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Research Article

L-Carnitine Administration to Cirrhotic Patients with Sarcopenia Improves Nutritional State Including Controlling Nutritional Status (CONUT) Score

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Abstract

Background: Sarcopenia is a disease characterized by reduced skeletal muscle mass. We investigated the frequency of sarcopenia in patients with liver cirrhosis and the effects of administering L-carnitine to cirrhotic patients with sarcopenia.

Methods: A total of 77 patients with liver cirrhosis (31 males and 46 females) were enrolled in this study between April 2012 and September 2015. All patients were treated with L-carnitine 600 mg 3 times (1800 mg per day) as part of a nutritional supplementation regimen for at least 1 year and underwent diagnostic CT during their clinical courses.

Results: Sarcopenia was confirmed in 23 of the 31 males (71.4%) and 33 of the 46 females (71.7%). Sarcopenic patients had lower body mass indexes and higher Child-Pugh scores than non-sarcopenic patients. Sarcopenia patients had higher rate with HCC than non-sarcopenic patients Administration of L-carnitine maintained Skeletal Muscle Index (SMI). L-carnitine supplementation significantly improved albumin, total cholesterol, and Controlling Nutritional Status (CONUT) in sarcopenic patients with liver cirrhosis.

Conclusion: L-carnitine administration in cirrhotic patients with sarcopenia improves CONUT score as nutrition support.

Keywords: Sarcopenia; CONUT score; L-carnitine

Introduction

Patients with liver cirrhosis are known to be prone to developing Protein-Energy Malnutrition (PEM) [1-7]. Advanced liver disease is also considered to promote catabolism and to cause muscle wasting [8].

The consensus on sarcopenia, issued by the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010, defines age-related sarcopenia as primary sarcopenia and non-age-related sarcopenia as secondary sarcopenia. Advanced liver diseases are considered to be a risk factor for secondary sarcopenia [9].

Recently, many studies have reported the prognosis of cirrhosis patients with sarcopenia to be poor and that the survival rate is low for patients with Hepatocellular Carcinoma (HCC) [10,11].

The survival rate of patients who underwent hepatectomy or liver transplantation was reported to correlate with skeletal muscle mass, and sarcopenia reportedly shows an independent correlation with mortality in patients with liver cirrhosis. Under these circumstances, the development of specific therapeutic measures against sarcopenia is eagerly awaited. Studies on sarcopenia in the field of liver disease have attracted considerable clinical attention. Nutritional therapy might be among these highly anticipated measures, but as yet no published studies have focused on the efficacy of nutritional therapy in sarcopenic patients.

Hence, carnitine is a vitamin-like substance that is essential for beta oxidation of fatty acids, and liver cirrhosis is considered to be a form of secondary carnitine deficiency [12].

Carnitine deficiency impedes the use of fatty acids as an energy source, leading to various symptoms, including non-ketotic hypoglycemia, hyperammonemia, muscular weakness, and cardiac failure. Even if amino acids and lipids are administered to improve nutritional status, carnitine deficiency will cause the body to lose the ability to utilize lipids, making the patient prone to hypoglycemia and amino acid hyper-catabolism [13].

Given the importance of the liver as an organ involved in fatty acid metabolism, carnitine administration is anticipated to contribute to the amelioration of conditions suffered by patients with advanced liver disease.

Several recent studies have examined the possibility of assessing nutritional status in cirrhotic patients with some protocols, such as the Prognostic Nutritional Index (PNI) or Controlling Nutritional Status (CONUT) score, which are comprised exclusively of analytical data [14,15]. However, the relationship between nutritional status including CONUT score and sarcopenia in cirrhosis has not extensively studied and there is little data on the administration of L-carnitine for sarcopenic patients with cirrhosis. Therefore, we evaluated the morbidity of sarcopenia in patients with liver cirrhosis using Computed Tomography (CT) and investigated the effects of

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Table 1: Comparisons between Patients with and without Sarcopenia.

