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Electrolyte Imbalance As A Key Contributor To Unexplained Pain In Chronic Kidney Disease Patients Undergoing Haemodialysis: An Observational Study

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Abstract:
Background: Chronic kidney disease (CKD) patients on hemodialysis often experience unexplained pain, potentially exacerbated by electrolyte imbalances. This study aims to investigate the prevalence of pain in this population and its association with mineral levels, particularly phosphorus and calcium.
Methods: An observational study was conducted involving 62 CKD patients undergoing hemodialysis. Demographic data, pain prevalence, location, severity, and frequency were assessed using structured questionnaires. Blood urea, phosphorus, calcium, potassium, and creatinine levels were measured pre- and post-dialysis. Statistical analyses, including chi-square tests, were employed to explore relationships between mineral levels and pain characteristics.
Results: Of the participants, 66.13% reported experiencing pain, predominantly localized in the legs (40.32%) and arms (19.35%). The majority rated their pain as mild (58.53%) and reported it as occasional (87.80%). Notably, 53.23% exhibited elevated phosphorus levels, while 91.93% had low calcium levels. Chi-square analysis demonstrated significant associations between mineral imbalances and pain experiences ($\chi^2 = 167.51$, $p < 0.00001$), highlighting a potential correlation between elevated phosphorus and low calcium levels with reported pain.
Discussion: This study underscores the high prevalence of pain among hemodialysis patients and the critical need for comprehensive pain assessment and management. The observed associations between electrolyte imbalances and pain suggest that careful monitoring of phosphorus and calcium levels may be essential for improving patient outcomes.
Conclusion: Electrolyte imbalances, particularly elevated phosphorus, and low calcium, significantly contribute to pain in CKD patients undergoing hemodialysis. Enhanced monitoring and targeted interventions to address these imbalances are crucial for improving pain management and overall quality of life in this vulnerable population.

Key words: Mineral Imbalance, Chronic Kidney Disease, Pain, Haemodialysis, Phosphorus, Calcium.

Introduction:

Pain serves as a fundamental physiological signal, alerting the body to potential harm and facilitating appropriate responses. The pain signaling system encompasses multiple components that detect unpleasant stimuli, convert them into nerve impulses, and relay these signals along the spinal cord to the brain, where they are interpreted and acted upon [1]. Margo McCaffery's definition of pain as "whatever the experiencing person says it is, existing whenever and wherever the person says it does" emphasizes its subjective nature, a notion supported by the International Association for the Study of Pain (IASP), which characterizes pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage [2].

The nociceptive process is a complex interplay of four critical steps:

1. **Transduction:** Nociceptors, specialized sensory neurons, respond to harmful stimuli by converting them into electrical signals.
2. **Transmission:** These signals are transmitted to the brain via the spinal cord.
3. **Perception:** The brain interprets these signals, manifesting the sensation of pain.
4. **Modulation:** The body can alter the perception of pain by focusing attention on the affected area, influencing the emotional and cognitive aspects of pain [3].

Electrolyte Imbalance in Chronic Kidney Disease (CKD)

Electrolytes are vital for numerous physiological functions, including maintaining cellular electrical neutrality, facilitating action potentials in muscles and nerves, and regulating fluid balance. Key electrolytes—sodium, potassium, chloride, calcium, phosphate, and bicarbonates—are predominantly derived from dietary sources. Dysregulation of electrolyte

levels can lead to severe health consequences, particularly in patients with chronic kidney disease (CKD), where the balance between calcium and phosphate is frequently disrupted. Elevated phosphate levels (hyperphosphatemia) and diminished calcium levels (hypocalcemia) stimulate the secretion of parathyroid hormone (PTH), promoting bone resorption and subsequently releasing calcium and phosphate into the bloodstream. This pathological process not only compromises bone integrity but also contributes to bone pain and fractures, exacerbating the overall burden of pain in CKD patients [4-6].

Potassium Homeostasis

Potassium, primarily an intracellular ion, plays a crucial role in cellular functions. The sodium-potassium ATPase pump is primarily responsible for maintaining the equilibrium between sodium and potassium ions. In CKD, potassium homeostasis can be significantly altered due to impaired renal function. Normal serum potassium levels range from 3.6 to 5.5 mmol/L; hypokalemia occurs when levels fall below 3.6 mmol/L, while hyperkalemia is defined as levels exceeding 5.5 mmol/L. Dysregulation of potassium levels can have profound effects on muscle and nerve function, contributing to the perception of pain [7].

