Effect of levocarnitine administration in patients with chronic liver disease

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Received March 5, 2020; Accepted July 28, 2020

Abstract. L-carnitine administration was reported to improve sarcopenia in patients with cirrhosis. However, the amount of evidence from previous studies is not sufficient. The present study aimed to clarify the effect of levocarnitine (L-carnitine) administration on body composition in patients with chronic liver disease (CLD). In the present study, 85 patients with L-carnitine administration and 87 control patients were enrolled and divided them into two groups, the L-carnitine administration group (LAG, n=44) and the without L-carnitine administration (controls, n=44) group, by using propensity score matching for age, sex, body mass index (BMI) and serum albumin. Δ skeletal muscle mass index (SMI)/year, Δ intramuscular adipose tissue content (IMAC)/year and Δ bone mineral density (BMD)/year were examined during L-carnitine administration. Each parameter was measured by computed tomography (CT) or dual-energy X-ray absorptiometry. The median age overall was 69 years (IQR, 64.0, 75.0); 36 were men and 52 were women. The median SMI was 37.4 cm²/m² (IQR, 34.01, 44.34). The initial CT scans showed similar median values of SMI for the two groups [37.74 (34.17, 43.58) and 37.16 (33.83, 44.34), P=0.67]. However, the median ΔSMI/year for the LAG and controls were 0.95% (-3.07, 6.10) and -2.34% (-5.34, 0.53), respectively (P=0.003). The median Δ whole body BMD/year for the LAG and controls were -0.24% (-1.20, 0.91) and -1.04% (-2.16, 0.47), respectively (P=0.038). The median ΔIMAC/year and Δ lumbar spine BMD were not significantly different between the LAG and controls. L-carnitine administration may prevent the loss of skeletal muscle mass and BMD; therefore, it may be used as a new treatment option for osteoporosis and sarcopenia in patients with CLD.

Introduction

Sarcopenia is defined as a decrease in muscle strength and physical function and skeletal muscle mass depletion (1,2). Primary sarcopenia is caused by aging; secondary sarcopenia is caused by malnutrition, sedentary behavior, and various clinical conditions, such as inflammatory disease, endocrine disease, and liver disease (3,4). The prevalence of sarcopenia in patients with chronic liver disease (CLD) is ranged from 10 to 70% in Japan (4,5). Recent studies have revealed that sarcopenia exacerbates survival, quality of life, and outcome after liver transplant in patients with liver cirrhosis (LC) (6-12). Since hepatocytes perform the function of glucose, lipid, and protein metabolism, liver dysfunction causes a glycogen storage dysfunction in the liver that facilitates the utilization of glycogen and branched amino acid from skeletal muscle, resulting in the progression of proteolysis (13,14). Therefore, preventative treatment is needed to reduce the onset and progression of sarcopenia due to skeletal muscle depletion in patients with CLD.

Levocarnitine (L-carnitine) is an essential nutrient that plays a pivotal role in fatty acid metabolism (15). L-carnitine is involved in β-oxidation of fatty acids. It is a conditionally synthesized nutrient from amino acids methionine and lysine in the brain, liver, and kidney. Carnitine is obtained mainly from food; however, one-fourth of carnitine is synthesized in the kidney and liver (14,16). In other words, L-carnitine deficiency occurs more frequently in patients with LC or CLD. Several reports about L-carnitine administration in patients with LC revealed that it improved muscle cramps, suppressed hepatic...
encephalopathy, and improved hyperammonemia (17,18). Furthermore, L-carnitine administration may improve sarcopenia in patients with LC (14,19). However, enough evidence has not been obtained in previous studies. Thus, this study aimed to clarify the effect of L-carnitine administration on body composition [skeletal muscle mass and bone mineral density (BMD)] in patients with CLD.

