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Original Article

Role of Serum Electrolytes and Serum Vitamin D in Cirrhotic Patients with Muscle Cramps

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ABSTRACT

Background: Skeletal muscle cramps (MCs) are observed in around 29–88 % of patients who have liver cirrhosis (LC). They commonly result in sleep disturbance and considerably affect quality of life (QoL). This study aimed to evaluate the validity of measuring serum electrolytes (Na, K, Ca, Mg, and P) and vitamin D among cirrhotic patients who had skeletal muscle cramps.

methods: We performed this case-control study on 72 patients with LC who were allocated into 2 groups: group A (case group of LC patients with skeletal MCs) and group B (control group of LC patients without skeletal MCs). Detailed history taking was collected from all patients; they underwent full clinical examination, pelviabdominal ultrasonography (US), and hematological and biochemical investigations, including measurement of serum electrolytes (Na, K, Ca, Mg, and P) and vitamin D.

Results: Serum calcium and vitamin D levels were significantly less among group A than in group B (8.17 ± 0.53 mg/dL versus 8.48 ± 0.57 mg/dL; P=0.017 and 8.1ng/mL vs 18.45ng/mL; P <0.001 respectively). The best cutoff of serum vitamin D in the prediction of MCs among cases with LC is ≤ 12.6 ng/mL with the area under curve 0.87, sensitivity of 88.9 %, specificity of 77.8 %, positive predictive value of 80 %, negative predictive value of 87.5 % and overall accuracy 83.3 %; p < 0.001. Serum calcium (with Confidence interval (CI) of 0.070-0.898 and adjusted odds ratio (AOR) of 0.252) and vitamin D (with CI of 0.648-0.865 and AOR of 0.749) were the only two independent risk factors of muscle cramps.

Conclusions: The study findings suggested a substantial relationship between serum calcium and serum vitamin D and MCs in cirrhotic patients. No remarkable relationship was revealed between serum sodium, potassium, magnesium, and phosphorus with MCs in cirrhotic patients.

Keywords: Liver cirrhosis; skeletal muscle cramps; serum vitamin D.

INTRODUCTION

Chronic inflammation eventually gives way to fibrotic tissue and regenerative nodules, which in turn cause portal hypertension and ultimately lead to liver cirrhosis. In its early phase, liver cirrhosis is asymptomatic (compensated cirrhosis), while in its later phase, the disease is symptomatic (decompensated cirrhosis). Decompensated cirrhosis is a leading cause of hospitalization, poor quality of life, and death due to its complications [1].

Rest and sleep can bring on painful tonic contractions of the skeletal muscles, a condition known as muscle cramps. Painful involuntary skeletal muscle contractions may be separated into true cramps, contracture, tetany, or dystonia based on their signs and symptoms. A large percentage of cirrhotic patients experience muscle cramps. Research that followed found that hepatic encephalopathy, which includes muscle cramping, negatively impacts the health-related quality of life (QoL) of cirrhotic liver patients [2].

Electrolyte disturbances in patients with liver cirrhosis could play a crucial role in the pathogenesis of muscle cramps in those patients. Nevertheless, the specific process via which muscular cramps manifest remains a mystery. Therefore, there is no widely agreed-upon prescription regarding the optimal supplementation or medication (or combination of the two) for the treatment of this ailment, making its management a challenge [3]. Electrolyte disturbances in patients with liver cirrhosis are profound and not easily correctable and are linked to disease severity and progression. Hyponatremia (serum Na < 130 mmol/L) is the most common disturbance that occurred in electrolytes among patients who had advanced liver cirrhosis (22 %) and could predict a poor prognosis [4]. Furthermore, cirrhotic patients often have low serum potassium levels due to factors such as malnutrition, enteric potassium losses (diarrhea), magnesium deficiency, renal tubular acidosis, and the use of loop diuretics [5]. Aside from low serum calcium, phosphorus, and magnesium levels, the most common trivalent ion changes seen in cirrhotic individuals are other disturbances of the electrolytes [6].