Calcium's Role in Pain Perception

Calcium is a vital extracellular cation that is essential for blood coagulation, muscle contraction, nerve impulse transmission, and hormone secretion. Dietary intake, supplemented by the active form of vitamin D (1,25-dihydroxy vitamin D3), regulates calcium absorption in the intestines. PTH also influences calcium secretion in the kidneys, while calcitonin reduces serum calcium levels by acting on bone cells. Normal serum calcium levels range from 8.8 to 10.7 mg/dL. Hypocalcemia, defined as serum calcium levels below 8.8 mg/dL, and hypercalcemia, occurring when levels exceed 10.7 mg/dL, can significantly affect pain perception and muscle function [8,9].

Phosphate Regulation and Implications for Pain

Phosphorus, another critical extracellular cation, is essential for numerous metabolic processes and is predominantly stored in bones and teeth as hydroxyapatite. It is regulated in concert with calcium by PTH, calcitonin, and vitamin D3, with the kidneys serving as the primary organ for phosphate excretion. In CKD, phosphate imbalance can arise from impaired renal excretion, gastrointestinal disturbances, or inadequate dietary intake. Normal phosphate levels range from 3.4 to 4.5 mg/dL, with hypophosphatemia defined as levels below 2.5 mg/dL and hyperphosphatemia as levels greater than 4.5 mg/dL. The resultant mineral imbalances may contribute to bone pain and fracture risk, exacerbating the chronic pain experienced by CKD patients [10,11].

Assessing Renal Function

The kidneys are integral to the excretion of waste products, regulation of fluid balance, and maintenance of electrolyte homeostasis, alongside the production of hormones such as erythropoietin and 1,25-dihydroxy vitamin D. Serum creatinine, a by-product of muscle metabolism, is primarily filtered by healthy kidneys. Elevated creatinine levels indicate reduced renal clearance, with normal levels ranging from 0.74 to 1.35 mg/dL for adult men and 0.59 to 1.04 mg/dL for adult women. Blood urea, produced in the liver during protein metabolism, is excreted mainly through the kidneys. Increased serum urea levels are indicative of compromised renal function, with normal levels falling between 5 and 20 mg/dL [12,13].

Study Objectives

This observational study aims to elucidate the relationship between mineral imbalances and unexplained pain in patients with chronic kidney failure undergoing hemodialysis. By investigating the intricate interplay of electrolyte levels and pain perception, we hope to provide valuable insights that could enhance pain management strategies for this vulnerable population, ultimately improving their quality of life and clinical outcomes. Understanding the role of mineral imbalance in the context of chronic pain may pave the way for targeted therapeutic interventions, thereby addressing an important gap in the management of CKD patients.

Materials and Methods:

STUDY SITE:

The study was conducted in dialysis unit of Nephrology department at Paalana Institute of Medical Sciences, Kerala. The duration of study was 6 months.

Recruitment of patients:

Inclusion criteria:

- Both male and female of age 18 years and above, who were undergoing hemodialysis
- The patients who were willing to participate in the study.

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Exclusion criteria:
- Acute kidney failure patients.
- Cases under toxicological department.
- Pregnancy and lactating women.

The Study was approved by the human ethics committee before data collection and informed contest was obtained from volunteer participants. A pre-designed data collection form was used to collect the necessary information like the patient demographics, past medical and medication history, laboratory values, blood pressure, pulse rate, frequency of hemodialysis, and current medications and collected data was analyzed and recorded to assess the association between pain and mineral imbalances. This study was conducted as 10 minutes interview with patients directly [14].
Sample size was calculated using Daniel's sample size equation [15]:

$$N = Z^2 \frac{P(1-P)}{d^2}$$

N= Population size
Z= Statistic for a level of confidence,
P= Expected prevalence or proportion (If the expected prevalence is 20%, then P=0.2),
d= Precision (If the precision is 5%, then d=0.05).

Statistical Analysis:
The statistical methods used in this study include Chi-Square Test was used to assess the association between mineral levels (phosphorus, calcium, potassium, creatinine) across different categories (low, normal, high), with a significant result ($\chi^2 = 167.51$, $p < 0.00001$) indicating a strong relationship. Descriptive Statistics was followed for frequencies and percentages to describe demographic variables (e.g., gender, age, blood group), prevalence of pain, and dialysis-related variables. These methods provided insights into the distribution and associations within the study population.

