Vitamin D deficiency in cirrhosis and Muscle Cramps

Ibrahim M. Ibrahim[1], Elsaid Galal El-badrawy[1], Mohammed Mohammed Ismail[1], Amal jouda[1], Eman Mohamed Awad[2]

1 Tropical Medicine Department, Faculty of Medicine - Zagazig University, Egypt

2 Clinical Pathology Department, Faculty of Medicine - Zagazig University, Egypt

Email: mi8743022@gmail.com

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Abstract

Background: Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, resulting in improved management, quality of life and life expectancy of cirrhotic patients. Vitamin D deficiency has been defined as serum 25(OH)D levels lower than 20 ng/mL (i.e. 50 nmol/L) and vitamin D insufficiency has been defined as serum levels between 20 and 30 ng/mL (i.e. 50-75nmol/L). According to the Institute of Medicine (IOM) of the National Academies in the United States, vitamin D concentration of 20 ng/mL is adequate. However, the Endocrine Society (Maryland, USA) recommends levels of at least 30 ng/mL (i.e. 75 nmol/L) as adequate and concentrations between 40 and 60 ng/mL (i.e. 100-150 nmol/L) as optimal. Th ere is still no definition regarding the optimal vitamin D levels for patients with chronic liver diseases. Vitamin D insufficiency and deficiency are considered to be common in the general population and more frequent among elderly people and individuals with chronic diseases. It has been reported that 1 billion people have inadequate serum levels of 25(OH)D levels. However, the normal range of vitamin D levels has been debated. In general, optimal vitamin D status ranges from 30 to 50 ng/mL (i.e. 75-125 nmol/L). Muscle cramps in this patient population are a usual and high event (88%). With an electromyogram, the activation of involuntary potential action of the motor units was rather high, over 150 Hz. The behaviour of the peripheral nervous system is not connected to nerve degeneration. The cause that supports the presence of cramps remains inconclusive. The presence of cramps varies depending on the muscle area: cervical (9%), thigh (43%), calf (70%), toe (50%), abdominal muscles (12%), and fingers (74%). More areas of the body can be affected. No direct relationship is established between age or specific causes that lead to cirrhosis (alcohol, infection, etc.). No connectable cause or specific treatments are known to avoid the onset of cramps in patients with cirrhosis.

Keywords: Vitamin D deficiency, cirrhosis, Muscle Cramps

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The liver, the largest internal organ in the body, is essential in keeping the body functioning properly. It removes or neutralizes poisons from the blood, produces immune agents to control infection, and removes germs and bacteria from the blood. It makes proteins that regulate blood clotting and produces bile to help absorb fats and fat-soluble vitamins (**1).**

In liver cirrhosis, scar tissue replaces normal, healthy tissue, blocking the flow of blood through the organ and preventing it from working as it should. Cirrhosis is the twelfth leading cause of death, killing about 26,000 people each year. Also, the cost of cirrhosis in terms of human suffering, hospital costs, and lost productivity is high (**1).**

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, resulting in improved management, quality of life and life expectancy of cirrhotic patients (**2).**

At present, liver transplantation remains the only curative option for a selected group of patients, but pharmacological therapies that can halt progression to decompensated cirrhosis or even reverse cirrhosis are currently being developed. This concise overview focuses on diagnosis, complications and management of cirrhosis, and novel clinical and scientific developments (**3).**

The pathological mechanisms in the development of cirrhosis are persisting inflammation and necrosis, deposition and accumulation of aberrant extracellular matrix (fibrosis), "capillarization" of sinusoids, vascular reorganization, with thrombosis, obliteration, recanalization of veins and arteriovenous shunts, neo-angiogenesis with formation of new vessels and collaterals, and regeneration (**4).**