Variables	Sarcopenia	Non Sarcopenia	P-value
Gender (Male/Female)	23/33	8/13	P=0.813
Age (years)	71.53±10.03	70.33±8.08	P=0.624
Etiology (HBV/HCV/NASH/ Others)	9/23/8/16	0/5/8/8	P=0.035
HCC/No HCC	24/32	3/18	P=0.019*
Albumin (g/dL)	3.63±0.49	3.45±0.60	P=0.191
T.Bil (mg/dL)	0.68±0.37	0.91±0.70	P=0.068
Child-Pugh	6.91±1.67	6.06±1.67	P=0.013*
NH_3 (mg/dL)	60.77±41.25	57.53±28.87	P=0.782
Na (mEq/L)	139.87±2.61	139.70±2.92	P=0.813
BMI (kg/m^2)	22.63±3.32	28.62±4.32	P=0.009*
Type IV collagen (ng/mL)	5.79±2.74	6.88±4.02	P=0.276
TLC (/mL)	1363.31±722.67	1545.18±784.67	P=0.383
T.Cho (mg/dL)	163.74±35.03	168.65±42.02	P=0.613
HbA1C (%)	5.67±0.72	5.87±0.62	P=0.279
CONUT score	3.41±2.41	3.38±2.93	P=0.978

BMI: Body Mass Index, **HCC:** Hepatocellular Carcinoma, **T.Bil:** Total Bilirubin, **TLC:** Total Lymphocytes, **T.Cho:** Total Cholesterol, **CONUT score:** Controlling Nutritional Status score.
*denote statistical significance at the P<0.05, **n.s:** not significant.

carnitine administration as a nutritional therapy for sarcopenia.

Methods

Between April 2012 and September 2015, a total of 77 patients with liver cirrhosis (31 males and 46 females) excluding complicating other diseases were enrolled in this study. All patients were treated with L-carnitine (L-cartin tablets; OTSUKA Pharmaceutical Co. Ltd., Tokyo, Japan) 600 mg 3 times (1800 mg per day) as part of a nutritional supplementation regimen for at least 1 year and underwent diagnostic CT during their clinical courses.

Skeletal muscle mass was determined based on the skeletal muscle cross-sectional area (cm^2) at the third lumbar (L3) level on CT using image. The skeletal muscle cross-sectional area at the L3 level was divided by the square of body height (m^2) to calculate the Skeletal Muscle Index (SMI). New sarcopenia cutoff values for patients with cirrhosis have been reported (L3 SMI: ≤42 cm^2/m^2 for women and ≤ 50 cm^2/m^2 for men [16].

Sarcopenia status and clinical improvement in response to L-carnitine were comparatively evaluated in our 77 patients with liver cirrhosis.

The CONUT score was calculated using the serum albumin concentration, peripheral lymphocyte count and the total cholesterol concentration during treatment [15].

Statistical Analysis

Prior to this study, all demographic and clinico-pathological data had been prospectively collected in a computer database. Background clinical characteristics were compared by the Student's test, Chi-Squared test, mxn contingency tables, Wilcoxon rank sum test and Mann-Whitney U test.

Statistical processing was performed using Stat View version 5.0 software (SAS Institute, Cary., N.C., USA). All reported P values are 2-sided, with P<0.05 considered statistically significant.

Results

Sarcopenia was confirmed in 23 of the 31 males (71.4%) and 33 of the 46 females (71.7%) who received L-carnitine. Sarcopenic patients had lower body mass indexes and higher Child-Pugh scores than non-sarcopenic patients. Sarcopenia patients had higher rate with HCC than non-sarcopenic patients. Albumin, total lymphocytes, total cholesterol and CONUT score are not significantly difference between sarcopenia group and non-sarcopenia group (Table 1).

L-carnitine administration maintained SMI in sarcopenic patient's irrespective advanced liver disease, especially females. However, there were no significant differences in any of the parameters examined between sarcopenic patients with and without SMI improvement.

In sarcopenic patients with liver cirrhosis, L-carnitine administration was associated with significant improvements in albumin, total cholesterol, and CONUT score (Table 2).