Results:
Demographic classification of Study Population
Figure 1 illustrates the distribution of the study population (n=62) across various demographic and health-related variables. In terms of gender, most participants were male (82%) compared to female (18%), indicating a skewed gender representation within the study population. The age distribution showed that only 3% of participants fell into the 18-27 age group, while 13% were in the 28-37 age range. The 38-47 age group accounted for 19%, and the 48-57 age group represented 23% of the population. The highest proportion was observed in the 58-67 age group (32%), with 10% of participants aged 68-77. Regarding blood group composition, the most common blood type was B^{+ve} (33.87%), followed closely by A^{+ve} (30.64%), and O^{+ve} (25.8%). A^{-ve} and AB^{-ve} blood types were minimally represented at 1.62% each, while AB^{+ve} comprised 6.45%. Analysis of lifestyle habits revealed that 11.29% of participants reported smoking, 8.06% engaged in alcoholism, while a significant majority (80.65%) reported no such habits. Additionally, only 6.45% of participants had a history of kidney transplant, whereas 93.55% had no surgical history. Overall, the categorization of the study population reveals a diverse group concerning gender, age, blood group, lifestyle habits, and surgical history, providing a foundational understanding of the participants' demographic and health characteristics essential for subsequent analyses and discussions in this research.

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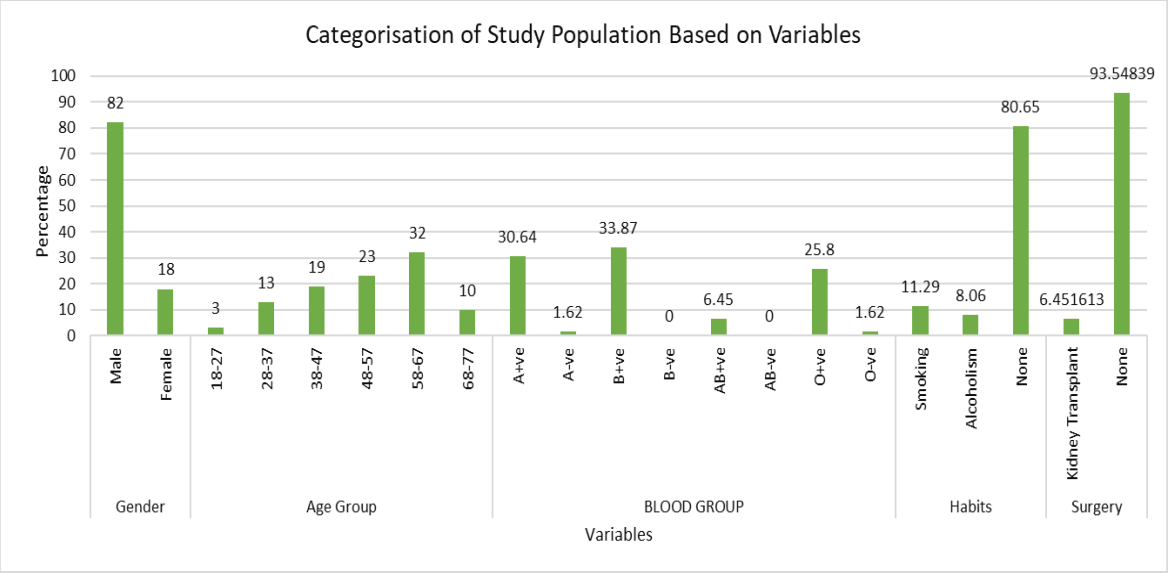

Figure 1: Categorization of Study Population Based on Variables

This bar chart illustrates the distribution of the study population (n=62) across various categories, including gender, age group, blood group, lifestyle habits, and history of surgery. Each bar represents the percentage of participants within a specific category, offering a visual comparison of the different variables among the population.

Prevalence of Pain Among Study Population

The data indicate that 66.13% of participants reported experiencing pain, a substantial majority of the study population (n=62) as shown in Table 2. This high prevalence highlights that pain is a major concern in this demographic, which is known to experience various physical and psychological challenges due to CKD and its treatment. The results suggest that healthcare providers should prioritize pain assessment as part of routine care for patients undergoing hemodialysis. Unexplained pain can significantly impair quality of life, necessitating systematic evaluation and management strategies. Pain was reported predominantly in the legs (40.32%) and arms (19.35%), with severity ratings mostly falling between 1 and 3 on a scale of 10. This distribution provides insight into where patients may be experiencing discomfort, potentially correlating with specific physical or functional limitations associated with CKD and its treatments. The majority (87.80%) of participants reported pain as occasional rather than frequent or constant. This finding suggests that while pain is a common experience, it may not be chronic in many cases. Nonetheless, the episodic nature of pain can still lead to significant distress and functional impairment.

