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Effect of L-carnitine supplementation on muscle cramps in liver cirrhosis: results from a retrospective cohort study

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Abstract

Background Muscle cramps are among the common debilitating complications of liver cirrhosis. Since this complication lacks effective treatments, we aimed to evaluate the effectiveness of L-carnitine supplementation in reducing the frequency, duration, and severity of muscle cramps in patients with liver cirrhosis.

Methods The present retrospective cohort was conducted on adult patients referred between November 2022 and December 2023 to a tertiary referral hospital in Shiraz, Iran. Patients with confirmed liver cirrhosis who had muscle cramps ≥ 4 times per month without other secondary etiologies for muscle cramps were evaluated for inclusion. They were included if they had taken an oral L-carnitine supplement of 1000 mg/day for one month and had available medical records of the assessment of their cramps before and one month after starting the supplement.

Results From the 702 patients screened, 195 (27.8%) had muscle cramps, and 91 (13.0%) met the inclusion criteria. The respective median age and cirrhosis duration (interquartile range (IQR)) of the included patients were 61.0 (16.0) and 2.0 (3.0) years, and 48 (53%) were male. Median daily, weekly, and monthly cramp frequency and severity were higher in females (P-values < 0.05). We noted reduced daily, weekly, and monthly frequency of the cramps, their severity, and their mean duration following L-carnitine supplementation (respective median (IQR) of absolute percentage change: 100 (100.0), 60 (88.33), 50 (75.0), 50 (77.5), and 40.0 (44.58); P-values < 0.001). Additionally, daily, weekly, and monthly cramps completely resolved in 29 (31.9%), 21 (23.1%), and 13 (14.3%) after supplementation. BMI correlated with the percentage change of all the mentioned cramp indices (P-values < 0.05), and age correlated with the percentage change in the monthly frequency of cramps (P-value = 0.042). Changes in cramp indices did not differ significantly between males and females.

Conclusions L-carnitine supplementation seems to be a promising therapeutic option for cramps in liver cirrhosis. Further studies with control groups and larger samples are required to confirm this finding.

Keywords L-carnitine, Muscle cramps, Liver cirrhosis, Retrospective cohort

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Introduction

Muscle cramps account for one of the most common complications in liver cirrhosis [1, 2], with a significant impact on the patient's quality of life [3–5]. Although the exact etiology is unclear, muscle cramps in cirrhosis could be attributed to volume and electrolyte imbalance, myocyte incapability of energy metabolism, neuropathy, micronutrient insufficiency [2], and malnutrition [6]. Other secondary etiologies leading to muscle cramps include exercise, pregnancy, aging, psychiatric diseases, neurologic diseases and neuropathies, endocrine-metabolic etiologies, renal failure, medications, and malignancy [2, 7]. Co-occurrence of these etiologies with liver cirrhosis may further complicate the state of muscle cramps. Muscle cramps may be observed in up to 88% of patients with cirrhosis [1]. Nevertheless, effective treatments for this common condition remain limited [8], highlighting the need for further explorations.

L-carnitine is a dietary supplement involved in the mitochondrial transport of long-chain fatty acids for β-oxidation and energy production in myocytes. L-carnitine is mainly produced in the liver [9, 10], thus its deficiency is expected in cirrhosis [8]. Additionally, malnutrition and malabsorption in liver cirrhosis could further exacerbate L-carnitine deficiency [11]. L-carnitine deficiency is associated with muscle weakness, fatigue, and cramps [9, 10]. The antioxidant and ammonia-reducing potential of L-carnitine may play a role in mitigating oxidative stress and sarcopenia [8, 12]. Nevertheless, studies on the role of L-carnitine supplementation in alleviating cirrhotic cramps are limited [8]. Thus, our study aims to evaluate the effectiveness of L-carnitine supplementation in reducing the frequency, duration, and severity of muscle cramps in patients with liver cirrhosis.

