Muscle Cramps in Liver Disease

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The article has an accompanying continuing medical education activity on page e80. Learning Objectives—At the end of this activity, the successful learner will be able to better assess and manage patients with muscle cramps in liver disease.

Muscle cramps are common in patients with liver disease and adversely influence quality of life. The exact mechanisms by which they occur remain unclear, although a number of pathophysiological events unique to liver disease may contribute. Clinical studies have identified alterations in 3 areas: nerve function, energy metabolism, and plasma volume electrolytes. Treatments have focused on these particular areas with varied results. This review will focus on the clinical features of muscle cramps in patients with liver disease and review potential mechanisms and current therapies.

Keyword: Chronic Liver Disease.

Muscle cramps are defined as involuntary painful contractions at rest or during sleep of a muscle or muscle group that may last for seconds to minutes and are usually self-limiting. Cramps are commonly found in a variety of diseases including liver disease (Table 1). Although generally benign, the frequency and severity of cramps may be debilitating and have a significant negative effect on the quality of life (QOL) in affected patients. Despite the association of muscle cramps with liver disease, there is a paucity of information regarding pathogenesis and treatment in these patients.

Prevalence and Clinical Significance

The first report of an association between cirrhosis and muscle cramps was made by Konikoff and Theodor in 1986. Of 33 patients with cirrhosis who were studied, 88% were found to have experienced more than 2 cramps in calf muscles within the prior week. Since this report, several subsequent studies have demonstrated a 22%–88% prevalence of muscle cramps in patients with liver disease, depending on differing definitions, frequency, and inclusion criteria (Table 2). The majority of studies have found a higher prevalence of cramps in cirrhotic patients relative to control groups. In addition, patients with cirrhosis in comparison with noncirrhotic patients with liver disease have been found to have a greater prevalence of cramps, 31% vs 5%, respectively. Abrams et al compared patients with cirrhosis with those with congestive heart failure and found a significantly higher prevalence of weekly or daily cramps with cirrhosis (22%) vs patients with congestive heart failure (5%). Interestingly, there was no difference in diuretic use or dosing between the 2 groups, supporting that factors other than diuretic-mediated effects explained the differences. Together, these studies suggest that unique physiological changes may occur in cirrhosis and predispose to the development of cramps.

Pathophysiology

The pathophysiological mechanisms of muscle cramps in patients with cirrhosis are not clearly elucidated. However, a number of mechanisms have been considered and explored. Potential mechanisms may be divided into alterations in 3 overlapping areas: (1) nerve function, (2) energy metabolism, and (3) plasma volume and electrolytes (Figure 1).

Nerve Function

The first studies examining the role of nerve dysfunction in patients with liver disease were conducted 30 years ago. At that time, it was postulated that nerve dysfunction was likely due to impaired membrane conduction as a result of oxidative stress. Histologic studies revealed that those with liver disease exhibited thinly myelinated nerve fibers and axonal loss, supporting the presence of structural damage. In addition, patients with cirrhosis were observed to have involuntary bursts of action potentials that appeared as fasciculations on electromyo-
gram with origins in the peripheral nerve. These findings suggested a chronically depolarized and hyperexcitable motor neuron in patients with liver disease, thus inducing inappropriate high-frequency repetitive firing of the motor nerve action potentials, resulting in muscle cramps. This concept was expanded by Ng et al, who performed direct nerve studies on the median and peroneal motor nerves in patients with cirrhosis. The study found increased nerve excitability that was due to depolarization of the resting axonal membrane potential resulting from a significant reduction in threshold potential. These studies supported that nerve dysfunction, possibly related to oxidative injury and structural alterations, plays an important role in sustained muscle contractions and the development of muscle cramps. Therefore, a number of treatments have focused on decreasing the excitability of motor neurons and relieving oxidative injury within nerves.