Table 2: Categorisation of Study Population Based on Pain

Variable	Category	Percentage (%)
Pain	Having pain	66.12903
	No pain	33.87097
Location of Pain	Head	16.13
	Chest	11.29
	Abdomen	6.45
	Arms	19.35
	Legs	40.32
	Shoulder	3.22
Severity of Pain	1-3	58.53
	4-6	39.02
	7-9	0
	10	2.43
Frequency of Pain	Occasional	87.80
	Frequent	9.75
	Constant	2.43

This table presents the distribution of the study population (n=62) based on various pain-related variables. It includes the proportion of participants experiencing pain, the location of their pain, the severity, and the frequency of pain episodes.

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Initiation of Hemodialysis:

- **<1 year (32.25%) and 1-2 years (38.70%):** A combined total of 70.95% of participants are relatively new to hemodialysis, having initiated treatment within the last two years. This suggests a significant number of patients may be in the early stages of kidney disease, indicating a potential need for enhanced management and education for these individuals to address their health needs.
- **2-3 years (11.29%) and >3 years (17.74%):** The remaining 29.05% of participants have been on hemodialysis for longer durations. This may indicate that these individuals are experiencing more advanced stages of chronic kidney disease, which could lead to greater complications and the necessity for closer monitoring and possible interventions.

Frequency of Hemodialysis:

- **2 Times (62.90%):** Most patients (over half) undergo hemodialysis two times a week. This frequency is often considered the minimum required for adequate clearance of toxins and fluid management in patients with chronic kidney failure, implying that many may still have manageable conditions that do not require more frequent dialysis.
- **3 Times (37.09%):** A significant portion of patients (almost 40%) receives hemodialysis three times weekly, suggesting that they may have more severe kidney impairment or additional comorbidities necessitating more frequent treatments. This highlights the varying levels of disease severity within the study population and underscores the importance of individualized treatment plans Table 3.

Table 3: Categorisation of Study Population Based on Dialysis

Variable	Category	Percentage (%)
Initiation Of Haemodialysis	<1 year	32.25
	1-2 years	38.70
	2-3 years	11.29
	>3 years	17.74
Frequency of Haemodialysis	2 Times	62.90
	3 Times	37.09

This table summarizes the study population according to the initiation and frequency of haemodialysis.

Blood Urea Levels Before and After Dialysis:

Pre-dialysis Levels are categorized as Mild (Pre: 48.38%), a significant portion of patients presents with mild urea levels before dialysis, indicating a possible early intervention point in the disease trajectory where management strategies could be implemented to prevent progression, Moderate (Pre: 35.48%), where nearly one-third fall into the moderate category, reflecting a concerning level of waste accumulation that might require more intensive monitoring and management strategies and Severe (Pre: 9.67%), a small percentage (9.67%) indicates severe pre-dialysis urea levels, highlighting a critical need for immediate intervention to prevent complications associated with high urea toxicity.

Post-dialysis Levels of mild (Post: 46.77%) category are nearly half of the patients, suggesting that dialysis is effective in reducing urea levels but may not always achieve the optimal goal of bringing levels back to a normal range. While a substantial percentage of patients fall into the moderate category (Post: 38.70%) post-dialysis, indicating that while dialysis helps, many patients do not achieve adequate clearance of urea, pointing to a need for enhanced treatment modalities or adjustments in dialysis protocols. The reduction in severe cases (Post: 8.06%) (from pre- to post-dialysis) indicates effective treatment. However, the remaining cases suggest there may be patients who are not responding adequately to the current dialysis regimen, necessitating further assessment and possibly different treatment approaches Table 4.

Table 4: Categorisation of Study Population Based on Blood Urea Levels

	Mild		Moderate		Severe	
Range	Pre (50-80)	Post (5-25)	Pre (80-120)	Post (25-40)	Pre (>120)	Post (>50)
Percentage (%)	48.38	46.77	35.48	38.70	9.67	8.06

This table categorizes the study population by the severity of their blood urea levels, both before (Pre) and after (Post) dialysis, based on the following ranges: mild, moderate, and severe.

