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Serum Electrolyte Profiles and Clinical Severity of Recurrent Nocturnal Leg Cramps in Adults: A Frequency-Matched Case-Control Study

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ABSTRACT

Background: Nocturnal leg cramps are muscle contractions that disrupt sleep. Their relationship with biochemical abnormalities remains uncertain. This study compared electrolyte abnormalities in adults with recurrent nocturnal leg cramps and adults without cramps attending a primary healthcare clinic.

Methods: A single-center, frequency-matched case-control study was conducted at Continental Medical College, Lahore, Pakistan, from March 2025 to January 2026. It included 100 adults with recurrent nocturnal leg cramps and 100 controls without nocturnal or resting leg cramps during the preceding six months, frequency matched by sex and 10-year age group. Characteristics, medication exposure, fluid intake, standing duration, and cramp features were recorded. Sodium, potassium, corrected calcium, magnesium, phosphate, creatinine, albumin, and urea were measured. Multivariable logistic regression identified factors associated with cramp status.

Results: At least one electrolyte abnormality was present in 48.0% of cases and 19.0% of controls (odds ratio 3.94, 95% confidence interval 2.08–7.43; $p<0.001$). Hypomagnesemia was most frequent (25.0% vs 7.0%), followed by hypocalcemia (18.0% vs 6.0%) and hypokalemia (15.0% vs 5.0%). Among cases, abnormalities were more frequent across higher cramp-frequency categories and were associated with greater pain, longer episodes, sleep interruption, residual soreness, and fatigue. Any electrolyte abnormality remained associated with nocturnal leg cramps after adjustment (adjusted odds ratio 3.58, 95% confidence interval 1.84–6.98; $p<0.001$). Low fluid intake and prolonged standing were independently associated.

Conclusion: Adults with recurrent nocturnal leg cramps had more electrolyte abnormalities than frequency-matched controls. These findings demonstrate association but do not establish causality, temporality, or benefit from screening or correction.

Keywords: Muscle cramp; electrolytes; hypomagnesemia; hypocalcemia; hypokalemia; primary health care

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INTRODUCTION

Nocturnal leg cramps are sudden, involuntary contractions of the muscles of the lower limb that occur during the night or while the person is asleep and are painful. Most often they affect the calf or foot with the thigh sometimes affected. Episodes typically last for seconds to minutes, and can be associated with ongoing pain or discomfort after the episode [1]. Episodes may happen again and again and disrupt sleep, daily functioning and overall health-related quality of life. Many affected sufferers do not seek diagnosis from healthcare providers, but rather, deal with the symptoms through stretching, massage, walking, hydrating and at-home remedies [2,3].

Nocturnal leg cramps are not well understood. Suggested mechanisms involve peripheral motor-neuron hyperexcitability, neuromuscular control changes, muscle–tendon unit shortening, persistent plantar flexing while sleeping, vascular disorders, metabolic disturbances and exposure to medications [4,5]. Leg cramps have been linked to the use of diuretics, long-acting beta-agonists and certain other drugs that act on fluid or electrolyte balance [6]. Other factors that have been examined are reduced physical activity, prolonged occupational standing, and sustained lower limb muscle loading, which may vary with age, comorbidities, and occupational factors [7].

Electrolytes are essential for the maintenance of resting membrane potential, nerve conduction, excitation–contraction coupling, and skeletal-muscle relaxation. Potassium helps to repolarize membranes, calcium is involved in neuromuscular transmission and muscle contraction, and magnesium affects membrane stability, calcium and potassium transport. Such disturbances of clinically important electrolytes may result in muscle weakness, fasciculations, muscle spasms, tetany, or painful contraction [8]. The occurrence of a nocturnal leg cramp, however, does not in itself indicate an electrolyte deficiency, and a single serum measurement may not necessarily reflect chronic dietary intake, intracellular levels or total body mineral stores.