Vitamin D is an important chemical for maintaining healthy muscle and bone metabolism. It also regulates the immune system as an anti-inflammatory and reduces the likelihood of tumor development in several organs. Serum vitamin D levels in cirrhotic livers are linked to the severity, course, and outcome of the disease [7].

This study aimed to estimate the relationship between serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus) and vitamin D and muscle cramps in patients suffering from liver cirrhosis.

methods

We performed this case-control study on 72 patients with liver cirrhosis in Tropical medicine and clinical pathology departments affiliated with the faculty of medicine of Zagazig University. Ethical consideration: approval for the study was obtained from the Zagazig University Institutional Review Board (ZU-IRB) (approval number 10809 on 31/5/2023). Patient recruitment started in August 2023 and ended in February 2024. In compliance with the principles outlined in the Declaration of Helsinki, all participants in this study were required to provide written informed consent before any use of their samples or clinical data could be made and this publication could be published. Epi Info 6 (Atlanta, GA, USA) was used to determine the sample size. If the mean ± SD for 25-hydroxycholecalciferol is 21±3 versus 19±3 in the no cramps versus cramps group, at 80% power and 95% CI, the estimated sample size will be 72 patients, 36 patients in each group [7].

Liver cirrhosis was diagnosed based on a combination of pelviabdominal ultrasonography clinical and laboratory data of patients. Subjects were categorized into 2 groups: group A (case group) of 36 patients with liver cirrhosis with skeletal muscle cramps, and Group B (control group) of 36 patients with liver cirrhosis without skeletal muscle cramps.

Exclusion criteria included patients who refused to give informed consent to participate in this study, patients unable to take the muscle cramp questionnaire, non-cirrhotic patients, patients with renal impairment, patients with parathyroid or other endocrinal dysfunctions that can affect serum electrolytes levels, malignant patients, including those with HCC, and cirrhotic pregnant females.

Thorough clinical examinations, including taking complete medical histories, were administered to all study participants, and pelviabdominal ultrasonography with special attention to manifestations and complications of liver cirrhosis. Patients also underwent evaluation of the frequency, distribution, and intensity of their muscle cramps according to the muscle cramp questionnaire by Chatrath et al. [7] (**Figure 1**).

Blood samples were withdrawn from all patients under strict aseptic circumstances. Five mL of venous blood was taken from each patient. A complete blood count (CBC) was performed using 1 mL of sample in a sterile EDTA vacutainer tube, liver and kidney function tests (LFT and KFT, respectively), Prothrombin time (PT) and International normalized ratio (INR), serum electrolytes, and vitamin D were measured using 2 mL of sample in a sterile plain vacutainer vial.

The Japanese company Sysmex Corporation's automated cell counter, "Sysmex XS," was used to conduct the CBC. The automated analyzer "Roche Cobas 8000-c702" (Roche Diagnostics, Germany) was used to measure phosphorus, calcium, and magnesium in the blood. In contrast, the Sensa Core ST-200 Plus Electrolyte Analyzer (Sensa Core, India) was used to measure sodium and potassium in the blood. PT and INR were measured by the Sysmex CS 2100 coagulometer (Sysmex Corporation, Japan).

Serum vitamin D was measured by an electrochemiluminescence binding test, which could

quantify a total of 25-hydroxycholecalciferol levels in human serum. Vitamin D values were measured utilizing the automated analyzer "Roche Cobas 6000-e 601" (Roche Diagnostics, Germany) following the manufacturer's instructions. Vitamin D was considered deficient when levels were ≤ 20 ng/mL and vitamin D insufficiency when levels were in the range of 21-29 ng/ml [8]. All patients were subjected to Child-Pugh scoring to assess the degree of liver cirrhosis [9].

STATISTICAL ANALYSIS

The statistical package SPSS (IBM SPSS, Version 26.0. Armonk, NY, USA) was used to analyze the collection of data. We used the chi-square test and, when applicable, the Fisher exact test to compare categorical variables, which were reported as frequencies. To ensure that the assumptions of parametric tests were correct, the Shapiro-Wilk test was used. According to the type of data, quantitative variables were presented as median and interquartile range or as means and standard deviations. A Mann-Whitney U test (for data that does not follow a normal distribution) and an independent sample t-test (for data that does) were used to compare the two sets of quantitative data. In order to determine the specific risk factors associated with muscular cramps in the study population, binary logistic regression was employed.