Mineral Imbalances: Prevalence and Impact

A significant finding is the elevated phosphorus levels observed in 53.23% of participants, categorized as high. Elevated phosphorus is often linked to renal osteodystrophy, cardiovascular disease, and other complications in CKD patients. The association between high phosphorus levels and various health complications underscores the need for vigilant monitoring and management of mineral levels. Conversely, 91.93% of participants exhibited low calcium levels, which can have adverse effects on bone health and may exacerbate pain through bone-related disorders Table 5. The co-occurrence of low

calcium and high phosphorus may create a detrimental cycle affecting patients' overall health and comfort. The chi-square statistic ($\chi^2 = 167.51$, $p < 0.00001$) indicates a highly significant association between the mineral levels of phosphorus, calcium, potassium, and creatinine and the categorization of these minerals into low, normal, and high Table 6. The extremely low p-value suggests that the observed differences in mineral distributions across categories are not likely due to chance, reinforcing the existence of a genuine relationship. Each cell in the chi-square table indicates observed counts (actual participant numbers) versus expected counts (based on independence of variables), along with contributions to the chi-square value. This detail emphasizes the extent to which each mineral's distribution deviates from what would be expected if there were no association, highlighting phosphorus's particularly notable contribution to the overall chi-square statistic Figure 2.

Table 5: Categorisation of Study Population Based on Mineral Level

Minerals	**Category**	**Percentage (%)**
Phosphorus (3.4 - 4.5mg/dl)	Low	14.51613
	Normal	32.25806
	High	53.22581
Calcium (8.8 - 0.7mg/dl)	Low	91.93
	Normal	6.45
	High	1.61
Potassium (3.6 - 5.5mmol/l)	Low	11.29
	Normal	70.96
	High	17.74
Creatinine (0.59-1.35mg /dl)	Mild(2-6mg/dl)	14.51
	Moderate(6-12mg/dl)	69.35
	Severe(>12mg/dl)	16.12

This table presents the distribution of the study population (n= 62) based on their mineral levels, including phosphorus, calcium, potassium, and creatinine. The percentages represent the proportion of participants within each mineral category (low, normal, high, or severity levels), reflecting the variability in mineral concentrations among the population.

Table 6: Chi-Square Analysis of Phosphorus, Calcium, Potassium, and Creatinine Levels Across Different Categories

Variables	**Low**	**Normal**	**High**	***Row Totals***
Phosphorus	9 (20.50) [6.45]	20 (27.75) [2.16]	33 (13.75) [26.95]	62
Calcium	57 (20.50) [64.99]	4 (27.75) [20.33]	1 (13.75) [11.82]	62
Potassium	7 (20.50) [8.89]	44 (27.75) [9.52]	11 (13.75) [0.55]	62
Creatinine	9 (20.50) [6.45]	43 (27.75) [8.38]	10 (13.75) [1.02]	62
Column Totals	82	111	55	**248 (Grand Total)**

The table categorizes individuals based on phosphorus, calcium, potassium, and creatinine levels into Low, Moderate, and High categories. The Chi-Square Test ($\chi^2 = 167.51$, $p < 0.00001$) shows a significant relationship between these variables and their distribution, indicating the observed differences are unlikely due to chance. Each cell shows the observed count, the expected count (in parentheses), and the contribution to the overall chi-square value (in square brackets). The significant p-value confirms the association between these variables and the distribution across the categories.

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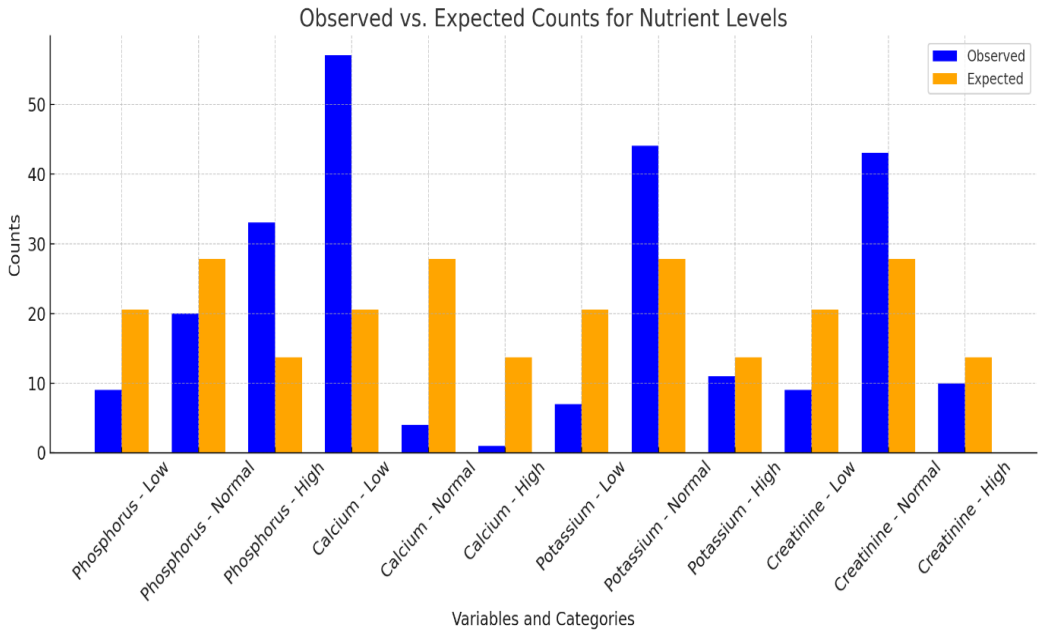