Materials and methods

The current retrospective cohort is conducted on adult patients referred between November 2022 and December 2023 to Motahari Cirrhosis Clinic in Namazi Hospital, a tertiary referral hospital in Shiraz, Iran. Patients with liver cirrhosis confirmed with clinical, laboratory, and radiologic evaluations who had muscle cramps ≥ 4 times per month were evaluated. These patients were included if they had taken an oral L-carnitine supplement of 1000 mg/day for at least one month and had available medical records of the assessment of their cramps before and one month after starting the supplement.

Exclusion criteria were the discovery of other secondary etiologies for cramps in the patients. These etiologies included benign etiologies (exercise-induced, pregnancy, and benign nocturnal muscle cramps in the elderly), neurologic complications (central and peripheral nervous system diseases and myopathies), and systemic conditions. Systemic conditions included end-stage kidney disease, altered function of the thyroid or parathyroid gland, adrenal insufficiency, and malignancy. We also investigated clinical records and laboratory data to ensure that patients with acute kidney injury (AKI), dehydration, and significant dyselectrolytemia (defined as serum sodium < 130 mmol/L or > 145 mmol/L, or potassium < 3.5 mmol/L or > 5.0 mmol/L), are not included.

After the screening, baseline characteristics (including age, gender, body mass index (BMI), and cirrhosis duration) and the frequency, duration, and severity of cramps before and after L-carnitine therapy were gathered in a form. To ensure patient confidentiality, only the main physician of the patients would review their files for the information of interest and would add de-identified patient data to the form. Cramp severity was assessed and recorded based on the Visual Analog Scale (VAS) [13].

The Kolmogorov-Smirnov Test assessed the normal distribution of the sample. Quantitative variables were reported with mean and standard deviation (SD), whereas categorical variables were reported with the number in each category and their frequency. For quantitative variables without a normal distribution, mean and SD were substituted with median and interquartile range (IQR). Values before and after supplementation were compared with the Wilcoxon Signed-Rank test and Paired-Samples T-Test for non-parametric and parametric variables, respectively. Post-hoc analysis of the power was performed with G*Power version 3.1.9.4. Independent Samples T-Test and Mann-Whitney U test were used for between-group comparison of parametric and nonparametric variables, respectively. Correlation was assessed with Pearson's Correlation Coefficient and Spearman's Rho for parametric and nonparametric variables, respectively. IBM SPSS version 25 was used for statistical analysis, and a p-value < 0.05 was considered significant.

Results

A total of 702 patients were screened, of whom 195 (27.8%) had muscle cramps, and 91 (13.0%) met the inclusion criteria. The median age (IQR) of the included patients was 61.00 (51.00–67.00) years, and 48 (53%) were male. The median BMI and cirrhosis duration were 25.73 (23.95–29.06) kg/m^2 and 2.00 (1.00–4.00) years, respectively. The characteristics of the patients' cramps before and after taking the L-carnitine supplement are summarized in Table 1.

Median daily, weekly, and monthly cramp frequency and severity were higher in females, whereas cramp duration did not differ between genders (Table 2). BMI was higher in females (28.19 vs. 25.09, $P < 0.001$), and other baseline measures did not differ between genders. After controlling for BMI, only cramp severity remained

Table 1 Muscle cramp indices before and after treatment with L-carnitine

Variables	Before treatment*	One month after treatment*	The absolute median percentage of change (IQR)	Wilcoxon statistic (95% CI of differences)	Number of respondents (%)	*P*-value
Daily cramps	1.00 (1.00–2.00)	0.00 (0.00–0.00)	100.0 (100)	0.0 (1.30–1.72)	35 (38.5)	**< 0.001**
Weekly cramps	4.00 (2.00–7.00)	1.00 (1.00–3.00)	60.0 (88.33)	61.0 (2.79–4.65)	66 (72.5)	**< 0.001**
Monthly cramps	12 (6.00–28.00)	5.00 (2.00–10.00)	50.0 (75.0)	82.0 (8.27–12.84)	67 (73.6)	**< 0.001**
Mean expressed duration (minutes)	5.00 (3.00–15.00)	3.00 (1.00–5.00)	50.0 (77.5)	84.5 (6.22–12.62)	66 (72.5)	**< 0.001**
Mean expressed VAS severity	8.00 (7.00–10.00)	5.00 (2.00–7.00)	40.0 (44.58)	1.0 (4.01–4.99)	69 (75.8)	**< 0.001**