RESULTS

Table 1 compares both groups in terms of demographic, clinical, and sonographic data of studied patients. It shows non-statistically significant differences between both groups as regards these data except for gender. Female patients suffer from cramps more frequently than male patients; females made up 72.2% in group A vs. 50% in group B (P=0.05).

Table 2 shows a comparison between both groups as regards hematological and biochemical data. It revealed that serum calcium and vitamin D levels were significantly less among group A than in group B (8.17 ± 0.53 mg/dL versus 8.48 ± 0.57 mg/dL; P=0.017 and 8.1ng/mL vs 18.45ng/mL; P <0.001 respectively). The best cutoff of serum vitamin D in the prediction of MCs among cases with LC is ≤ 12.6 ng/mL with the area under curve 0.87, sensitivity of 88.9 %, specificity of 77.8 %, positive predictive value of 80 %, negative predictive value of 87.5 % and overall accuracy 83.3 %; p < 0.001.

Table 3 summarizes the frequency, severity, duration, and distribution of muscle cramps experienced by patients in group A. **Table 4** showed that vitamin D deficiency was more prevalent among patients in group A than in group B (100 % vs 69.4 %; p < 0.001).

Multivariate analysis of independent factors most associated with muscle cramps showed that serum calcium (with Confidence interval (CI) of 0.070-0.898 and adjusted odds ratio (AOR) of 0.252) and vitamin D (with CI of 0.648-0.865 and AOR of 0.749) were the only two independent risk factors of muscle cramps with p values of 0.034 and 0.001 respectively (**Table 5**)

Table (1): Comparison between the studied groups regrading demographic, clinical, sonographic data and Child score:

	Case group	**Control group**	**t**	**p**
	Mean±SD	**Mean**±SD		
Age (year)	61.78 ± 16.58	59.97 ± 12.48	0.522	0.603
	N=36 (%)	**N=36 (%)**	χ^2	p
Sex: **Female** **Male**	 18 (50%) 18 (50%)	 10 (27.8%) 26 (72.2%)	3.74	0.05*
Hematemesis/melena	12 (33.3%)	16 (44.4%)	0.935	0.334
Abdominal tenderness	21 (58.3%)	18 (44.4%)	0.503	0.478
Ascites				
No	8 (22.2%)	8 (22.2%)	2.576	0.109
Mild	2(5.55%)	15(44.44%)		
Moderate	12(33.3%)	2(5.55%)		
Tense	14(38.8%)	11(27.7%)		
Lower limb edema	26 (72.2%)	18 (50%)	3.74	0.053
Jaundice	2 (5.6%)	2 (5.6%)	0	>0.999

	Case group	Control group	t	p
Anorexia	18(50%)	22(61%)	0.9	0.343
constipation	8(22.22%)	6(16.66%)	0.355	0.551
diarrhea	12(33.33%)	16(44.4%)	0.935	0.334
Fever	14(38.8%)	16(44.4%)	0.229	0.633
Urinary tract infection	2(5.55%)	2(5.55%)	0	>0.999
Chest infection	10(27.7%)	10(27.7%)	0	>0.999
Liver condition: **Cirrhotic** **Coarse**	 36 (100%) 0 (0%)	 34 (94.4%) 2 (5.6%)	 Fisher	 0.493
Ascites **No** **Mild** **Moderate** **Marked**	 8 (22.2%) 2 (5.6%) 12 (33.3%) 14 (38.9%)	 8 (22.2%) 15 (41.7%) 2 (5.6%) 11 (30.6%)	 2.575	 0.109
Spleen **Average** **Enlarged**	 2 (5.6%) 34 (94.4%)	 2 (5.6%) 34 (94.4%)	 0¥	 >0.999
Grade A B C	 2(5.55%) 16(44.4%) 18(50%)	 2(5.55%) 18(50%) 16(44.4%)	 0.155	 0.694
	Mean ± SD	**Mean ± SD**	t	p
Spleen diameter (cm)	16.47 ± 2.23	16.0 ± 2.12	0.914	0.364