Materials and methods

Study design and patients. In this retrospective study, we reviewed 592 patients with CLD between 2015 and 2018 at Saiseikai Niigata Hospital. Of those patients, 85 were treated with L-carnitine (Otsuka Pharmaceutical, Tokyo, Japan) and underwent computed tomography (CT) twice during L-carnitine administration. The interval of CT scans was within 6-18 months. These 85 patients met the following inclusion criteria: i) Subsequent CT scans were conducted within 6-18 months that enabled evaluation of the change in skeletal muscle mass and clinical parameters and BMD by dual energy X-ray; and ii) they continued L-carnitine administration during the observational period. Patients with hepatocellular carcinoma (HCC) were excluded (Fig. 1). In this study, the L-carnitine dose ranged from 1,500 to 3,000 mg/day, and the dose was selected by the attending physician. The reasons for L-carnitine administration were hepatic encephalopathy, muscle cramps, hyperammonemia, hypoalbuminemia, or combination of these conditions. We evaluated the effects of L-carnitine on body composition in patients with CLD. Moreover, 87 patients with CLD who did not receive L-carnitine and underwent paired CT scans to screen for HCC within 6-18 months were enrolled as controls. Cases (patients who received L-carnitine) and controls were matched for age, sex, and underwent scanning of the subcutaneous fat (21). To evaluate the yearly change in SMI, ΔSMI/year (%) was calculated as follows:

$$\Delta \text{SMI/year} = \left( \frac{\text{SMI on the second CT} - \text{SMI on the initial CT}}{\text{SMI on the initial CT}} \times 100 \right) \times \frac{365}{\text{interval between CT (day)}}$$

Evaluation of BMD. All patients underwent scanning of the total lumbar spine (L2-L4) BMD (LSBMD), and whole body BMD (WBBD) by dual energy X-ray absorptiometry (DEXA) at each CT. To evaluate the yearly change in both BMD, ΔBMD/year (%) was calculated as follows:

$$\Delta \text{BMD/year} = \left( \frac{\text{BMD on the second DEXA-BMD on the initial DEXA}}{\text{BMD on the initial DEXA}} \times 100 \right) \times \frac{365}{\text{interval between DEXA (day)}}$$

Clinical and laboratory assessment. Patients underwent blood tests and CT on the same day. Clinical data were collected for the etiology of liver disease, BMI, and blood test results (white blood cells, platelet counts (Plt), serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), cholinesterase, and hemoglobin A1c). The albumin-bilirubin (ALBI) score in each participant was calculated by the following formula as reported previously: ALBI score = [log10 total bilirubin (µmol/l) x 0.66] + [serum albumin (g/l) x -0.085], while ALBI grade was classified into the following: ALBI score ≥-2.60, grade 1; -2.60 <ALBI score ≤ -1.39, grade 2; and ALBI score >-1.39, grade 3 (22,23). The fibrosis-4 index (FIB-4) in each participant was calculated by the following formula as reported previously: FIB-4 = age (years) x AST (IU/l) + [platelets (109) x ALT (IU/l)] (24-26).

Statistical analysis. Continuous variables are presented as median and interquartile range (IQR) and analyzed using the Mann-Whitney U test. Categorical variables and nominal variables are presented as frequency (percentage) and analyzed using Fisher's exact test. We applied 1:1 propensity score matching to balance the assignment of patients with L-carnitine administration. The variables were age, sex, BMI, and serum albumin. Variables that affect sarcopenia were selected. Clinical features of CLD patients with sarcopenia were elderly, low BMI, and low albumin, and SMI depended on sex (27). Values of P<0.05 were considered statistically significant. All statistical analyses were performed using EZR ver. 1.37 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (28).

Results

Patient characteristics and body composition at baseline and endpoint. We enrolled 85 patients with L-carnitine administration and 87 control patients in this study and divided these patients into two groups, namely, patients with L-carnitine administration (LAG, n=44) and patients without L-carnitine administration (controls, n=44), by using propensity score matching to balance the assignment of patients with L-carnitine administration. The variables were age, sex, BMI, and serum albumin. Variables that affect sarcopenia were selected. Clinical features of CLD patients with sarcopenia were elderly, low BMI, and low albumin, and SMI depended on sex (27). The median age was 69 years (IQR, 64.0, 75.0). The median SMI was 37.4 cm²/m² (IQR, 34.01, 44.34). The etiology of CLD was hepatitis B virus infection (n=10), hepatitis C virus infection (n=35), alcoholism (n=8), nonalcoholic steatohepatitis and nonalcoholic fatty liver disease (n=23), primary biliary cholangitis (n=5), autoimmune hepatitis (n=5), and others (n=2). No significant difference in variables were found between the LAG and controls at baseline as well as at the endpoint (Table I).