Discussion

Sarcopenia, initially introduced by Rosenberg [17], has been proposed to be an age-related muscle atrophy (pre-sarcopenia) that appears in combination with low muscle strength and/or physical performance condition in the criteria of the European Working Group on Sarcopenia in Older People (EWGSOP) [18]. In general, sarcopenia including muscle atrophy is frequently observed with aging, while it has also been shown to be associated with Chronic-Diseases [e.g., heart failure, obstructive pulmonary disease, diabetes mellitus, kidney disease, connective tissue disease, tuberculosis infection, and other wasting conditions] [19].

Sarcopenia was originally defined as the reduction of skeletal muscle mass but the scope has gradually expanded to also include muscular weakness and functional deterioration.

The consensus article issued by the European Society for Clinical Nutrition and Metabolism (ESPEN) defines sarcopenia as a condition accompanied by reduced muscle mass and muscular weakness, while the Society on Sarcopenia Cachexia and Wasting Disorders (SCWD) defines sarcopenia as a condition that involves reduced muscle mass and a decline in physical function.

Sarcopenia can be related to aging (primary sarcopenia) or to other conditions, such as inactivity, disease, and undernutrition (secondary sarcopenia); secondary sarcopenia is the form that apparently develops in patients with hepatic cirrhosis. Nutritional therapy is important for preventing sarcopenia associated with liver cirrhosis.

Cirrhotic patients frequently develop sarcopenia, which worsens their prognosis [9]. While oral intake of branched chain amino acid formulations has been indicated to potentially improve the prognosis of sarcopenic patients; there are no reports on carnitine administration [20].

Carnitine deficiency can be classified by etiology into primary and secondary forms, and the latter is considered to be the condition associated with liver cirrhosis.

Table 2: Effects of L-Carnitine Treatment for Sarcopenia Patients on Clinical Variables.

Variables	Baseline	After 1 year	P-value
Albumin (g/dL)	3.63±0.49	3.74±0.46	P=0.023*
T.Cho (mg/dL)	163.74 ±35.03	178.03±31.08	P=0.003*
TLC (/mL)	1363.31±722.67	1446.05±763.10	P=0.261
Child-Pugh	6.06±1.67	5.91±1.78	P=0.474
CONUT score	3.41±2.41	2.64±1.88	P=0.007*

T.Cho: Total Cholesterol**, TLC:** Total Lymphocytes**, CONUT score:** Controlling Nutritional Status score
*denote statistical significance at the P<0.05**.**

However, there have been no previous reports on the relationship between sarcopenia with liver cirrhosis and efficacy of L-carnitine as nutritional status. As nutritional evaluation, we used CONUT score. The CONUT score, which was reported to correlate with the Subjective Global Assessment (SGA), was developed to evaluate the nutritional status more easily and more objectively [15].

This is therefore the first report to evaluate the prognostic significance of the CONUT score in cirrhotic patients with sarcopenia.

In the present study, sarcopenia was confirmed in 23 of the 31 males (71.4%) and 33 of the 46 females (71.7%) who received L-carnitine. Sarcopenic patients had lower body mass indexes and higher Child-Pugh scores than non-sarcopenic patients.

L-carnitine administration maintained SMI in sarcopenic females. However, there were no significant differences in any of the parameters examined between sarcopenic patients with and without SMI improvement.

In sarcopenic patients with liver cirrhosis, L-carnitine administration was associated with significant improvements in albumin, total cholesterol, and CONUT.

Given the importance of the liver as an organ involved in fatty acid metabolism, blood carnitine levels might be a useful parameter for assessing the conditions of patients with liver disease. Herein, we aimed to examine the possibility of important sarcopenia by administration of L-carnitine.

Lymphocyte count improvement is observed in sarcopenia with liver cirrhosis patients receiving L-carnitine supplementation, supporting its possible role in immunological improvement. Whether L-carnitine contributes to the suppression of naive and/or recurrent HCC, as well as to better survival, remains to be seen.

L-carnitine provides diverse benefits and is expected to serve as part of the nutritional therapeutic strategy for liver diseases. Further studies are needed to validate its efficacy for various hepatic conditions and to determine differences among potential regimens.

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