Fibrosis is not strictly "scarring" but rather dynamic balance of fibrogenesis and fibrinolysis and restoration. In general, the cirrhotic liver shows elements of both progression and regression, the balance determined by the severity and persistence of the underlying disease. On a cellular level, common pathogenic mechanisms exist: hepatic stellate cells (HSC) and fibroblasts are the effectors of fibrogenesis, while parenchymal regeneration relies on hepatocytes and hepatic stem/ progenitor cells (**5).**

Patients with cirrhosis can be asymptomatic or symptomatic, depending on whether their cirrhosis is clinically compensated or decompensated. In compensated cirrhosis, patients are usually asymptomatic, and their disease is detected incidentally by labs, physical exams, or imaging. One of the common findings is mild to moderate elevation in aminotransferases or gamma-glutamyl transpeptidase with possible enlarged liver or spleen on the exam (**6).**

On the other hand, patients with decompensated cirrhosis usually present with a wide range of signs and symptoms arising from a combination of liver dysfunction and portal hypertension. The diagnosis of ascites, jaundice, hepatic encephalopathy, variceal bleeding, or hepatocellular carcinoma in a patient with cirrhosis signifies the transition from a compensated to a decompensated phase of cirrhosis. Other cirrhosis complications include spontaneous bacterial peritonitis and hepatorenal syndrome, which occur in patients who have ascites (**7).**

Vitamin D deficiency in cirrhosis

Vitamin D insufficiency and deficiency are considered to be common in the general population and more frequent among elderly people and individuals with chronic diseases. It has been reported that 1 billion people have inadequate serum levels of 25(OH)D levels. However, the normal range of vitamin D levels has been debated. In general, optimal vitamin D status ranges from 30 to 50 ng/mL (i.e. 75-125 nmol/L) (**8).**

Vitamin D deficiency has been defined as serum 25(OH)D levels lower than 20 ng/mL (i.e. 50 nmol/L) and vitamin D insufficiency has been defined as serum levels between 20 and 30 ng/mL (i.e. 50-75nmol/L). According to the Institute of Medicine (IOM) of the National Academies in the United States, vitamin D concentration of 20 ng/mL is adequate. However, the Endocrine Society (Maryland, USA) recommends levels of at least 30 ng/mL (i.e. 75 nmol/L) as adequate and concentrations between 40 and 60 ng/mL (i.e. 100-150 nmol/L) as optimal. Th ere is still no definition regarding the optimal vitamin D levels for patients with chronic liver diseases (**9).**

Vitamin D and chronic liver disease

Vitamin D has an important role in various chronic diseases, such as infectious and cardiovascular diseases, diabetes mellitus and some types of cancer. In addition, vitamin D has been associated with chronic liver diseases and it has been reported that low vitamin D status is a common feature in different types of liver diseases (**10).**

According to recent studies, the prevalence of vitamin D insufficiency and deficiency is higher in patients with chronic liver disease than in general population ranging between 64 and 92%. It has been also reported that the incidence of vitamin D deficiency increases as the liver disease progresses. In a study by Fisher et al, vitamin D deficiency was higher in cirrhotic patients in Child-Pugh class C than in patients in Child-Pugh class A. Similar results were demonstrated from studies that evaluated vitamin D levels in patients with NAFLD and non-alcoholic steatohepatitis (NASH) (**11).**

According to Barchetta et al, patients with NAFLD had lower 25(OH)D than controls (14.8±9.2 versus 20.5±9.7 ng/mL). As summarized by Stokes et al, a variety of mechanisms contribute to vitamin D deficiency. In chronic liver diseases, the decreased vitamin D levels are associated with both malnutrition and low exposure to sunlight. Moreover, liver disease is characterized by low intestinal absorption of vitamin D and low levels of binding proteins and albumin, which can transfer the hormone to the liver and kidney, in order to be activated. In addition, hepatic hydroxylation of vitamin D is impaired leading to low production of the active hormone, whereas the catabolism of the vitamin is increased (**12).**