Evaluation of SMI. The SMI was calculated as follows: IMAC/year = [IMAC on the second CT-IMAC on the initial CT]/[interval between CT (day)/365].
Comparison of change in SMI and body composition between the LAG and controls. The initial CT showed similar median values of SMI for the two groups (37.74 (34.17, 43.58) and 37.16 (33.83, 44.34), P=0.67). However, the median ΔSMI/year for the LAG and controls were 0.95% (-3.07, 6.10) and -2.34% (-5.34, 0.53), respectively (P<0.01) (Fig. 2A). The median ΔIMAC/year for the LAG and controls were -0.00 (-0.03, 0.03) and 0.01 (-0.02, 0.04), respectively (P=0.46) (Fig. 2B). The median ΔWBBMD/year for the LAG and controls were -0.24% (-1.20, 0.91) and -1.04% (-2.16, 0.47), respectively (P=0.04) (Fig. 2C). The median ΔLSBMD/year for the LAG and controls were -0.67% (-2.87, 1.80) and -0.18% (-1.99, 2.99), respectively (P=0.18) (Fig. 2D).

Discussion

Our results revealed that L-carnitine administration prevents skeletal muscle mass loss and osteoporosis. To our knowledge, this study is the first to report that L-carnitine may improve both sarcopenia and osteoporosis. Thus, the results of this study are of clinical significance for patients with CLD who have sarcopenia and osteoporosis.

The median ΔSMI/year in our results was 0.69% for all patients, 0.95% for the LAG and -2.34% for the controls. Especially, the median ΔSMI/year of the LAG was significantly better than that of the controls. According to previous studies, ΔSMI/year or Δ skeletal muscle area/year of patients with LC ranged from -2.2 to -0.22% (19,29). Our results show that skeletal muscle loss is suppressed compared with the results of these reports. In Japan, L-carnitine has been administered as a treatment for hepatic encephalopathy, hypoalbuminemia, and muscle cramps in patients with LC (17,18). Our study includes patients with CLD who take L-carnitine for various purposes. However, the skeletal muscle mass of the LAG was significantly increased, suggesting that L-carnitine may prevent skeletal muscle mass loss.

There are multiple hypotheses that carnitine administration suppresses skeletal muscle loss in patients with LC. Carnitine plays a central role in transporting long-chain fatty acids from the cytosol to the mitochondrial matrix. Carnitine binds to the long-chain acyl coenzyme A and is converted to acylcarnitine. Acylcarnitine is transported to the mitochondria and degraded by β-oxidation (14,30). Thus, carnitine administration improves energy metabolism disorders in the mitochondria in the liver (31). Improvement of these energy metabolism disorders is considered to suppress hyperammonemia in patients with LC (32). This is because the urea cycle, particularly localized in the liver, is a metabolic system that requires a lot of energy. Hyperammonemia activates myostatin and decreases muscle protein synthesis (33). Therefore, preventing hyperammonemia prevents skeletal muscle loss. Hiramatsu et al (19) reported that L-carnitine administration may suppress the progression of sarcopenia in conjunction with the improvement of hyperammonemia. The required dose of carnitine expected to inhibit...
the progression of sarcopenia is ≥1,274 mg/day (19), and the carnitine dose administered in this study (1,500-3,000 mg/day) exceeded that. However, since this is a retrospective study, serum ammonia was not measured in many cases. Prospective studies are needed to clarify the relationship between formed ammonia levels and skeletal muscle mass.