The clinical relationship between electrolyte abnormalities and recurrent nocturnal leg cramps therefore remains uncertain. There has been little evidence of any empirical magnesium supplementation that is beneficial for those with idiopathic skeletal-muscle cramps who have not been selected for supplementation in systematic reviews [9]. Some evidence of beneficial effects on nocturnal leg-cramp outcomes has been reported with a randomized controlled trial of magnesium oxide monohydrate, but the overall evidence is inconclusive and there is no evidence to support routine mineral supplementation in all patients with cramps [10]. These findings should not be taken as evidence that patients with objectively measured biochemical abnormalities are not a clinically distinct group. Therefore, laboratory proven abnormalities must be distinguished from presumed deficiency if only based on symptoms.

There is still insufficient evidence from Pakistan. Arshad et al studied Pubitiğin young adults in relation to nocturnal leg cramps and found that factors related to their profession and occupational standing were relevant [11]. Farid et al. also investigated nocturnal leg cramping risk factors in a Pakistani population and found that prolonged standing was associated with the occurrence of nocturnal leg cramps [12]. However, these studies primarily evaluated prevalence and clinical or occupational factors and did not comprehensively compare laboratory-measured sodium, potassium, corrected calcium, magnesium, and phosphate profiles between adults with recurrent nocturnal leg cramps and adults without cramps. Consequently, the local relationship between recurrent nocturnal leg cramps and previously unrecognized electrolyte abnormalities remains insufficiently characterized [13].

We hypothesized that adults with recurrent nocturnal leg cramps would have higher odds of at least one previously undiagnosed electrolyte abnormality than adults without nocturnal or resting leg cramps. The primary objective was to compare the occurrence of electrolyte abnormalities between adults with recurrent nocturnal leg cramps and frequency-matched controls. The secondary objectives were to identify the most frequently observed electrolyte abnormalities and evaluate their relationships with cramp frequency, pain intensity, episode duration, sleep interruption, medication exposure, fluid intake, occupational standing, and other relevant clinical characteristics [14].

MATERIALS AND METHODS

A single-center, frequency-matched case-control study was conducted at Continental Medical College, Lahore, Pakistan, from March 2025 to January 2026. Adults with recurrent nocturnal leg cramps constituted the case group, while adults without nocturnal or resting leg cramps constituted the control group. Controls were recruited from the same clinical setting and frequency matched to cases according to sex and 10-year age categories. Matching was performed at the group level rather than by individual pairing.

The sample size was calculated for comparison of two independent proportions, assuming that at least one electrolyte abnormality would be present in 35% of cases and 17% of controls. The following formula was used:

$$n = \frac{\left[Z_{(1-\alpha/2)} \times \sqrt{2\bar{P}(1-\bar{P})} + Z_{(1-\beta)} \times \sqrt{P_1(1-P_1) + P_2(1-P_2)} \right]^2}{(P_1 - P_2)^2}$$

where P1P_1P1 and P2P_2P2 represented the expected proportions among cases and controls, respectively, and P¯=(P1+P2)/2\bar P=(P_1+P_2)/2P¯=(P1 +P2)/2. At a two-sided significance level of 5%, power of 80%, and a 1:1 allocation ratio, approximately 92 participants were required in each group. To allow for refusals, poor quality blood samples, and incomplete measurements, the target was raised to 100 participants per group, leading to 200 participants.

Non-probability sampling technique was adopted, specifically consecutive sampling. Adults aged 18–70 years who attended the study centre were eligible for screening. At least two episodes of nocturnal leg cramps were needed for a case to report them. A nocturnal leg cramp was defined as a sudden, painful, involuntary contraction of the calf, foot or thigh that occurred during sleep or during the night's rest, that was associated with visible or palpable tightening of the muscle, and that was relieved by stretching, ankle dorsiflexion, massage, walking, or spontaneous relaxation. All controls denied nocturnal and resting leg cramps in the 6 months before the study. A total of 100 cases and 100 controls were eligible, with 18 adults excluded and 10 adults refusing venous blood sampling from 228 adults screened.