χ^2 Chi square test t independent sample t test ¥Chi square for trend test

Table (2): Comparison between the studied groups regarding haematological, liver and kidney functions, electrolytes and Vitamin D data**:**

	Case group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
Haemoglobin (g/dl)	10.08 ± 2.55	9.98 ± 1.52	0.213	0.832
PT (Sec)	13.47 ± 2.26	13.0 ± 1.65	1.005	0.318
INR	1.27 ± 0.22	1.21 ± 0.19	1.166	0.247
Total protein (g/dl)	6.21 ± 0.82	6.15 ± 0.69	0.34	0.735
Serum albumin (g/dl)	2.79 ± 0.49	2.84 ± 0.53	-0.373	0.71
Sodium (mmol/L)	133.17 ± 4.91	135.11 ± 4.18	-1.808	0.075
Potassium (mmol/L)	3.79 ± 0.56	3.8 ± 0.38	-0.148	0.883
Magnesium (mg/dl)	2.14 ± 0.37	2.02 ± 0.09	1.892	0.066
Calcium (mg/dl)	8.17 ± 0.53	8.48 ± 0.57	-2.451	0.017*
Phosphorus(mg/dl)	2.65 ± 0.45	2.74 ± 0.61	-0.735	0.465
	Median (IQR)	**Median (IQR)**	**Z**	**p**
WBC (10^3/mm^3)	4.15(3.5 – 5.6)	5.05(3.5 – 6.3)	-0.824	0.41
Platelet count (10^3/mm^3)	80(60 – 129)	73(60 – 151.25)	-0.225	0.822
Total bilirubin (mg/dl)	1.4(0.9 – 2.98)	1.2(0.9 – 2.1)	-1.016	0.31
Direct bilirubin (mg/dl)	0.7(0.4 – 2)	0.8(0.4 – 1.28)	-0.914	0.361
ALT(IU/L)	19(14 – 28.25)	20(14.25 – 46)	-0.744	0.457
AST(IU/L)	31.5(25 – 50)	47(25 – 55)	-0.293	0.769
Creatinine (mg/dl)	0.83(0.7 – 1)	0.83(0.6 – 1.15)	-0.209	0.835
BUN (mg/dl)	16.3(12.2 – 22)	12.2(11.5 – 18.3)	-1.635	0.102
Vitamin D (ng/ml)	8.1(4.6 – 12.1)	18.45(12.8 – 26.2)	-5.397	<0.001**
Deficiency Insufficiency	36 (100%) 0 (0%)	25 (69.4%) 11 (30.6%)	Fisher ¥	<0.001**

t independent sample t test Z Mann Whitney test IQR interquartile range ¥Chi square test

Table (3): Clinical evaluation of muscle cramps among group A based on skeletal muscle cramps questionnaire

Muscle cramps	Number=36 (100 %)
Frequency	
1-2 times	16(44.44%)
3-5 times	10(27.77%)
>5times	10(27.77%)
Severity	
-Mild	14(38.88%)
-Moderate	10(27.77%)
-Severe	12(33.33%)
Duration	
1-2 Mins	16(44.44%)
2-3 Mins	12(33.33%)
3-5 Mins	8(22.22%)
Distribution	
-abdomen	6(16.66%)
- upper limp	12(33.33%)
-lower limp	18(50%)