Vitamin D and hepatitis C virus (HCV) infection

The majority of patients with chronic hepatitis C have vitamin D deficiency compared to controls (serum 25(OH)D, 25.07 mg/L versus 43.06 mg/L). According to a cohort study including 468 patients, low serum vitamin D levels at baseline were associated with failure to achieve sustained virological response (SVR) in HCV genotypes 1, 2, and 3 following treatment with pegylated interferon and ribavirin (**Ebadi et al., 2019).**

Other studies showed that patients with chronic HCV infection (genotypes 1, 2/3) using oral vitamin D supplements had higher response to therapy and lower relapse rates. Data from in vitro studies supported the significance of vitamin D in chronic hepatitis C, suggesting 25(OH)D as a suppressive factor of HCV replication. Vitamin D ameliorates the necro-inflammatory process and inhibits liver fibrosis, and subsequently, its deficiency could contribute to the progression of chronic hepatitis (**12).**

NAFLD

NAFLD is the most common chronic liver disorder in economically developed countries, and its prevalence is strongly linked to current lifestyle. Approximately 30% of patients with NAFLD have NASH in liver biopsy which might progress to liver cirrhosis. Insulin resistance, a component of metabolic syndrome, is implicated in the progression to NASH. Vitamin D has a great impact on NASH, considering that an optimal vitamin D status reduces the incidence of metabolic syndrome (**13).**

25(OH)D improves insulin resistance by accelerating the metabolism of proinsulin to insulin. According to (**14**) vitamin D deficiency is implicated in steatosis, necroinflammation and liver fibrosis, regardless of other aspects of metabolic syndrome. Nakano et al, using a rat model, examined the role of vitamin D produced by phototherapy on the progression of NASH. Phototherapy reduced inflammation and fibrosis of hepatic cells compared to controls. It has been also suggested that phototherapy improves insulin resistance and inhibits the expression of profibrotic factors, such as transforming growth factor (TGF)-β (**12).**

Vitamin D and liver cirrhosis

The deranged metabolism of vitamin D in liver cirrhosis was first reported in the late ‘70s and it was mainly attributed to impaired 25(OH)-vitamin D hydroxylation of the precursor vitamin D due to insufficient liver function. Before the year 2000, the majority of the studies on vitamin D in cirrhosis focused on the association of hepatic insufficiency with bone demineralization, osteomalacia, osteoporosis, minerals metabolism/equilibrium (calcium, phosphorus), possible endocrine disturbances (parathormone – secondary hyperparathyroidism) and, in general, with the homeostasis involving the liver-kidney-gut-calcium axis. In the past two decades, there have been considerable advances in the understanding of the pathophysiology of vitamin D and its possible clinical implications in chronic liver diseases (**12).**

Serum levels of vitamin D in patients with liver cirrhosis

Vitamin D deficiency in cirrhosis is related to liver dysfunction rather than aetiology and it is no longer considered prevalent only in cholestatic disorders. Malham et al compared vitamin D status between patients with alcoholic cirrhosis (ALC) and PBC. ALC patients had lower vitamin D levels compared to PBC patients.

A number of studies have supported the prevalence of hypovitaminosis D in chronic liver disease and cirrhosis with one study reporting a low prevalence of 25(OH)D deficiency in a cohort of patients with genotype 1 chronic HCV infection and compensated liver disease (15% cirrhotic patients): 48% and 16% of the cohort had vitamin levels of < 75 nmol/L and <50 nmol/L, respectively (**13).**

Relationship between vitamin D and liver fibrosis

An association of low 25(OH)D levels with advanced fibrosis has been reported in both HCV mono-infected and HCV-HIV co-infected cohorts. In the latter study, a significant correlation of 25(OH)D levels with the histological METAVIR fibrosis score was observed. Two recent genetic studies have further supported the relation between vitamin D and fibrosis. Baur et al studied both 25(OH)D serum levels and VDR gene (NR1I1) polymorphisms in a cohort of patients with chronic hepatitis C. The authors concluded that both deficient 25OHD levels and presence of an unfavorable bat- haplotype (bAt[CCA]-haplotype, ApaI rs7975232 CC genotype) increased the risk for fibrosis progression(**13).**