Participants were excluded if they had previously diagnosed electrolyte disorders, were taking magnesium, calcium, potassium, sodium, or phosphate supplements, had acute vomiting or diarrhea, febrile illness, or had lower-limb trauma in the previous six months or had advanced chronic kidney disease, dialysis dependence, decompensated liver disease, active malignancy, uncontrolled thyroid disease, clinically significant peripheral arterial disease, deep-vein thrombosis, inflammatory myopathy, motor-neuron disease, or major neurological disability. Patients with peripheral neuropathy, vascular claudication, periodic limb-movement disorder and with symptoms suggestive of RLS were also excluded. Mineral or multivitamin use before the study was reported separately if they had previously used them but not during the study.

Data was obtained using a structured interviewer administered questionnaire on sociodemographic characteristics, smoking, physical activity, medical history, medications, daily fluid intake, occupational status and environmental heat exposure. Medications used were diuretics, laxatives, beta-agonists, statins, and proton pump inhibitors. Less than 1.5 litre of fluid per day was considered low, working more than 4 hours per day was long-standing, and less than 150 minutes of moderate activity per week was low physical activity. Exposure to high heat was defined as work outdoors or in poorly-ventilated areas for 4 or more hours per day and 5 or more days per week.

The duration of symptoms, site of the symptom, frequency of the episode in a month, intensity of the pain, residual soreness, sleep interruption, daytime tiredness, suspected triggers, and previous medical consultation, and practices used for symptom-relief were assessed. Pain was assessed on an 11-point numerical rating scale (0-10). Cramp frequency was categorized as low at 2–3 episodes per month, moderate at 4–7 episodes, and high at eight or more episodes. Sleep interruption was defined as awakening or delayed sleep due to cramps on at least two occasions per month.

Weight was measured to the nearest 0.1 kg using a calibrated digital scale, and height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice, five minutes apart, after at least five minutes of seated rest, and the average value was recorded.

A 5-mL venous blood sample was collected between 8:00 and 10:00 a.m. after an 8–10-hour overnight fast and before initiation of mineral supplementation. Samples were allowed to clot and centrifuged at 3,000 rpm for 10 minutes. Serum sodium and potassium were measured by ion-selective electrode, while calcium, magnesium, phosphate, albumin, creatinine, and urea were measured using automated colorimetric methods on a Roche Cobas c311 analyzer. Normal- and abnormal-level quality-control materials were analyzed daily, and laboratory personnel were blinded to participants' group status. Corrected calcium was calculated as:

$$\text{Corrected calcium (mg/dL)} = \text{Total calcium (mg/dL)} + 0.8 \times [4.0 - \text{serum albumin (g/dL)}]$$

Hyponatremia was defined as sodium below 135 mmol/L, hypokalemia as potassium below 3.5 mmol/L, hypocalcemia as corrected calcium below 8.5 mg/dL, hypomagnesemia as magnesium below 1.7 mg/dL, and hypophosphatemia as phosphate below 2.5 mg/dL. A previously undiagnosed electrolyte abnormality was defined as a value outside a prespecified threshold in a participant without a documented electrolyte disorder. "Any electrolyte abnormality" indicated at least one abnormal sodium, potassium, corrected calcium, magnesium, or phosphate result.

The primary outcome was the presence of at least one previously undiagnosed electrolyte abnormality among cases compared with controls. Secondary outcomes included individual electrolyte abnormalities and their relationships with cramp frequency, pain intensity, episode duration, sleep interruption, residual soreness, fatigue, medication exposure, fluid intake, occupational standing, heat exposure, and physical activity.

Data were analyzed using IBM SPSS Statistics version 27. Continuous-variable distributions were assessed using histograms, quantile–quantile plots, and the Shapiro–Wilk test. Normally distributed variables were presented as mean ± standard deviation and compared using the independent-samples t test. Non-normally distributed variables were presented as median and interquartile range and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the chi-square or Fisher's exact test. Odds ratios with 95% confidence intervals were calculated for categorical electrolyte abnormalities.