*Values are reported as Median (IQR). Wilcoxon Signed-Rank test was used to compare the pairs. Respondents were defined as patients with decreased cramp indices following L-carnitine supplementation. P-value < 0.05 was considered significant

Table 2 Comparison of cramp indices between male and female

Variables	Male ($n = 48$) *	Female ($n = 43$) *	*P*-value
Daily frequency	0.00 (0.00–1.00)	1.00 (0.00–2.00)	**0.016**
Weekly frequency	2.50 (2.00–5.00)	4.00 (2.00–10.00)	**0.034**
Monthly frequency	10.00 (6.00–20.00)	20.00 (8.00–30.00)	**0.047**
Duration	5.00 (4.25–13.75)	5.00 (2.00–20.00)	0.608
Severity	8.00 (5.25–9.75)	9.00 (8.00–10.00)	**0.011**

*Values are reported as Median (IQR). Comparisons were made with the Mann-Whitney U test. P-value < 0.05 was considered significant

significantly higher in females (Correlation coefficient = 0.287, p-value = 0.006). Cramp frequency, severity, and duration did not correlate with the patient's BMI (p-value > 0.05).

A comparison of the indices before and after taking the L-carnitine supplement demonstrated that L-carnitine significantly reduced the daily, weekly, and monthly frequency of the cramps, their severity, and their mean duration ($P < 0.001$, Table 1; Fig. 1). Additionally, daily, weekly, and monthly cramps completely resolved in 29 (31.9%), 21 (23.1%), and 13 (14.3%) of the patients following L-carnitine supplementation. Post-hoc power analysis was conducted, indicating an achieved power of 1.0 and an effect size of 0.86, suggesting that the study had a high likelihood of detecting the observed effect. BMI correlated with the percentage change of all the mentioned cramp indices, and age correlated with the percentage change in the monthly frequency of cramps (Table 3). Despite other correlations, the correlation of BMI with the percentage change in the weekly and monthly frequency of cramps remained significant after controlling for age and gender (Correlation coefficients: 0.257 and 0.239; p-value: 0.016 and 0.025). Changes in cramp indices did not differ significantly between males and females.

Discussion

Muscle cramps are a frequent yet neglected complication in liver cirrhosis that significantly affects the patient's quality of life [3–5]. The prevalence of cramps ranges from 22 to 88% in the literature, depending on the definition criteria of muscle cramps and the characteristics of the studied population [2]. Muscle cramps were present in 27.8% of the patients assessed in the present cohort, necessitating attention to this common complication of liver cirrhosis.

Cramp frequency and severity were higher in females of the present study, consistent with previous studies [3, 14, 15]. This gender difference could be attributed to the lower muscle mass in females than males, making them prone to muscle cramps following cirrhotic sarcopenia [14]. The higher prevalence of muscle mass reduction in patients with cirrhotic cramps [6] also justifies this finding. However, similar to the findings of Hiraoka et al. [15], age did not correlate with muscle cramps, suggesting that senile muscle mass reduction is probably not a contributing factor to cirrhotic cramps. Additionally, it highlights the possible unknown multifactorial etiology of muscle cramps in liver cirrhosis.

Although higher muscle mass can protect against muscle cramps [14], our study found no association between baseline BMI and cramp frequency and severity. This lack of correlation raises questions about the reliability of BMI as a surrogate for muscle mass. Patients with obesity or edema may have normal or elevated BMI despite significant muscle loss [16]. This underscores the need for alternative methods to assess sarcopenia, such as imaging techniques [17]. Therefore, we recommend clinicians against relying solely on BMI to evaluate sarcopenia in liver cirrhosis.