To date, carnitine administration has been suggested to increase lipid utilization in the skeletal muscle during low exercise and improve exercise performance (34). We considered that carnitine not only increased skeletal muscle mass but also improved the quality and examined changes in IMAC, the quality indicator of skeletal muscle (21), but did not yield significant results in our study. Studies reported that fatty infiltration of the muscle (myosisteatosis) exacerbates hepatic encephalopathy in LC (35) and is a prognostic factor for liver transplant patients (21,36). Therefore, there is a need for treatments that improve not only skeletal muscle mass but also muscle quality. However, since the exercise and activity levels are not managed in this study, the effect of carnitine administration group; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; FIB-4, fibrosis-4; IQR, interquartile range; γ-GTP, glutamyl transpeptidase; ALBI, ALBI, albumin-bilirubin.

### Table I. Comparison of clinical and biochemical characteristics between the LAG and controls at baseline.

| Factor                              | All patients (IQR) | LAG (IQR) | Controls (IQR) | P-value |
|-------------------------------------|--------------------|-----------|----------------|---------|
| Number of patients                  | 88                 | 44        | 44             | 0.523   |
| Age (years)                         | 69.00 (54.00, 75.00)| 70.50 (65.00, 75.25)| 68.00 (54.00, 75.00) | 0.523   |
| Sex                                 |                    |           |                | 0.829   |
| Male                                | 36                 | 19        | 17             |         |
| Female                              | 52                 | 25        | 27             |         |
| Body mass index (kg/m²)             | 23.12 (20.71, 25.14)| 23.39 (19.96, 25.99)| 22.48 (21.43, 24.98) | 0.507   |
| Skeletal muscle mass index (cm²/m²) | 37.40 (34.01, 44.34)| 37.74 (34.17, 43.58)| 37.16 (33.83, 44.34) | 0.67    |
| Intramuscular adipose tissue content| -0.20 (-0.30,-0.08) | -0.22 (-0.32,-0.10) | -0.19 (-0.27,-0.07) | 0.309   |
| Visceral fat area (cm²)             | 99.00 (61.79, 137.82)| 90.47 (53.98, 125.77)| 109.06 (77.08, 137.82) | 0.313   |
| Whole body bone mineral density (g/cm²) | 0.94 (0.86, 1.04) | 0.94 (0.86, 1.04) | 0.95 (0.87, 1.02) | 0.914   |
| Lumber spine bone mineral density (g/cm²) | 0.87 (0.75, 1.07) | 0.87 (0.74, 1.15) | 0.87 (0.78, 1.09) | 0.599   |
| Etiology                            |                    |           |                | 0.906   |
| HBV                                 | 10                 | 4         | 6              |         |
| HCV                                 | 35                 | 17        | 18             |         |
| Alcohol                             | 8                  | 4         | 4              |         |
| NASH and NAFLD                      | 23                 | 12        | 11             |         |
| PBC                                 | 5                  | 4         | 1              |         |
| AIH                                 | 5                  | 2         | 3              |         |
| Other                               | 2                  | 1         | 1              |         |
| ALBI score                          | -2.89 (-3.05,-2.70)| -2.88 (-3.05,-2.73)| -2.90 (-3.03,-2.68) | 0.877   |
| ALBI grade (1/2/3)                  | 0.757              | 76        | 37             | 39      |
| 1                                   |                    | 12        | 7              | 5       |
| 2                                   |                    | 0         | 0              | 0       |
| FIB-4 index                         | 2.30 (1.66, 3.14)  | 2.62 (1.82, 3.51) | 2.23 (1.58, 2.74) | 0.123   |
| White blood cells (x10⁵/µl)         | 55.00 (46.00, 62.25)| 55.50 (49.75, 63.50)| 53.50 (44.75, 61.00) | 0.251   |
| Platelet counts (x10⁴)              | 18.65 (7.10, 43.40) | 17.95 (15.28, 21.38)| 20.00 (15.00, 23.38) | 0.307   |
| Albumin (g/dl)                      | 4.10 (3.98, 4.32)  | 4.15 (4.00, 4.30) | 4.10 (3.90, 4.40) | 0.943   |
| Aspartate aminotransferase (U/l)    | 25.00 (21.00, 30.00)| 25.00 (21.00, 31.50)| 24.50 (19.00, 30.00) | 0.435   |
| Alanine aminotransferase (U/l)      | 17.00 (12.00, 25.00)| 17.00 (12.00, 23.50)| 17.00 (11.00, 25.00) | 0.947   |
| Cholinesterase (U/l)                | 297.00 (247.75, 340.00)| 282.00 (237.75, 332.25)| 297.50 (266.50, 353.25) | 0.346   |
| Triglyceride (mg/dl)                | 101.00 (73.00, 124.75)| 107.50 (71.75, 143.75)| 93.00 (73.25, 113.00) | 0.335   |
| γ-GTP (IU/l)                        | 17.50 (13.00, 32.75)| 18.00 (13.00, 35.50)| 17.00 (13.00, 30.50) | 0.904   |
| Total cholesterol (mg/dl)           | 186.00 (161.25, 212.00)| 184.00 (161.75, 212.25)| 186.50 (161.00, 210.00) | 0.893   |
| Hemoglobin A1c (%)                  | 5.80 (5.50, 6.20)  | 5.80 (5.45, 6.20) | 5.80 (5.53, 6.10) | 0.711   |
| Observational period (year)         | 0.98 (0.85, 1.10)  | 0.92 (0.74, 1.02) | 0.99 (0.90, 1.23) | 0.007   |

