loss of appetite and anorexia are the most common reasons. Second, the dietary restrictions that are commonly recommended for cirrhotic patients (such as restriction of sodium, protein, and fluids) can discount adequate oral intake. Third, weakness, fatigue, and low-grade encephalopathy can contribute to decreased oral intake (28). Some studies have shown that the problem of energy-protein malnutrition in patients with cirrhosis is an independent factor affecting the prognosis (23).

Our results also suggested that the carbohydrate intake in patients with chronic hepatitis and liver cirrhosis was higher than its consumption, which may indicate that patients with chronic liver disease cannot utilize carbohydrate well, with a notable decreasing glucose oxidation rate. The inability to use glucose may be due to insulin resistance in chronic liver disease patients (29). An increase in the RQ value can be used as a marker of recovery in these patients. Long-term oral supplementation with a BCAA mixture is better than ordinary food taken as a late evening snack for improving the serum albumin level and the energy metabolism of cirrhosis patients (30).

In conclusion, we demonstrated that patients with chronic hepatitis and liver cirrhosis had a lower resting energy metabolism per kg weight than patients with acute hepatitis, and liver cirrhosis patients had the lowest resting energy metabolism per kg weight. A higher protein oxidation rate and lower carbohydrate oxidation rate could be found in chronic hepatitis and cirrhosis patients, compared with acute hepatitis patients. Long-term poor intake may be one of the causes of this abnormal metabolism status. Therefore, physicians should pay more attention to early prevention and to the timely design and prescription of personalized nutritional strategies for the treatment of the patients’ malnutrition and abnormal metabolism status, thus improving their morbidity and mortality rates.

Conflict of interest
The authors have no conflict of interest.

Acknowledgement
This work was supported by grants from the Foundation of Capital Science Committee (H2020920020880) and the Development Foundation of Capital Medical Science (2005-2035). All authors had specific contributions to the work: Qing-Hua Meng conceived of the study, and participated in its design and coordination and helped to draft the manuscript. Hong-Wei Yu, Jin-Huan Wang, Juan Li, Jian Zhang and Qiang Zhang carried out the practical performance and collection of data. Yan-Mei Feng, Wei Hou, Xin Wang and Xuan Wang carried out data analyses and drafted the manuscript. Professor Ya Liu provided significant advice and consultation.

References

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