Likewise, **Grunhage et al** conducted a large-scale (712 patients) study of genetic variants affecting serum 25(OH)D levels in chronic liver disease (6.6% F3 and 57% F4 patients). Serum levels of 25(OH)D inversely correlated with transient elastography and fibrosis stages. Homozygous carriers of the rare DHCR7 allele or the common CYP2R1 allele had reduced 25(OH)- vitamin D levels. The variant rs12785878 in the DHCR7 locus was correlated with liver stiff ness in transient elastography (12).

Their results imply that vitamin D has a greater impact on the initiation than on the progression of liver fibrosis. Petta et al studied the association between liver fibrosis and certain genetic variants affecting 25(OH)D serum levels, in a cohort of 260 biopsy-proven genotype 1 chronic HCV-infected patients (17.3% F3, 11.2% F4 fibrosis). DHCR7 GG genotype was 3756 Identified as an independent risk factor for severe fibrosis and was associated with lower vitamin D serum levels. In a recent meta-analysis by Garcıa – Alvarez et al, a significant association between vitamin D status and liver fibrosis off s of 10 ng/mL (odds ratio, OR: 2.37, 95% CI: 1.20-4.72) and 30 ng/mL (OR: 2.22, 95% CI: 1.24-3.97)] was observed (**14).**

Electrolytes disturbance in cirrhosis

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury that leads to portal hypertension and end-stage liver disease. Alcoholic liver disease and hepatitis C are the most common causes in the western world, while hepatitis B prevails in most parts of Asia and sub-Saharan Africa. Hyponatremia is the most common electrolyte abnormality observed in hospitalized patients and is a common finding in patients with advanced cirrhosis (**15).**

Hyponatremia in cirrhosis is currently defined as a serum sodium level of less than 130 meq/L being the most common electrolyte disorder in this setting. Indeed, about 20% of the patients have values lower than 130 mmol/L, which is the current definition of hyponatremia in cirrhosis. The prevalence of hyponatremia is around 57 and 40% in hospitalized and ambulatory patients of cirrhosis with ascites, and 25% in stable patients with cirrhosis, respectively (**16).**

Even though severe hypernatremia (>150 mmol/L) shows low prevalence in cirrhosis (0.4%), moderate hypernatremia (>145 mmol/L) has been reported in up to 4% of these patients. The serum potassium concentration can vary widely in unstable cirrhotic patients, with a higher prevalence of hypokalaemia (20%) than hyperkalaemia (12%) in this group (**17).**

Hypokalaemia can be caused either by a decreased intake of potassium or by excessive losses of potassium in the urine or through the gastro intestinal (GI) tract/ Gastrointestinal losses of potassium usually are due to prolonged diarrhoea or vomiting, chronic laxative abuse, intestinal obstruction, or infections. The intracellular shifting of potassium can also result in severe hypokalaemia. The sympathetic nervous system stimulation, insulin administration, familial periodic paralysis, and thyrotoxicosis are a few of the reasons for hypokalaemia. Chronic liver disease complicated by hepatocellular carcinoma or cholangiocarcinoma is a known cause of hypercalcemia (**17).**

Chronic liver disease, per se, as the cause of hypercalcemia in this subset of patients is not clearly established. Two cases developed hypercalcemia during the advanced chronic liver disease. This type of hypercalcemia is relatively easy to treat and requires minimal intervention. The study will be an add-on evidence about the

various aspects of electrolyte disturbance in the chronic liver disease patients enabling the treating physician to take appropriate steps in its management. So, the study was done to estimate the level of electrolyte disturbance and its association with severity, complication, and outcome in chronic liver disease patients attending a hospital in the Kumaon region of Uttarakhand (**12).**