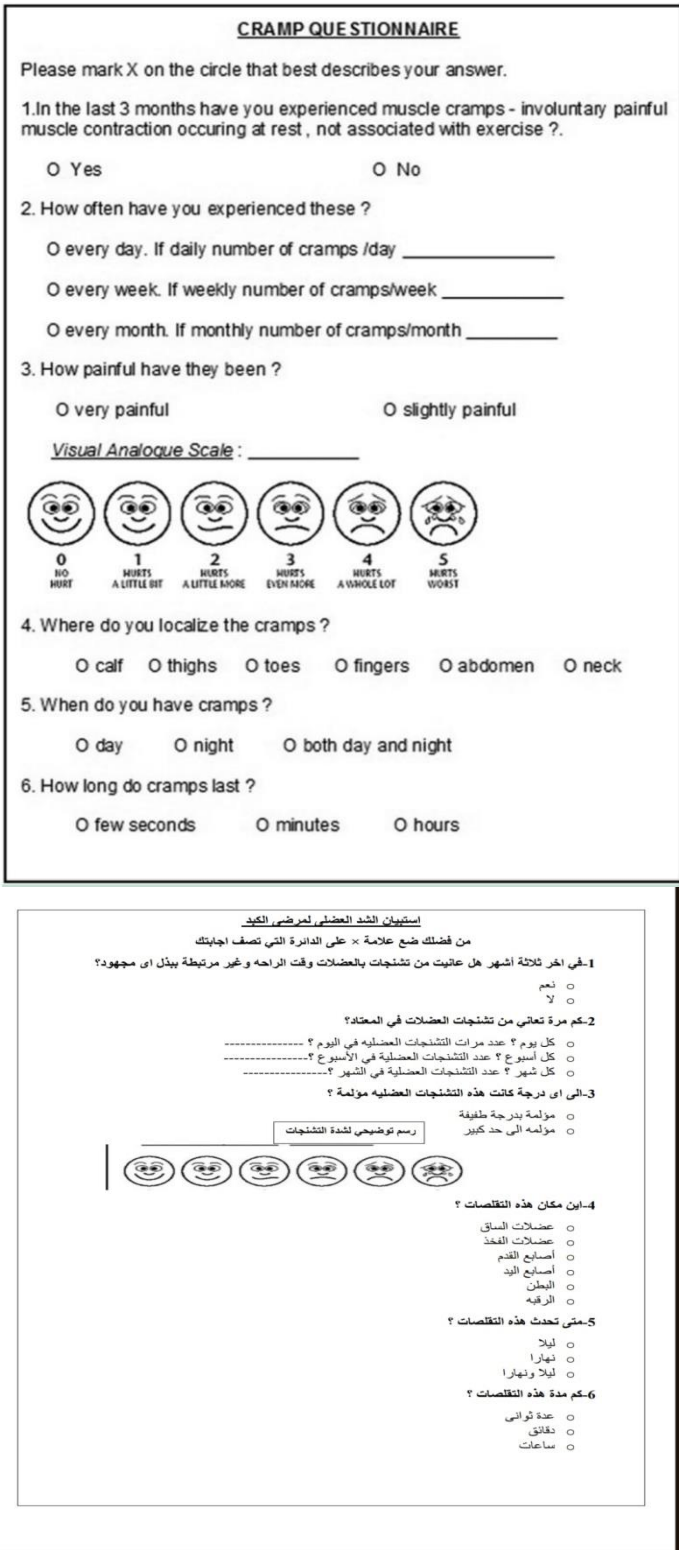
Table (4): comparison between studied groups as regards diuretics use

	Group A N=36 (%)	Group B N=36 (%)	χ^2	p
Loop diuretics dose				
no	9(25%)	10(27.7%)		
1 tab	11(30.6%)	10(27.7%)		
2tabs	14(38.8%)	13(36.1%)	0	>0.999
3tabs	2(5.5%)	3(8.3%)		
4tabs	0 (0%)	0 (0%)		
Spironolactone dose				
no	8(22.2%)	8(22.2%)		
1 tab	12(33.3%)	12(33.3%)	0.017	0.895
2tabs	14(38.8%)	13(36.1%)		
3tabs	2(5.5%)	3(8.3%)		
4tabs	0	0		

Table (5): Multivariate regression analysis of factors associated with muscle cramps among studied patients**.**

	B	P	AOR	95% C.I.	
				Lower	Upper
Calcium (mg/dl)	-1.380	0.034*	0.252	0.070	0.898
Vitamin D (ng/ml)	-0.289	0.001**	0.749	0.648	0.865

*p<0.05 is statistically significant **p≤0.001 is statistically highly significant AOR adjusted odds ratio CI Confidence interval



CRAMP QUESTIONNAIRE

Please mark X on the circle that best describes your answer.