Possible contributing factors to muscle mass reduction and sarcopenia in liver cirrhosis include elevated serum ammonia, impaired protein synthesis, reduced anabolic hormones, and an inflammatory state in liver cirrhosis [18]. Herein, nutritional supplements aiming at alleviating these conditions can potentially benefit cirrhotic cramps without significant side effects [19]. L-carnitine is among these supplements that can alleviate

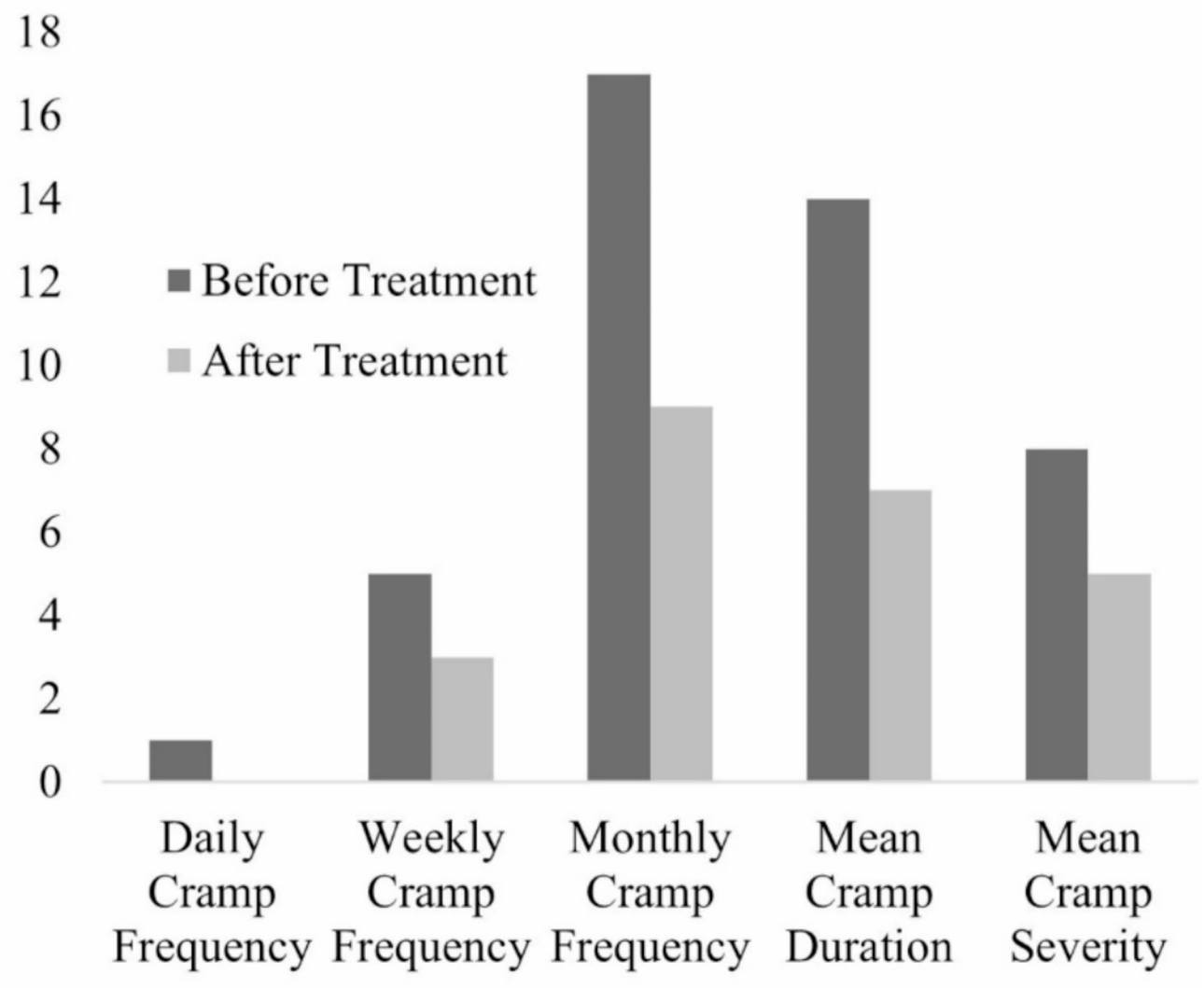

Fig. 1 Mean value of cramp indices before and after L-carnitine supplementation

Table 3 Correlation of age and body mass index with the percentage changes in cramp indices

Variables	Cramp indices changes	Correlation coefficient	Fisher's Z transformation (95% CI)	*P*-value
Body Mass Index	Daily frequency	0.318	0.33 (0.12–0.54)	**0.032**
	Weekly frequency	0.289	0.30 (0.09–0.51)	**0.005**
	Monthly frequency	0.290	0.30 (0.09–0.51)	**0.005**
	Duration	0.218	0.22 (0.01–0.43)	**0.038**
	Severity	0.214	0.21 (0.01–0.43)	**0.042**
Age	Daily frequency	0.142	0.14 (-0.06–0.35)	0.345
	Weekly frequency	0.204	0.21 (-0.002–0.42)	0.053
	Monthly frequency	0.214	0.22 (0.01–0.43)	**0.042**
	Duration	-0.001	-0.001 (-0.21–0.21)	0.991
	Severity	0.105	0.11 (-0.10–0.31)	0.323

Comparisons were conducted with Spearman Rho. P-value < 0.05 was considered significant

hyperammonemia and increase muscle mass [18], potentially reducing muscle cramps [18, 19].

L-carnitine supplementation can alleviate muscle cramps through different mechanisms, including restoration of muscular carnitine and enhanced mitochondrial β-oxidation [9, 10]. By replenishing intracellular free coenzyme A (CoA), it improves CoA-dependent cellular metabolic functions impaired by