Hyponatremia in the present study was seen in 47%, hypokalaemia in 30%, hypocalcaemia in 16% of the patients. The prevalence of hyponatremia was 21.6, 14.9, and 29.8% in the study done by **Angeli *et al.*, Kim *et al.*,** and **Borroni *et al*.** In another study by **Shaikh *et al.*,** the incidence of hyponatremia was 26.7%. The prevalence of hypokalaemia was found in 33, 15, and 6.4% of the patients in the study done by **Devrajani *et al.*, Kashyap *et al.*, and Mumtaz *et al.*,** respectively (**12).**

49.0% of the patients were in Class B, 45.0% were in Class C, and 6.0% were in Class A categories, respectively. The study done by **Almani *et al*.** showed that 37% of the patients were in Class A, 37% were in Class B, and 26% were in Class C categories. **Yan *et al*.** (2006) reported that 22% of the patients were in Class A, 41% in Class B, and 36% in Class C categories (**12).**

Anaemia was the most common complication (55.0%), followed by the upper GI bleed (50.0%), encephalopathy (49.0%), etc. In a study by **Almani *et al.*,** ascites were reported as the commonest complication (59%) (**14).**

19.1% of mortality was seen among the patients with sodium levels ≤130 meq/L, 12.5% in patients with sodium levels 131–135 meq/L, however, no mortality was seen in the patients with sodium levels 136–145 meq/L. The study done by **Sersté T *et al***. reported 55% of mortality in patients with hyponatremia. The study done by **Younas *et al*.** reported that sodium levels of <130 meq/L were associated with higher morbidity and mortality rates (**15).**

Muscle Cramps

Muscle cramps result in continuous, involuntary, painful, and localized contraction of an entire muscle group, individual single muscle, or select muscle fibres. Generally, the cramp can last from minutes to a few seconds for idiopathic or known causes with healthy subjects or in the presence of diseases. Palpating the muscle area of the cramp will present a knot (**16).**

Exercise-associated muscle cramps are the most frequent condition requiring medical/therapeutic intervention during sports. The specific aetiology is not well understood and possible causes depend on the physiological or pathological situation in which the cramps appear. It is important to note that a painful contraction that is limited to a specific area does not mean that the cause of the cramp is necessarily local. A cramp is almost never a local effect but involves the whole-body system, such as somatic and emotional (**15).**

Aetiology

The aetiology of the cramp depends on the situation in which it occurs. It is not possible to draw up the causes, and the possible physiological or pathological differences in which the cramp occurs must be highlighted, as different scenarios give rise to cramps. Heat-associated muscle cramping is often seen during sports and rigorous exercise or physical activity. In this situation, large losses of sweat and electrolytes are believed to be the underlying pathologic mechanism (**16).**

Cramps have always existed in human history. The literature does not report the exact moment in which the first cramp phenomenon is described in medicine, distinguishing it from a benign event with respect to a symptomatologicl event (**17).**

For a patient examination, in addition to the medical history, the patient's posture must be observed, both in an upright position and during walking. It is necessary to understand if muscular imbalances are present. The muscles must be palpated to make sure that the tissue is homogeneous on both body sides (**Hu et al., 2022).**

The patient is asked to stimulate the muscle area where cramps usually appear (voluntary contraction) for the practitioner to understand whether repeated mechanical active stress causes the cramp. It should also carry out a passive stretching of the muscle to verify if the cramp appears in the absence of active stress by the patient. A cramp caused by a passive stretch could be related to a symptom and not to a benign event. Several pathological conditions present with muscle cramps.(**18)**

Muscle cramps in this patient population are a usual and high event (88%). With an electromyogram, the activation of involuntary potential action of the motor units was rather high, over 150 Hz. The behaviour of

the peripheral nervous system is not connected to nerve degeneration. The cause that supports the presence of cramps remains inconclusive. The presence of cramps varies depending on the muscle area: cervical (9%), thigh (43%), calf (70%), toe (50%), abdominal muscles (12%), and fingers (74%). More areas of the body can be affected. No direct relationship is established between age or specific causes that lead to cirrhosis (alcohol, infection, etc.). No connectable cause or specific treatments are known to avoid the onset of cramps in patients with cirrhosis (**19).**