A chi-square test for trend assessed changes in the frequency of electrolyte abnormalities across cramp-frequency categories. Spearman correlation analyses, restricted to cases, evaluated relationships between electrolyte concentrations, monthly cramp frequency, pain intensity, and episode duration. Unconditional multivariable binary logistic regression was performed with cramp status as the dependent variable. Age and sex were retained because they were frequency-matching variables, while diabetes, diuretic use, proton-pump inhibitor use, low fluid intake, prolonged standing, physical inactivity, and any electrolyte abnormality were included according to clinical relevance and univariable findings. Adjusted odds ratios with 95% confidence intervals were reported. Multicollinearity was assessed using variance inflation factors, model calibration using the Hosmer–Lemeshow test, and explanatory performance using Nagelkerke R2R^2R2. No formal adjustment for multiple comparisons was made for secondary analyses, which were considered exploratory and so should be interpreted with caution. All tests were two tailed and a $p<0.05$ was used as the threshold for significance. We used complete-case analysis, as all the participants in the analysis had complete data.

The study was approved by the Institutional Review Board of Continental Medical College under approval number 76/IRB/CMC and was conducted according to the Declaration of Helsinki. All participants gave written informed consent. Coded identifiers were used to preserve confidentiality and those with clinically important abnormalities were referred for further clinical evaluation.

RESULTS

A total of 200 adults were included, comprising 100 participants with recurrent nocturnal leg cramps and 100 controls without nocturnal or resting leg cramps. Controls were frequency matched to cases by sex and 10-year age categories. Complete clinical and biochemical data were available for all participants.

The mean age was 48.7 ± 11.8 years in the cramp group and 47.9 ± 12.0 years in the control group. The cramp group included 42 men and 58 women, while the control group included 44 men and 56 women. No significant between-group differences were observed in age, sex distribution, body mass index, diabetes mellitus, hypertension, current smoking, or environmental heat exposure. Diuretic use, proton-pump inhibitor use, fluid intake below 1.5 L/day, occupational standing for more than four hours/day, and physical inactivity were significantly more frequent among participants with nocturnal leg cramps (Table 1).

Among participants with nocturnal leg cramps, the median symptom duration was 12 months (IQR, 6–24), and the median cramp frequency was 5 episodes/month (IQR, 3–9). The calf was the most frequently affected site in 74 participants, followed by the foot in 19 and the thigh in 7. Thirty-five participants experienced 2–3 episodes/month, 36 experienced 4–7 episodes/month, and 29 experienced at least 8 episodes/month. The median episode duration was 1.9 minutes (IQR, 1.0–3.0), and the median pain-intensity score was 7 (IQR, 6–8). Sleep interruption was reported by 68 participants, residual muscle soreness by 49, and daytime fatigue by 37.

Twenty-four participants had previously consulted a healthcare professional specifically for their cramps. Stretching was used for symptom relief by 72 participants, massage by 61, walking by 43, and increased fluid intake by 38. Previous unsupervised use of magnesium, calcium, potassium, or multivitamin preparations was reported by 31 participants.

Participants with nocturnal leg cramps had significantly lower mean serum sodium, potassium, corrected calcium, and magnesium concentrations than controls. No significant differences were observed in serum phosphate, creatinine, albumin, or urea. At least one electrolyte abnormality was detected in 48 participants with cramps and 19 controls (48.0% vs 19.0%; OR, 3.94; 95% CI, 2.08–7.43; $p<0.001$).