carnitine deficiency [20]. L-carnitine also enhances energy metabolism by increasing carbohydrate utilization and reducing protein breakdown [21]. Furthermore, it exhibits anti-oxidative and anti-inflammatory effects by suppressing nuclear factor-kappa B (NF-κB) activation, reducing inflammatory cytokines, and increasing the anti-inflammatory cytokine interleukin-10. Additionally, L-carnitine helps prevent muscle loss by reducing inflammation, suppressing NF-κB, activating the Insulin-like Growth Factor-1 (IGF-1) pathway, inhibiting pro-apoptotic genes in myocytes [22], and promoting myocyte differentiation through myogenic regulatory factors [23]. The mentioned mechanisms may also contribute to improved patient survival [24].

The present study revealed that L-carnitine consumption was associated with a significant decrease in the frequency, severity, and duration of muscle cramps in patients with liver cirrhosis. Improvement in cramp frequency, duration, and severity were observed in around three-quarters of the patients receiving L-carnitine supplement. Additionally, daily, weekly, and monthly cramps completely resolved in 31.9%, 23.1%, and 14.3% of the patients, respectively. Comparably, Nakayashi et al. demonstrated that 300 mg L-carnitine administered three times a day for eight weeks significantly decreased the frequency and severity of cramps and reduced the cramps in 88.1% of the 42 studied participants. A dose-dependent response was also observed in their study [25]. In the study of Tsuda et al. on 23 patients with cirrhosis, administration of L-carnitine 300 mg twice daily reduced muscle cramps in 90% of the patients [26]. In another study, Hiraoka et al. studied the combination of L-carnitine, branched-chain amino acids, and exercise on 11 patients with cirrhotic cramps. They discovered that although this treatment reduced cramp frequency, it failed to alleviate its severity in their studied population [27]. Altogether, our study and the previous ones confirm the positive effect of L-carnitine on muscle cramps in liver cirrhosis. Considering the general safety and effectiveness of this supplementation, clinicians may consider this treatment option for muscle cramps in liver cirrhosis, although further studies are required.