1.In the last 3 months have you experienced muscle cramps - involuntary painful muscle contraction occuring at rest , not associated with exercise ?.

O Yes O No

2. How often have you experienced these ?

O every day. If daily number of cramps /day _____

O every week. If weekly number of cramps/week _____

O every month. If monthly number of cramps/month _____

3. How painful have they been ?

O very painful O slightly painful

Visual Analogue Scale : _____

4. Where do you localize the cramps ?

O calf O thighs O toes O fingers O abdomen O neck

5. When do you have cramps ?

O day O night O both day and night

6. How long do cramps last ?

O few seconds O minutes O hours

استبيان الشد العضلي لمرضى الكبد

من فضلك ضع علامة × على الدائرة التي تصف اجابتك

1-في اخر ثلاثة أشهر هل عانيت من تشنجات بالعضلات وقت الراحه وغير مرتبطة ببذل اى مجهود؟

○ نعم
○ لا

2-كم مرة تعاني من تشنجات العضلات في المعتاد؟

○ كل يوم ؟ عدد مرات التشنجات العضليه في اليوم ؟ ----------
○ كل أسبوع ؟ عدد التشنجات العضلية في الأسبوع ؟----------
○ كل شهر ؟ عدد التشنجات العضلية في الشهر ؟----------

3-الى اى درجة كانت هذه التشنجات العضليه مؤلمة ؟

○ مؤلمة بدرجة طفيفة
○ مؤلمه الى حد كبير

رسم توضيحي لشدة التشنجات

4-اين مكان هذه التقلصات ؟

○ عضلات الساق
○ عضلات الفخذ
○ أصابع القدم
○ أصابع اليد
○ البطن
○ الرقبه

5-متى تحدث هذه التقلصات ؟

○ ليلا
○ نهارا
○ ليلا ونهارا

6-كم مدة هذه التقلصات ؟

○ عدة ثوانى
○ دقائق
○ ساعات

Figure 1: Cramp questionnaire to capture description of muscle cramps [7]

DISCUSSION

Cirrhosis of the liver is associated with frequent, sometimes debilitating muscle cramps that might lower patients' QoL. Several things appear to be contributing to the cramps. This study aims to assess the correlation between vitamin D levels, serum electrolytes, and muscle cramps in individuals with cirrhosis [6].

As regards demographics, no significant difference was found regarding the age of patients. This was

agreed with Chatrath et al. [7], who found that patients with or without cramps were comparable in age (55 versus 57 years). In the present study, females were found to be more likely to develop muscle cramps. This seemed logical because females are more likely to suffer from hypocalcemia than males because of the sex hormonal differences, the less exposure to sunlight that activates vitamin D, and the decreased bone density due to relative deficiency experienced during pregnancy and lactation. This gender difference comes in agreement with Iwasa et al. [2] and Sawada et al. [10], who found that It was found that females with liver disease had a far higher likelihood of developing muscle cramps compared to males, which was a statistically significant difference between the studied groups.

In the present study, no significant differences were revealed regarding any clinical and radiological data of both groups, including presenting symptoms or signs, ultrasonographic findings of liver condition, spleen size, Portal vein, gall bladder findings, presence or grade of ascites. Also, no significant difference was found between both groups as regards Child-Pugh score of patients and drug history of diuretics use. These results were in agreement with Chatrath et al. [7], who found that patients with or without cramps were similar in the presence and grade of ascites and diuretics. The present results also coincide with Vidot et al. [11], who reported that there was no association between the incidence of muscle cramps and ascites and diuretic use.