Relation between Vitamin D deficiency in Cirrhotic Patients with Muscle Cramps

The association of muscle cramps with cirrhosis was first reported by Konikoff and Theodor in 1986 when they made their observation of repeated painful muscle cramps by patients with cirrhosis. They proposed that the strikingly high incidence and uniformity of the phenomenon may justify the inclusion of painful muscle cramps among the recognized symptoms of cirrhosis. Subsequently, several studies have confirmed that muscle cramps are a common symptom of cirrhosis (**19).**

Patients experiencing muscle cramps often describe them as sudden, uncomfortable squeezing or contraction of a muscle, lasting seconds to minutes. An electromyogram of a cramping muscle reveals involuntary repetitive firing of motor unit action potentials at high rates (up to 150 per second) producing a sustained muscle contraction. These cramps are not associated with any progressive motor neuron disease or chronic neuromuscular disability and are different from muscle contracture, dystonia, and tetany. The prevalence is varied and ranges from 29% to 88% depending on the inclusion criteria used by the investigators (**21).**

The exact mechanism behind the occurrence of muscle cramps remains elusive. Potential primary hypotheses include neurologic, muscular, endocrine, or electrolyte imbalance. Diuretic use in cirrhotic patients also has been implicated as a cause of muscle cramps through its effects on serum electrolyte balance and plasma volume (**19).**

However, Abrams et al found that patients with congestive heart failure had a lower prevalence of cramps compared with patients with cirrhosis despite higher diuretic use, suggesting that diuretic use may not be the primary precipitating factor for muscle cramps. A subsequent study by Angeli et al also reported that cramps were associated with cirrhosis irrespective of its cause, diuretic consumption, serum electrolyte alterations, or differences in Child's classification. However, additional analysis in their cohort for pathophysiologic associations revealed that the presence of ascites, lower mean arterial pressure, and higher plasma renin activity were independent predictive factors for the occurrence of cramps (**20).**

Although muscle cramps are benign in nature, their occurrence is associated with bodily pain and decreased physical and social functioning. General health-related quality of life, measured by instruments such as the Medical Outcome Study Short Form-36 and the Nottingham Health Profile questionnaires, is diminished in cirrhotic patients with cramps. However, the Chronic Liver Disease Questionnaire (CLDQ) is a more sensitive and specific instrument to assess quality of life in patients with liver disease, but the effect of muscle cramps on the quality of life as measured by the CLDQ is not known (**20).**

Patients with certain medical conditions, such as hyper-parathyroidism and vitamin D insufficiency after bariatric surgery, also report muscle cramps. Several recent studies have established that vitamin D deficiency is common in patients with cirrhosis and is associated with muscle pain. It would thus be of interest to investigate the relationship between vitamin D levels and muscle cramps in patients with cirrhosis (**21).**

Patients with cirrhosis often report muscle cramps with varied frequency and severity. Because of the intermittent nature of the symptoms, lack of objective findings, and inability to measure an individuals' predisposition to muscle cramping by means of any diagnostic tool, these symptoms are often dismissed. The current study highlights the high prevalence (67%) of muscle cramps in cirrhotic patients and describes in detail various characteristics, such as location (lower extremities > upper extremities), duration (lasting several minutes in up to 65%), severity of associated pain (63% had > 3 on a 0–5 scale), and prevalence of clinically significant cramps (49% had CSS > 12). Muscle cramps from hypokalaemia are a known side effect of furosemide (**21).**