Hypomagnesemia was the most frequent abnormality and was present in 25 participants with cramps and 7 controls (25.0% vs 7.0%; OR, 4.43; 95% CI, 1.82–10.80; $p<0.001$). Hypocalcemia was present in 18 participants with cramps and 6 controls (18.0% vs 6.0%; OR, 3.44; 95% CI, 1.30–9.07; $p=0.009$), whereas hypokalemia was present in 15 and 5 participants, respectively (15.0% vs 5.0%; OR, 3.35; 95% CI, 1.17–9.62; $p=0.018$). Hyponatremia and hypophosphatemia were more frequent among participants with cramps, but the differences were not statistically significant. Two or more electrolyte abnormalities were detected in 17 participants with cramps and 4 controls (17.0% vs 4.0%; OR, 4.92; 95% CI, 1.59–15.19; $p=0.003$) (Table 2 and Figure 1).

Within the cramp group, at least one electrolyte abnormality was detected in 20 of 42 men (47.6%) and 28 of 58 women (48.3%; $p=0.947$). Among controls, electrolyte abnormalities were detected in 8 of 44 men (18.2%) and 11 of 56 women (19.6%).

The frequency of electrolyte abnormalities increased across the cramp-frequency categories. At least one abnormality was detected in 10 of 35 participants with 2–3 episodes/month (28.6%), 17 of 36 participants with 4–7 episodes/month (47.2%), and 21 of 29 participants with at least 8 episodes/month (72.4%; p for trend <0.001).

Participants with an electrolyte abnormality had a higher median monthly cramp frequency than those with normal electrolyte measurements (7 [IQR, 5–10] vs 4 [IQR, 2–6] episodes/month; $p<0.001$). They also had higher median pain-intensity scores (8 [IQR, 7–9] vs 6 [IQR, 5–8]; $p<0.001$) and longer median episode duration (2.3 [IQR, 1.4–3.5] vs 1.5 [IQR, 0.8–2.5] minutes; $p=0.006$).

Sleep interruption occurred in 39 of 48 participants with an electrolyte abnormality and 29 of 52 participants with normal electrolyte measurements (81.3% vs 55.8%; $p=0.006$). Residual muscle soreness occurred in 30 of 48 and 19 of 52 participants, respectively (62.5% vs 36.5%; $p=0.009$). Daytime fatigue occurred in 23 of 48 and 14 of 52 participants (47.9% vs 26.9%; $p=0.030$), while high-frequency cramps occurred in 21 of 48 and 8 of 52 participants (43.8% vs 15.4%; $p=0.002$).

Correlation analyses were restricted to participants with nocturnal leg cramps. Serum magnesium was inversely correlated with monthly cramp frequency (Spearman $\rho=-0.39$; $p<0.001$) and pain intensity ($\rho=-0.35$; $p<0.001$). Corrected serum calcium was inversely correlated with monthly cramp frequency ($\rho=-0.31$; $p=0.002$) and pain intensity ($\rho=-0.27$; $p=0.007$). Serum potassium was also inversely correlated with monthly cramp frequency ($\rho=-0.28$; $p=0.005$) and pain intensity (ρ=−0.24; p=0.016). Serum sodium and phosphate were not significantly correlated with cramp frequency or pain intensity.

Table 1: Baseline characteristics of participants with and without nocturnal leg cramps

Characteristic	Nocturnal leg cramps, n=100	Controls, n=100	p value
Age, years	48.7 ± 11.8	47.9 ± 12.0	0.635
Sex			0.775
Male	42 (42.0)	44 (44.0)	
Female	58 (58.0)	56 (56.0)	
Body mass index, kg/m²	27.3 ± 4.4	26.5 ± 4.2	0.190
Diabetes mellitus	30 (30.0)	22 (22.0)	0.197
Hypertension	38 (38.0)	29 (29.0)	0.178
Current smoking	18 (18.0)	15 (15.0)	0.568
Diuretic use	22 (22.0)	10 (10.0)	0.021
Proton-pump inhibitor use	19 (19.0)	9 (9.0)	0.042
Fluid intake below 1.5 L/day	44 (44.0)	26 (26.0)	0.008
Standing more than 4 hours/day	41 (41.0)	24 (24.0)	0.010
High environmental heat exposure	34 (34.0)	22 (22.0)	0.059
Physical inactivity	46 (46.0)	32 (32.0)	0.042