Data were presented as number of patients or median (interquartile range). LAG, Levocarnitine administration group; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; AIH, autoimmune hepatitis; FIB-4, fibrosis-4; IQR, interquartile range; γ-GTP, glutamyl transpeptidase; ALBI, ALBI, albumin-bilirubin.
### Table II. Comparison of clinical and biochemical characteristics between the LAG and controls at endpoint.

| Factor                        | All patients (IQR) | LAG (IQR) | Controls (IQR) | P-value  |
|-------------------------------|--------------------|-----------|----------------|----------|
| Number of patients            | 88                 | 44        | 44             | 0.166    |
| Skeletal muscle mass index (cm²/m²) | 37.99 (32.98, 44.08) | 39.58 (34.63, 44.46) | 36.15 (32.43, 43.49) | 0.166    |
| Intramuscular adipose tissue content | -0.20 (-0.30, -0.07)  | -0.22 (-0.33, -0.08)  | -0.19 (-0.26, -0.08)  | 0.367    |
| Visceral fat area (cm²)       | 102.48 (62.22, 137.26) | 92.38 (58.48, 147.07) | 114.33 (66.44, 135.65) | 0.404    |
| All bone mineral density (g/cm²) | 0.93 (0.85, 1.03)  | 0.93 (0.86, 1.04)  | 0.93 (0.85, 1.02)  | 0.764    |
| LS bone mineral density (g/cm²) | 0.87 (0.76, 1.08)  | 0.86 (0.74, 1.05)  | 0.87 (0.78, 1.09)  | 0.384    |
| ALBI score                    | -2.89 (-3.07, -2.73) | -2.83 (-3.05, -2.69) | -2.94 (-3.09, -2.77) | 0.206    |
| ALBI grade                    |                     | 176        | 36             | 40       |
|                               | 2                   | 12         | 8              | 4        |
|                               | 3                   | 0          | 0              | 0        |
| FIB-4 index                   | 2.20 (1.66, 2.88)   | 2.50 (1.88, 2.95) | 2.12 (1.45, 2.73) | 0.115    |
| White blood cells (x10⁴/µl)   | 58.00 (44.00, 70.25) | 57.00 (42.75, 68.00) | 59.00 (44.75, 70.50) | 0.907    |
| Platelet counts (x10⁴)        | 19.65 (16.17, 23.30) | 19.10 (15.35, 21.77) | 20.20 (17.38, 25.72) | 0.139    |
| Albumin (g/dl)                | 4.20 (4.00, 4.40)   | 4.10 (3.90, 4.32)  | 4.25 (4.00, 4.40)  | 0.242    |
| Aspartate aminotransferase (U/l) | 24.00 (20.75, 29.25) | 24.50 (21.00, 29.25) | 23.50 (19.75, 28.00) | 0.256    |
| Alanine aminotransferase (U/l) | 16.00 (12.00, 22.25) | 17.00 (13.00, 23.25) | 15.00 (10.75, 21.25) | 0.171    |
| Cholinesterase (U/l)          | 288.50 (250.50, 350.25) | 282.00 (221.75, 332.50) | 293.00 (254.75, 351.25) | 0.138    |
| Triglyceride (mg/dl)          | 94.00 (72.00, 123.75) | 106.00 (72.00, 126.00) | 92.00 (71.75, 121.75) | 0.349    |
| γ-GTP (IU/l)                  | 16.00 (12.00, 32.00) | 16.50 (12.75, 29.00) | 16.00 (12.00, 32.25) | 0.691    |
| Total cholesterol (mg/dl)     | 180.00 (161.25, 206.75) | 179.00 (162.75, 203.25) | 181.00 (160.25, 212.00) | 0.99     |
| Hemoglobin A1c (%)            | 5.80 (5.50, 6.25)   | 5.80 (5.50, 6.30)  | 5.80 (5.70, 6.10)  | 0.971    |