Muscle cramps, although nonlethal, have a significant impact on health-related quality of life. The current study shows that the cirrhotic patients with muscle cramps and hepatic encephalopathy had significantly lower health-related quality of life. A unique finding in the current study is the effect of muscle cramps on

health-related quality of life that is significant, impressive, and independent from the effect of hepatic encephalopathy. The lower CLDQ score in patients with hepatic encephalopathy is consistent with a recently published clinical trial. Another novel finding in the current study is the significant negative correlation between the CLDQ and the CSS, that is, higher CSS (product of frequency of cramps/week and severity of pain) is associated with lower CLDQ score. This finding may allow us to use the CSS as an additional outcome measure in clinical trials designed to measure the effectiveness of any therapy for muscle cramps (**21).**

The treatment of muscle cramps still remains rather empirical. Quinine sulphate was the most widely used agent for relief of muscle cramps, but it has fallen out of Favor because of the Food and Drug Administration warning prohibiting the off-label use of quinine in light of its potential cardiotoxicity. Some hepatologists often, for lack of a better therapy, resort to infusion of albumin on the basis of a single pilot study in which 9 of 12 patients had improvement in muscle cramps after albumin infusions. Prior neurophysiologic studies have shown that cramps arise from spontaneous discharges of motor nerves rather than from within the muscle itself (**21).**

It was speculated that decreased intravascular volume associated with hypoalbuminemia in liver disease results in increased muscle membrane hyper-excitability by lowering the "threshold frequency" required for the induction of a muscle cramp. In the current study, cirrhotic patients with cramps had significantly lower serum albumin levels, although the magnitude of difference (3.1 ± 0.6 g/dL vs 3.3 ± 0.7 g/dL) does not seem to be clinically significant. However, multivariable analysis failed to show that albumin levels were predictive of muscle cramps. Muscle cramps can be experimentally induced by repetitive electrical stimulation of peripheral nerves, and the minimum electrical stimulation frequency (Hz) at which a muscle cramps is termed "threshold frequency." (**21).**

Prior studies suggest that threshold frequency is generally indicative of an individual's predisposition to muscle cramping. Because of the lack of an effective therapy and high placebo response rates, there is confusion with regard to optimal therapy. The novel use of threshold frequency as a tool to quantitatively measure the response to various therapeutic interventions for muscle cramps is thus highly desirable (**21).**

References

1. Ginès P, Krag A, Abraldes JG, et al,)2021(. Liver cirrhosis. Lancet. Oct 9;398(10308):1359-1376. doi: 10.1016/S0140-6736(21)01374-X.
2. Irvine, K. M., Ratnasekera, I., Powell, E. E., & Hume, D. A. (2019). Causes and consequences of innate immune dysfunction in cirrhosis. Frontiers in immunology, 10, 293.
3. Loomba, R., Wong, R., Fraysse, J., Shreay, S., Li, S., Harrison, S., & Gordon, S. C. (2020). Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. Alimentary pharmacology & therapeutics, 51(11), 1149-1159.
4. Moon, A. M., Singal, A. G., & Tapper, E. B. (2020). Contemporary epidemiology of chronic liver disease and cirrhosis. Clinical Gastroenterology and Hepatology, 18(12), 2650-2666.
5. Wolf, E., Rich, N. E., Marrero, J. A., Parikh, N. D., & Singal, A. G. (2021). Use of hepatocellular carcinoma surveillance in patients with cirrhosis: a systematic review and meta-analysis. Hepatology, 73(2), 713-725.
6. Tapper, E. B., & Parikh, N. D. (2018). Mortality due to cirrhosis and liver cancer in the United States,

1999-2016: observational study. bmj, 362.