### Energy Metabolism

The liver has a central role in amino acid and protein metabolism and is responsible for the deamination and modification of amino acids and the synthesis of amino acids into proteins. The regulation of amino acid and protein metabolism is altered in those with cirrhosis, which is reflected by decreased plasma and skeletal muscle concentrations of taurine (the most abundant amino acid in skeletal muscle). Altered taurine concentrations appear to result from both decreased production related to an imbalance in the ratio of branched-chain amino acids to aromatic amino acids and increased release from muscle. Taurine concentrations influence the function of a number of critical ion channels, including voltage-dependent chloride channels and calcium-activated sodium and potassium channels, which modulate striated fiber electrical activity and stabilize the sarcolemma. The net result of taurine deficiency is a decrease in the threshold potential and hyperexcitability of skeletal muscle. Yamamoto et al directly measured the mean plasma taurine level in cirrhotic patients with and without muscle cramps in comparison with controls by using high-performance chromatography and found significant differences. The mean plasma taurine level in cirrhotic patients with cramps was 56.9 nmol/mL, whereas in those without cramps it was 79.3 nmol/mL, and healthy controls had a level of 90.1 nmol/mL. These findings support that taurine deficiency may alter skeletal muscle electrical properties, thereby predisposing these patients to cramps.

Another potential contributor to altered energy metabolism in cirrhosis is a reduction in adenosine triphosphate (ATP) production. Moller et al performed skeletal muscle biopsies in 10 cirrhotic patients and found a reduction in ATP, phosphocreatine, and total adenine nucleotide levels. A lack of ATP could diminish the cycling process of actin and myosin cross-bridging, causing prolonged muscle contraction particularly in the presence of abnormal electrical activity.

### Plasma Volume, Electrolytes, and Zinc

Electrolyte abnormalities including hyponatremia, hypokalemia, and hypomagnesemia as well as shifts in plasma volume that can influence intracellular concentrations of electrolytes or cause hypovolemia have been implicated as factors in producing cramps. Angeli et al sought to determine

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### Table 1. Diseases, Medications, and Physiological Changes Associated With Muscle Cramps

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>Amyotrophic lateral sclerosis</td>
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<tr>
<td></td>
<td>Spinal cord stenosis</td>
</tr>
<tr>
<td>End-stage disease</td>
<td>Liver (cirrhosis)</td>
</tr>
<tr>
<td></td>
<td>Renal requiring hemodialysis</td>
</tr>
<tr>
<td>Medications</td>
<td>Beta blockers</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>Conjugated estrogens</td>
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<tr>
<td></td>
<td>Raloxifene</td>
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<tr>
<td></td>
<td>Levalbuterol</td>
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<tr>
<td></td>
<td>Naproxen</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>Peripheral vascular disease (claudication)</td>
</tr>
</tbody>
</table>

### Table 2. Prevalence of Muscle Cramps in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of patients</th>
<th>Prevalence (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konikoff et al</td>
<td>1986</td>
<td>33</td>
<td>88</td>
<td>Severe pain occurring in calf muscles several times per week</td>
</tr>
<tr>
<td>Chao et al</td>
<td>1989</td>
<td>331</td>
<td>64</td>
<td>≥1 cramp per week that occurred mainly during sleep in the lower extremities and lasted for few minutes</td>
</tr>
<tr>
<td>Konikoff et al</td>
<td>1991</td>
<td>29</td>
<td>79</td>
<td>Cirrhotic patients with any severity, duration, or frequency of cramps</td>
</tr>
<tr>
<td>Kobayashi et al</td>
<td>1992</td>
<td>80</td>
<td>31</td>
<td>≥1 cramp per week</td>
</tr>
<tr>
<td>Abrams et al</td>
<td>1996</td>
<td>92</td>
<td>22</td>
<td>Weekly or daily cramps, either occurring at rest or when awakening a patient from sleep</td>
</tr>
<tr>
<td>Angeli et al</td>
<td>1996</td>
<td>171</td>
<td>29</td>
<td>≥3 crises per week</td>
</tr>
<tr>
<td>Baskol et al</td>
<td>2004</td>
<td>100</td>
<td>56</td>
<td>≥1 painful muscle cramp occurring at rest, strong enough to waken a patient from sleep, or occurring once a week during a period of more than 12 months</td>
</tr>
<tr>
<td>Chatrath et al</td>
<td>2012</td>
<td>150</td>
<td>67</td>
<td>Painful, involuntary contraction of skeletal muscles, occurring at rest or strong enough to wake the patient from sleep in the preceding 12 weeks</td>
</tr>
</tbody>
</table>
whether plasma volume, plasma renin activity (PRA), mean arterial pressure (MAP), serum albumin, and electrolyte concentrations affected the occurrence of muscle cramps in 224 patients with cirrhosis with and without ascites compared with 194 healthy controls. In multivariate analysis only higher PRA, presence of ascites, and lower MAP were predictors of cramps occurring in patients with cirrhosis because serum electrolyte concentrations of sodium, potassium, phosphorus, and magnesium had no effect on cramp occurrence. These studies would support that shifts in plasma volume may influence cramps, possibly by decreasing perfusion to nerves. In the same year, Abrams et al compared 92 patients with cirrhosis, 40 with chronic hepatitis without evidence of cirrhosis, and 40 patients with congestive heart failure to control for diuretic use. This study found similar results to that of Angeli et al in that no clinically significant difference in serum electrolyte concentrations was observed between cirrhotic patients with and without cramps. Also in multivariate analysis, diuretic use was not a significant contributor for the occurrence of cramps (\( P = .48 \)). Subsequent studies confirmed these results and found no significant difference in the concentrations of zinc, sodium, potassium, magnesium, or calcium in cirrhotic patients with and without cramps. Together, these results suggest that shifts in plasma volume may contribute to cramps, whereas serum electrolyte concentrations and diuretic use do not directly influence the frequency of cramps in patients with cirrhosis. However, intracellular concentrations of electrolytes could influence muscle excitability and have not been measured in cirrhotic patients with and without cramps.