Data were presented as number of patients or median (interquartile range). LAG, Levocarnitine administration group; FIB-4, fibrosis-4; IQR, interquartile range; γ-GTP, glutamyl transpeptidase; ALBI, albumin-bilirubin; LS, lumbar spine.

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**Figure 2.** Comparison of ΔSMI/year, ΔIMAC/year, ΔWBBMD/year, and ΔLSBMD in the LAG and controls. (A) Comparison of ΔSMI/year in the LAG and controls. (B) Comparison of ΔIMAC/year in the LAG and controls. (C) Comparison of ΔWBBMD/year in the LAG and controls. (D) Comparison of ΔLSBMD in the LAG and controls. Data were analyzed with the Mann-Whitney U test. Values of P<0.05 were considered statistically significant. LAG, levocarnitine administration group; IMAC, intramuscular adipose tissue content; NS, not significant; SMI, skeletal muscle mass index; IMAC, intramuscular adipose tissue content; WBBMD, whole body bone mineral density; LSBMD, lumbar spine bone mineral density.
Furthermore, our study suggested that carnitine administration may prevent BMD loss. The prevalence of osteoporosis in patients with LC cirrhosis is ~12–55%, which is higher than in healthy individuals (37). Along with sarcopenia, it is one of the issues that have a major influence on the health of patients with CLD. One of the mechanisms of osteoporosis in patients with CLD has been shown to activate osteoclasts by inflammatory cytokines (38). Because carnitine suppresses the production of inflammatory cytokines (39), it may have prevented the decrease in ΔWBMD in our study. However, ΔLSBMD showed no significant effect. Further research is needed to treat osteoporosis in patients with CLD.

This study had several limitations. First, this was a retrospective single-center study with a small sample size. Moreover, the observation period was different for each patient. Second, the purpose and dose of L-carnitine administration were decided by the attending physician. Thus, prospective studies are warranted to clarify the effects of L-carnitine on preventing skeletal muscle loss in patients with liver disease.

In conclusion, we showed that L-carnitine administration prevented the loss of skeletal muscle mass and BMD in patients with CLD. L-carnitine administration can be a new option for treating osteoporosis and sarcopenia. Further detailed studies are needed to confirm this possibility.

Acknowledgements
Not applicable.

Funding
No funding was received.

Availability of data and materials
All data generated or analyzed in this study are included in this published article.

Authors' contributions
KO and TI designed the research; TI and TY conducted the research; AH, TH evaluated SMI, IMAC and BMD. MS collected the medication data. HN, HH, FK, MK, SH, and KS collected the clinical and laboratory assessment data; KO, TI, and YM analyzed the data; KO summarized the data; KO and TI wrote the manuscript. All authors have read, checked, and approved the final manuscript.

Ethics approval and consent to participate
The present study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the ethics committees of Saiseikai Niigata Hospital (approval no. E17-27). Informed consent was obtained by the opt-out method on the website.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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