7. Okubo T, Atsukawa M, Tsubota A, Ono H, Kawano T, Yoshida Y, Arai T, Hayama K, Itokawa N, Kondo C, Kaneko K, Iwakiri K. Effect of Vitamin D Supplementation on Skeletal Muscle Volume and Strength in Patients with Decompensated Liver Cirrhosis Undergoing Branched Chain Amino Acids Supplementation: A Prospective, Randomized, Controlled Pilot Trial. Nutrients. 2021 May 30;13(6):1874. doi: 10.3390/nu13061874. PMID: 34070910; PMCID: PMC8228227.
8. Tae Hyung Kim , Seung Gyu Yun , Jimi Choi et al, (2020). Differential Impact of Serum 25-Hydroxyvitamin D3 Levels on the Prognosis of Patients with Liver Cirrhosis According to MELD and Child-Pugh Scores J Korean Med Sci. 18;35(19):e129.
9. Weiker, M. K., Nielsen, B., Waclawik, A. J., Staples, A. C., & Hansen, K. E. (2017). Muscle cramps do not improve with correction of Vitamin D insufficiency. WMJ: official publication of the State Medical Society of Wisconsin, 116(5), 200.
10. Malham, M., Jørgensen, S. P., Ott, P., Agnholt, J., Vilstrup, H., Borre, M., & Dahlerup, J. F. (2011). Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. World journal of gastroenterology: WJG, 17(7), 922.
11. Ceglia L., Morais M.D.S., Park L.K., Morris E., Harris S.S., Bischoff-Ferrari H.A., Fielding R.A., Dawson-Hughes B. Multi-step immunofluorescent analysis of vitamin D receptor loci and myosin heavy chain isoforms in human skeletal muscle. J. Mol. Histol. 2010;41:137–142. doi: 10.1007/s10735-010-9270-x.
12. Musso, C. G., Juarez, R., & Glassock, R. J. (2018). Water, electrolyte, acid–base, and trace elements alterations in cirrhotic patients. International Urology and Nephrology, 50(1), 81–89.
13. Attar, B. (2019). Approach to Hyponatremia in Cirrhosis. Clinical Liver Disease, 13(4), 98–101.
14. Abd-Elsalam, S., Ebrahim, S., Soliman, S., Alkhalawany, W., Elfert, A., Hawash, N., ... & Badawi, R. (2020). Orphenadrine in treatment of muscle cramps in cirrhotic patients: a randomized study. European journal of gastroenterology & hepatology, 32(8), 1042-1045.
15. Hu, H., Wang, C., Liang, K., He, Q., Song, J., Guo, X., ... & Yan, F. (2022). Relationship Between Muscle Cramps and Diabetic Retinopathy in Patients with Type 2 Diabetes. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, 827-837.
16. Iwasa M, Karino Y, Kawaguchi T, et al,) 2018(. Relationship of muscle cramps to quality of life and sleep disturbance in patients with chronic liver diseases: A nationwide study. Liver Int. ;38(12):2309-2316.
17. Kalia, S., Nath, P., Pathak, M., & Anand, A. C. (2022). Treatment of Muscle Cramps in Patients With Cirrhosis of Liver: A Systematic Review. Journal of Clinical and Experimental Hepatology, 12(3), 980-992.
18. Kanda, Tatsuo, Reina Sasaki-Tanaka, Naoki Matsumoto, Shuhei Arima, Shini Kanezawa, Masayuki Honda, Mai Totsuka, Tomotaka Ishii, Ryota Masuzaki, Masahiro Ogawa, and et al. 2023. "Muscle Cramps in Outpatients with Liver Diseases in Tokyo, Japan" Medicina 59, no. 9: 1506.
19. Katalin, K. E., & Carmen, C. A. O. (2021). Treatment Possibilities of Muscle Cramps in Patients with Liver Cirrhosis. Internal Medicine, 18(6), 35–52.
20. Vidot H, Carey S, Allman-Farinelli M, Shackel N. (2014). Systematic review: the treatment of muscle cramps in patients with cirrhosis. Aliment Pharmacol Ther. Aug;40(3):221-32. doi: 10.1111/apt.12827. Epub 2014 Jun 18. PMID: 24942957
21. Weiker, M. K., Nielsen, B., Waclawik, A. J., Staples, A. C., & Hansen, K. E. (2017). Muscle cramps do

not improve with correction of Vitamin D insufficiency. WMJ: official publication of the State Medical Society of Wisconsin, 116(5), 200.