**Treatment**

Therapies for muscle cramps in cirrhosis are generally directed at the 3 potential pathophysiological mechanisms or are empiric (Table 3).

**Nerve Function**

**Vitamin E.** Vitamin E is a fat-soluble vitamin with \( \alpha \)-tocopherol as the major biologically active form. It has potent antioxidant effects and also stabilizes the phospholipid bilayer of cell membranes. Vitamin E deficiency in animal models results in myocyte necrosis and in humans in myopathy. Von Herbay et al demonstrated that lower serum vitamin E levels were found in alcoholic liver disease, hemochromatosis, and Wilson’s disease compared with healthy controls. Two additional studies have reported on treatment with vitamin E for cramps in patients with cirrhosis. Konikoff et al recruited 29 patients with cirrhosis and found 23 with cramps. Those with cramps had significantly lower serum vitamin E levels than those without cramps (6.3 ± 3.2 vs 11.5 ± 4.8 \( \mu g/mL, P = .01 \)). Thirteen subjects were treated with vitamin E (200 mg 3 times daily for 4 weeks) and had significant improvement on the basis of a scoring system assessing cramp severity, frequency, and duration. A subsequent pilot randomized, double-blind, placebo-controlled crossover study in 9 adult cirrhotic subjects found no statistical significance between vitamin E and placebo in the frequency (\( P = .98 \)), duration (\( P = .93 \)), or severity of muscle cramps (\( P = .57 \)). However, treatment dosage and duration of treatment in the vitamin E arm were not reported.
Table 3. Potential Mechanisms of Action of Agents Used to Treat Cramps in Cirrhotic Patients

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Route of administration (dose studied)</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinidine sulfate</td>
<td>Increases the muscle refractory period and decreases the excitability of motor end plate to nerve stimulation</td>
<td>Oral (400 mg daily)</td>
<td>Mild diarrhea, thrombocytopenia, cardiac arrhythmias, cinchonism</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Important antioxidant in the cell membrane that acts to decrease circulating free radicals</td>
<td>Oral (200 mg 3 times daily)</td>
<td>None reported</td>
</tr>
<tr>
<td>Human albumin</td>
<td>Expansion of plasma volume and improvement of hypovolemia and possible subsequent ischemia to neurons</td>
<td>Intravenous (100 mL 25% human albumin solution)</td>
<td>None reported</td>
</tr>
<tr>
<td>Zinc</td>
<td>Unknown</td>
<td>Oral (220 mg twice daily)</td>
<td>Mild diarrhea</td>
</tr>
<tr>
<td>Taurine</td>
<td>Sarcolemma stabilization via calcium channel regulation and conductance</td>
<td>Oral (3 g daily)</td>
<td>None reported</td>
</tr>
<tr>
<td>Eperisone hydrochloride</td>
<td>Centrally acting muscle relaxant</td>
<td>Oral (150–300 mg daily)</td>
<td>Dizziness, fatigue, and epigastric discomfort</td>
</tr>
<tr>
<td>Branched-chain amino acids</td>
<td>Increases serum albumin and taurine production</td>
<td>Oral (4 g granules 3 times daily)</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Both studies identified no significant side effects to treatment. Further studies are needed to assess whether vitamin E is effective in treating cramps and to define whether serum vitamin E levels might predict responsiveness.