Table 2: Serum biochemical measurements and electrolyte abnormalities

Variable	Nocturnal leg cramps, n=100	Controls, n=100	Odds ratio	95% CI	p value
Serum sodium, mmol/L	138.1 ± 3.3	139.0 ± 2.7	—	—	0.036
Serum potassium, mmol/L	3.88 ± 0.46	4.08 ± 0.38	—	—	0.001
Corrected serum calcium, mg/dL	8.82 ± 0.50	9.05 ± 0.42	—	—	<0.001
Serum magnesium, mg/dL	1.77 ± 0.24	1.95 ± 0.21	—	—	<0.001
Serum phosphate, mg/dL	3.34 ± 0.57	3.47 ± 0.50	—	—	0.088
Serum creatinine, mg/dL	0.93 ± 0.24	0.89 ± 0.20	—	—	0.202
Serum albumin, g/dL	4.08 ± 0.33	4.13 ± 0.31	—	—	0.271
Serum urea, mg/dL	28.7 ± 8.2	27.4 ± 7.8	—	—	0.252
Any electrolyte abnormality	48 (48.0)	19 (19.0)	3.94	2.08–7.43	<0.001
Hypomagnesemia	25 (25.0)	7 (7.0)	4.43	1.82–10.80	<0.001
Hypocalcemia	18 (18.0)	6 (6.0)	3.44	1.30–9.07	0.009
Hypokalemia	15 (15.0)	5 (5.0)	3.35	1.17–9.62	0.018
Hyponatremia	8 (8.0)	3 (3.0)	2.81	0.72–10.92	0.121
Hypophosphatemia	9 (9.0)	4 (4.0)	2.37	0.71–7.98	0.152
Two or more abnormalities	17 (17.0)	4 (4.0)	4.92	1.59–15.19	0.003

Table 3: Multivariable logistic-regression analysis of factors associated with nocturnal leg cramps

Variable	Adjusted odds ratio	95% CI	p value
Any electrolyte abnormality	3.58	1.84–6.98	<0.001
Age, per 10-year increase	1.18	0.96–1.44	0.116
Female sex (reference: male)	1.07	0.58–1.98	0.826
Diabetes mellitus	1.29	0.68–2.45	0.438
Diuretic use	2.06	0.94–4.50	0.071
Proton-pump inhibitor use	1.69	0.73–3.91	0.221
Fluid intake below 1.5 L/day	1.88	1.00–3.53	0.049
Standing more than 4 hours/day	2.01	1.07–3.77	0.030
Physical inactivity	1.40	0.74–2.65	0.306

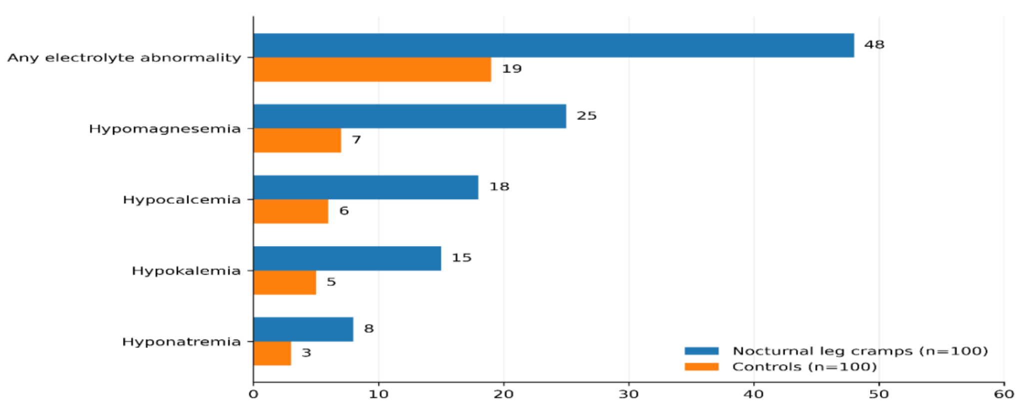

Figure 1: Prevalence of previously undiagnosed electrolyte abnormalities among participants with nocturnal leg cramps and controls