In this study, higher BMI was associated with a reduced response to L-carnitine supplementation. This may be explained by the adverse effects of obesity on metabolic function. Obesity is linked to insulin resistance and impaired mitochondrial activity, which can hinder glucose uptake in muscle cells and compromise the mitochondrial function of L-carnitine. Insulin resistance also reduces free carnitine levels [28, 29], further impairing mitochondrial energy production. Additionally, obesity-related inflammation and metabolic dysfunction-associated fatty liver disease (MAFLD) exacerbate hepatic and muscular dysfunction [30], which may contribute to muscle cramps. Future research should explore whether higher doses of L-carnitine are needed for individuals with elevated BMI.

This study employed a retrospective cohort design, leveraging comprehensive medical records on L-carnitine use in patients with liver cirrhosis treated at our institution. This approach enabled efficient analysis of a large dataset collected during routine clinical care, allowing for a timely evaluation of L-carnitine's potential benefits. Although prospective or randomized designs provide stronger control over confounding factors, logistical constraints and ethical considerations limited their feasibility in this setting. Notably, the retrospective design allowed the assessment of treatment effects in a real-world clinical setting, enhancing the generalizability of the findings. We acknowledge the inherent limitations of retrospective studies, including potential selection bias. To mitigate this, we applied strict inclusion criteria, requiring complete medical records for all eligible patients.

There are also other limitations to this study. Despite a relatively large sample size compared to previous studies, it remained small and lacked the capacity for robust analyses. Baseline patient characteristics and the long-term effectiveness of L-carnitine were not comprehensively assessed. Moreover, potential confounding factors—such as diet, physical activity, performance status, mild dyselectrolytemia, and acute kidney injury (AKI)—were not evaluated. Although patients with severe conditions were excluded, the absence of multivariate analysis limited adjustment for confounders. The lack of a control group further restricted the study, making it unclear to what extent the observed improvements were attributable to L-carnitine supplementation. Future studies with larger sample sizes, randomized controlled designs, dose-response analyses, multivariate adjustments, and subgroup evaluations are essential to address these limitations. In particular, further research is needed to assess the response in specific subgroups, such as patients with higher BMI, and to compare clinical features between patients with and without muscle cramps to validate these findings.

Conclusions

L-carnitine supplementation seems to be promising in reducing the frequency, duration, and severity of cirrhotic muscle cramps, a complication observed in 27.8% of the patients in our cohort. While we based our study on real-world clinical data, it serves as a pilot investigation into the potential benefits of L-carnitine in cramps associated with liver cirrhosis. Future well-designed, prospective studies with larger sample sizes and comprehensive baseline assessments are essential to validate these results, minimize potential biases, and establish the

efficacy, safety, and optimal dosing of L-carnitine supplementation in this population.

Abbreviations

AKI	Acute Kidney Injury
BMI	Body Mass Index
VAS	Visual Analog Scale
SD	Standard Deviation
IQR	Interquartile range
CoA	Coenzyme A
NF-κB	Nuclear factor-kappa B
IGF-1	Insulin-like Growth Factor 1
MAFLD	Metabolic Dysfunction-Associated Fatty Liver Disease

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Author contributions
AS, GRS, ARS, and RN were responsible for the conception and design of the study. AS and ARS gathered the data. EM performed the formal statistical analysis. The manuscript was drafted and revised by ARS, EM, GRS, RN, and AS. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was conducted in accordance with the Declaration of Helsinki. The Research Ethics Committee of the School of Medicine - Shiraz University of Medical Sciences granted approval for the present study with the ethics code of IR.SUMS.MED.REC.1403.134. All patients gave informed consent for the anonymous use of their data.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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