**Quinine sulfate.** Quinine, an alkaloid powder derived from the bark of the cinchona tree, was first reported as a treatment for muscle cramps in patients without cirrhosis in the 1940s. Although the mechanism of action of quinine in cramps is not elucidated, it is believed to reduce the excitability of the motor nerve by prolonging the refractory period of muscle to repetitive stimuli. A number of studies and a recent meta-analysis comparing quinine with vitamin E for the treatment of muscle cramps in noncirrhotic subjects found improvement with both agents but no significant difference in efficacy between them. A single study has investigated quinidine sulfate (optical isomer of quinine) for the treatment of muscle cramps in cirrhosis. Lee et al conducted a single-blind study in 31 cirrhotic patients with a history of cramps at least twice weekly for the preceding year. Sixteen patients received quinidine sulfate 200 mg twice daily for 4 weeks, and these patients had a significant reduction in the number of episodes of cramps during treatment (14.4 ± 1.7 to 4.4 ± 1.1, P < .0001) relative to the placebo group (11.8 ± 1.0 to 11.5 ± 1.5, P > .05). Mild diarrhea (31%) was the only side effect reported in the treatment group. Quinidine is no longer available over-the-counter in the United States because of rare significant adverse effects including thrombocytopenia, cardiac arrhythmias, hemolysis, and cinchonism. Therefore, the risk-benefit ratio for using quinine/quinidine in the treatment of cramps in cirrhosis is unfavorable.

**Eperisone hydrochloride.** Eperisone hydrochloride is a centrally acting muscle relaxant that appears to suppress sympathetic stimulation in skeletal muscle. Kobayashi et al treated 21 cirrhotic patients who reported having cramps more than once weekly in an open-label study with eperisone hydrochloride (150–300 mg) daily for 8 weeks. A complete disappearance of symptoms was found in 11 patients (61%), with decreased frequency in 6 patients (33%) and 1 patient with no change in symptoms. Adverse effects included epigastric discomfort, fatigue, and dizziness. Although there did appear to be a decrease in cramp frequency with treatment, the study was not blinded, there were significant side effects, and no long-term follow up data are available.

**Energy Metabolism**

**Taurine.** Three small open-label studies have evaluated taurine as a treatment for muscle cramps in cirrhosis. In the first study, 12 nonalcoholic cirrhotic patients were given 6 g taurine 3 times daily for 4 weeks. Eight patients had complete resolution of cramps, and 4 patients had a significant decrease in cramp severity by 1 month. No adverse effects were observed. In a second study, 35 cirrhotic patients were treated with 3 g taurine daily for 4 weeks. Twenty-five patients (71.4%) had significant improvement in cramps, with 13 (37.1%) having complete disappearance of symptoms. A third study by Yamamoto et al extended the prior studies by comparing plasma taurine concentrations in 15 cirrhotic patients with cramps and 13 without cramps. Plasma taurine concentrations were significantly lower in the cirrhotic patients with cramps. Nine of the cirrhotic patients with cramps were given 3 g taurine daily for 4 weeks, and all had increased plasma taurine levels and reported significant improvement in symptoms, with 6 (67%) reporting complete resolution. No adverse effects were reported. These encouraging studies support that taurine may be a useful agent to treat muscle cramps in cirrhotic patients, particularly in those with low plasma taurine levels. However, larger double-blind, placebo-controlled studies are needed to confirm these findings.

**Branched-chain amino acids.** Administration of branched-chain amino acids (isoleucine, leucine, and valine) in cirrhosis has been reported to improve serum albumin levels, increase taurine production, and possibly decrease progression of liver disease. Two studies have explored the possibility that branched-chain amino acid supplementation might also decrease the frequency of muscle cramps in patients with cirrhosis. Sako et al treated 8 patients in an open-label study with nocturnal branched-chain amino acid supplements for 3 months and found a significant increase in serum albumin levels and a significant decrease in frequency of cramps relative to pretreatment values (7.4 ± 2 to 0.3 ± 0.5 times/week,
P < .0001). Hidaka et al49 performed a small multicenter randomized study in 37 patients that compared daytime and nocturnal branched-chain amino acid supplementation for 3 months. The frequency of muscle cramps significantly decreased in both groups (P = .004), and no adverse effects were reported. These preliminary studies suggest that branched-chain amino acid supplementation may be an effective treatment for muscle cramps in cirrhosis.