In multivariable logistic-regression analysis, the presence of at least one electrolyte abnormality remained independently associated with nocturnal leg-cramp status after adjustment for age, sex, diabetes mellitus, diuretic use, proton-pump inhibitor use, fluid intake, occupational standing, and physical inactivity (aOR, 3.58; 95% CI, 1.84–6.98; p<0.001). Fluid intake below 1.5 L/day (aOR, 1.88; 95% CI, 1.00–3.53; p=0.049) and occupational standing for more than four hours/day (aOR, 2.01; 95% CI, 1.07–3.77; p=0.030) were also independently associated with nocturnal leg-cramp status.

Age, sex, diabetes mellitus, proton-pump inhibitor use, and physical inactivity were not independently associated with nocturnal leg cramps. Diuretic use showed an increased adjusted odds ratio but did not reach statistical significance (aOR, 2.06; 95% CI, 0.94–4.50; p=0.071). The regression model showed acceptable calibration according to the Hosmer–Lemeshow test (p=0.684), explained 27.6% of the variation in nocturnal leg-cramp status according to Nagelkerke R^2, and correctly classified 71.5% of participants (Table 3).

DISCUSSION

The present study found that electrolyte abnormalities detected at enrollment were substantially more frequent among adults with recurrent nocturnal leg cramps than among frequency-matched controls [1]. At least one abnormality was present in 48.0% of participants with cramps compared with 19.0% of controls, while hypomagnesemia, hypocalcemia, and hypokalemia were the most frequently observed disturbances. The accompanying pain, sleep interruption, residual soreness, and daytime fatigue are consistent with previous descriptions of nocturnal leg cramps as painful, sleep-disrupting episodes with important effects on daily functioning and health-related quality of life [2,3].

Nocturnal leg cramps are a multifactorial phenomenon with changes in motor-neuron excitability, age-related changes in muscle–tendon architecture, extended plantar flexed position, vascular disease, metabolic abnormalities, and medication exposure thought to play a role in the development of cramps [4]. They are important to distinguish clinically from restless legs syndrome, periodic limb movements, peripheral neuropathy, and vascular claudication, as each of these disorders can cause nocturnal symptoms of the lower limbs by different mechanisms. In addition, previous studies have associated nighttime leg cramps with sleep disturbances, cardiometabolic diseases, suboptimal health status, and drugs that can affect fluid or electrolyte levels [5,6].

Occupational standing time was found to be independently associated with nocturnal leg-cramp status in the current analysis. Delacour et al. found that physical-activity patterns and sitting were related to leg cramps in the elderly [7]. Arshad et al. and Farid et al. found that nocturnal leg cramps were prevalent in young adults who were working continuously for several hours, and prolonged standing was an important factor among working adults in Lahore, Pakistan [11,12]. The agreement between these studies suggests that sustained muscle loading, postural fatigue, and limited movement of the lower limbs might be relevant, but observational results cannot necessarily be assumed to have a direct causal relationship [8-10].

Hypomagnesemia had the highest individual correlation with cramp status and a negative correlation with monthly cramp frequency and pain intensity. Magnesium is important for membrane stability, neuromuscular transmission, relaxation of the skeletal muscle, and control of calcium and potassium transport [8]. However, there have been no consistent clinically significant effects seen with empirical magnesium supplementation in unselected adults with idiopathic cramps [9]. Barna et al. found that magnesium oxide monohydrate supplementation was associated with a reduction in cramp frequency, episode duration and sleep-related outcomes, but the different formulations, selection of participants, baseline magnesium status and methods used to assess the outcomes may account for inconsistencies between trials [10]. The current findings thus suggest an association with serum magnesium but do not necessarily demonstrate magnesium-related causation and/or treatment efficacy [11,12].