The present study findings showed non-significant differences between both groups in terms of CBC, LFT, KFT, coagulation profile, serum Na, K, Mg, and P. This finding was in agreement with Okubo et al. [12] and Kanda et al. [13], who revealed nonsignificant differences in the liver function tests between patients with and without muscle cramps. On the contrary, Vidot et al. [11] disagreed with these results as they found that higher total serum bilirubin levels and lower serum albumin levels were associated with muscle cramps. This disagreement may be due to their inclusion of more advanced cirrhotic patients complicated with jaundice and hypoalbuminemia, most of whom were alcoholics. Moreover, Iwasa et al. [2] reported that Muscle cramp patients had significantly lower levels of serum albumin, platelet count, and prothrombin time and significantly higher levels of serum AST compared to patients who had no muscle cramps and this may be due to their inclusion of wide range of patients of different age groups regardless of liver decompensation as 71 % of their patients were child Pugh class A and some patients were HCC patients [2].

In the present study, non-significant differences were revealed between both groups regarding serum sodium and serum potassium. These results agreed with Chatrath et al. [7], who showed that patients with or without cramps were similar in serum sodium and serum potassium. Our results are also in accordance with Sawada et al. [10], who categorized the patients into two groups: those experiencing muscle cramps and those without; serum potassium levels were not significantly different from one another ($P = 0.22$), and sodium levels were not significantly different ($P = 0.90$).

In the present study, no significant difference was found between either group regarding serum magnesium or serum phosphorus. These findings agreed with Weiker et al. [14], who found non statistically significant differences among the studied groups as regards serum magnesium and phosphorus. Baskol et al. [15] found that although serum Mg deficiency is common in cirrhotic patients, it wasn't associated with skeletal muscle cramps. This is due to the fact that skeletal muscle cramps are not attributed to serum Mg but to skeletal muscle Mg deficiency. Serum Mg only represents 1 % of total body Mg versus 20 % inside skeletal muscles. Moreover, Mg deficiency is more common in alcoholic cirrhosis than in viral cirrhosis.

The present study revealed that serum calcium was significantly lower in group A than in group B (8.17 ± 0.53 mg/dL versus 8.48 ± 0.57 mg/dL; P=0.017). This was agreed with Chung et al. [6], who showed that serum calcium decreased significantly among their case group rather than among their control group. On the contrary, Weiker et al. [14] showed a non-significant difference between the studied groups as regards total calcium. Their result might be due to the inclusion of post-menopausal females who were receiving calcium supplementations.

The present showed that vitamin D levels were significantly less among group A than in group B (8.1ng/mL vs 18.45ng/mL; P <0.001). This result agreed with Kim et al. [16], who reported that serum 25-hydroxy vitamin D3 level was a significant risk factor for cirrhotic patients with muscle cramps. They also reported that decreased serum vitamin D increased the frequency and duration of muscle cramps. However, our results were inconsistent with Chatrath et al. [7], who

showed that The inclusion of individuals taking vitamin D supplements may explain why serum vitamin D levels did not differ between those with and without muscular cramps and did not predict the development of muscle cramps.

The current study had some limitations. Firstly, the sample size might be relatively small, with 72 subjects. The results may not apply to a broader population because of this. Secondly, since the study was conducted in a specific hospital, there was a potential for selection bias. The patient population might not fully represent the diversity and characteristics of all individuals with vitamin D deficiency among cirrhotic patients who have skeletal muscle cramps. This could affect the external validity of the study.

Author Contributions

The research idea and the practical work were both chosen by E.G.E. E.G.E, I.M.I, M.M.I. and S.A.A recruited study participants and got them ready to participate. E.M.A. performed methodology, investigations, and analysis of results. A.J. edited the research for publication. The paper was written and reviewed by all authors. All authors approved the final manuscript version.

CONCLUSIONS

This study concludes that vitamin D deficiency is common among patients with liver cirrhosis. This study also found that serum vitamin D level was correlated with the frequency and duration of muscle cramps. Moreover, applying a multivariate regression model revealed that the only independent factors correlated to muscle cramps in cirrhotic patients are serum calcium and serum vitamin D.

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Conflicts of Interest: The authors declare that they have no conflicts of interest.

Data Availability: The data are available upon reasonable request from the corresponding author.

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