**Plasma Volume, Electrolytes, and Zinc**

**Human albumin.** A single small crossover study has reported the use of intravenous albumin for treatment of muscle cramps in cirrhosis.9 Twelve patients with compensated liver disease were given placebo or 100 mL 25% human albumin solution intravenously once weekly for 4 weeks. Compared with placebo administration, albumin significantly decreased cramp frequency (2.5 ± 2.9 vs 6.2 ± 2.5, P < .001) and also decreased PRA and improved MAP. These findings suggest that intravenous albumin may decrease cramps in cirrhosis, possibly by increasing intravascular plasma volume. From a practical perspective, the cost and requirement for intravenous access to deliver albumin limit feasibility as a therapy.

**Electrolytes and zinc.** Serum electrolyte concentrations do not differ in cirrhotic patients with and without cramps. Therefore, studies have not focused on electrolyte replacement as a treatment for cramps. Empiric replacement of low serum electrolyte concentrations in cirrhotic patients with cramps is common, although whether this improves symptoms is unknown. Zinc has been used as empiric treatment for muscle cramps in cirrhosis.30 In a small study of 12 patients with low serum zinc concentrations (<70 μg/dL), oral zinc sulfate 220 mg twice daily for 12 weeks significantly decreased cramp frequency and increased serum zinc concentrations (40 ± 4.09 vs 63.8 ± 5.11 μg/dL, P = .0001). One patient reported mild diarrhea as an adverse effect. A subsequent study found low serum zinc concentrations in cirrhotic patients relative to healthy controls but no difference in levels between cirrhotic patients with and without cramps.10 These studies raise the possibility that zinc supplementation may be beneficial in cirrhotic patients with low serum zinc concentrations, but more data are needed.

**Approach to the Cirrhotic Patient With Cramps**

In patients with cirrhosis who present with muscle pain, a careful history should be obtained to differentiate cramps (spontaneous, chronic, and often nocturnal) from other causes of pain (Figure 2). In particular, new-onset persistent muscle pain should trigger consideration of other diagnoses such as rhabdomyolysis, myositis, or acute kidney injury for which laboratory tests to assess electrolytes and other parameters would be appropriate. A standardized cramp questionnaire may be useful to define the presence and severity of cramps and in assessing the effectiveness of treatments (Figure 3).11,51 In those found to have cramps, consideration of etiologies other

![Figure 2. Approach to the cirrhotic patient with cramps. CK, creatinine kinase; CRP, C-reactive protein; CQ, cramp questionnaire; EMG, electromyogram; ESR, erythrocyte sedimentation rate.](image-url)
than cirrhosis should be contemplated (Table 2). Serum electrolyte concentrations are frequently measured and, when low, repleted. When cramps related to cirrhosis are present and are clinically significant, an attempt at treatment is reasonable. Although large controlled trials are lacking, the use of over-the-counter, inexpensive agents with favorable side effect profiles (branched-chain amino acids, taurine, and vitamin E) may be considered. Branched-chain amino acids and taurine may have the greatest potential benefit on the basis of effects on proposed mechanisms and on possible improvement in nutritional parameters. Other treatments as outlined previously are not currently recommended because of ineffectiveness, expense, and/or the risk of side effects.

**Conclusion**

Muscle cramps in patients with liver disease are common and are associated with a negative impact on QOL. Although a number of mechanisms for cramps in liver disease have been postulated and have been targeted by medical therapies, a clear picture of the causal events has not emerged. Several agents have shown benefit in small uncontrolled studies, although large randomized controlled trials are lacking. Treatments such as branched-chain amino acids and taurine may have the greatest potential benefit because they target proposed mechanisms and may also improve nutritional status.

**References**

38. Moss HK, Herrmann LG. Night cramps in human extremities; a clinical study of the physiologic action of quinine and prostigmine upon the spontaneous contractions of resting muscles. Am Heart J 1948;35:403–408.

Reprint requests
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Conflicts of interest
The authors disclose no conflicts.