Additionally, the symptom burden that was seen in the current study was similar to that of previous clinical studies. Hawke et al. reported that calf cramps at night were correlated with poor sleep and decreased physical dimensions of health-related quality of life [13]. Khandalavala et al. found that stretching, massage, walking, hydration, use of magnesium, potassium, and the use of non-prescription preparations were common and that there was significant variation in the perceived effectiveness [14]. Magrogin Maor et al., however, did not conclude that magnesium oxide was more effective than placebo in reducing the frequency, severity, duration of cramps, sleep impairment or effects on quality of life [15]. These are important findings for making the right clinical assessment before mineral supplementation, as patient-reported benefit is not evidence of biochemical deficiency nor of therapeutic efficacy [7].

The regular use of magnesium has also been called into doubt in earlier reviews. No convincing evidence of clinically important benefit was found in the available RCTs in the general population of adults with nocturnal leg cramps, according to Sebo et al. [16]. Rabbitt et al. characterized leg cramps at night in the elderly as a heterogeneous disorder secondary to neuromuscular aging, vascular disease, drug use, metabolic abnormalities, and other clinical variables [17]. Hypocalcemia and hypokalemia were much more frequent in the present study and, in 17% of cases, more than one abnormality was found, suggesting that the mineral/fluid balance abnormality may have been more general than affecting one mineral only. But dietary intake, vitamin D, parathyroid hormone, gastrointestinal losses, urinary electrolyte excretion and acid–base status were not assessed [13,15].

Evidence for routine mineral supplementation is inconsistent and conservative interventions are relevant. Hawke et al. found that joint calf and hamstring stretching seems to have some benefit on severity of cramp, but effects on cramp frequency and other outcomes were still scarce [18]. Hallegraeff and de Greef report that after a structured stretching program, they saw a decrease in cramp frequency and pain in their small pilot study, although the participants were older [19]. Later, Kuusipalo et al. compared compression stockings and magnesium supplementation to placebo and found that compression therapy led to improvement in several cramp outcomes while magnesium did not significantly lower cramp frequency [20]. These studies would indicate that stretching and other conservative treatments are appropriate initial interventions, but that the outcomes of treatment were not evaluated in this study [5].

Strengths of the study include the fact that the cases and controls were recruited in the same clinical setting, that the frequency of cases and controls was matched by age and sex, that the symptoms were standardized, that biochemical concentrations were prespecified, that the blood samples were fasted, and that the laboratory was blinded to the group status [7-11].

However, the single-center case-control design is susceptible to selection bias and cannot determine population prevalence, temporality, or causation. Electrolytes were measured only once, and serum magnesium may not accurately reflect intracellular or total-body magnesium status. Cramp frequency, fluid intake, physical activity, and occupational standing were self-reported, while multiple secondary analyses increased the possibility of chance findings. Nocturnal leg cramps are associated with numerous clinical and behavioral characteristics, and evidence regarding supplementation remains inconsistent; therefore, residual confounding and uncertainty about treatment implications should be recognized [5,8,9].

CONCLUSION

Adults with recurrent nocturnal leg cramps attending a single primary healthcare center had a higher frequency of electrolyte abnormalities than frequency-matched controls. Hypomagnesemia, hypocalcemia, and hypokalemia were the most commonly observed abnormalities. Among participants with cramps, electrolyte abnormalities were associated with greater cramp frequency, higher pain intensity, longer episode duration, sleep interruption, residual muscle soreness, and daytime fatigue. Low fluid intake and prolonged occupational standing were also independently associated with nocturnal leg-cramp status. These findings demonstrate clinical and biochemical associations but do not establish temporality, causation, or treatment effectiveness. Further prospective studies using repeated biochemical measurements and targeted intervention trials are required before routine electrolyte screening or empirical mineral supplementation can be recommended.

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

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