Figure 2: Comparison of Observed and Expected Counts for Nutrient Levels in Different Categories

This graph effectively illustrates the differences between observed and expected values for phosphorus, calcium, potassium, and creatinine levels across the Low, Normal, and High categories.

Discussion:

The study reveals critical insights into the relationship between mineral imbalances, especially phosphorus and calcium levels, and the prevalence of pain in patients undergoing hemodialysis due to chronic kidney disease (CKD). Pain in CKD patients is often multifactorial, and the role of electrolyte disturbances, such as low calcium and high phosphorus levels, plays a significant part in pain perception and overall quality of life.

Pain and Electrolyte Imbalances in CKD

Pain is a common issue among CKD patients, and its multifaceted nature was highlighted in this study, with 66.13% of participants reporting pain, primarily in the legs and arms. While pain may be attributed to various factors like uremic toxins or dialysis-related complications, the significant relationship between mineral imbalances and pain offers important insights. Low calcium levels (observed in 91.93% of participants) and elevated phosphorus levels (53.23%) were prominent findings, suggesting that disturbances in calcium-phosphate homeostasis may exacerbate musculoskeletal pain. These imbalances are likely contributing to bone resorption and disorders like renal osteodystrophy, leading to increased bone pain and fracture risk.

Role of Phosphorus and Calcium

The imbalance in phosphorus and calcium is crucial in the pathology of CKD-related pain. Hyperphosphatemia, as seen in more than half of the study participants, is associated with increased parathyroid hormone (PTH) secretion, which promotes bone resorption. The bone pain and fractures resulting from this process are major contributors to the high levels of discomfort reported by the patients. In contrast, hypocalcemia, which was highly prevalent, compromises neuromuscular function, further aggravating pain perception.

The chi-square analysis provided a highly significant association between mineral levels and the categorization of low, normal, and high levels across phosphorus, calcium, potassium, and creatinine. The p-value ($\chi^2 = 167.51$, $p < 0.00001$) underscores the strong relationship between these imbalances and the clinical manifestations, including pain. These findings align with previous studies that have linked electrolyte disturbances with increased pain perception in CKD patients.

Potassium Imbalance and Pain

While potassium levels in the study population showed less variation compared to calcium and phosphorus, it is still noteworthy that 17.74% of patients had elevated potassium levels (hyperkalemia), while 11.29% experienced hypokalemia. Given potassium's critical role in muscle and nerve function, any dysregulation can result in muscle cramps, weakness, or nerve pain, which may compound the physical discomfort experienced by these patients. The sodium-potassium ATPase pump, responsible for maintaining cellular electrochemical balance, is impaired in CKD, potentially contributing to abnormal pain responses.

Implications for Pain Management
The findings highlight the need for a comprehensive pain management strategy that addresses the underlying electrolyte imbalances. This could include optimizing calcium and phosphate levels through dietary adjustments, phosphate binders, or vitamin D supplementation, all of which could alleviate bone-related pain and improve overall musculoskeletal health. Additionally, regular monitoring of potassium levels is critical, as even mild deviations can have substantial effects on neuromuscular function and pain. Early interventions to correct these imbalances could prevent the progression of pain and other associated complications in CKD patients.

Limitations and Future Research
The study is limited by its relatively small sample size and the short duration of the observation period. Future studies should focus on a larger population over a longer period to validate these findings.

Conclusion
In conclusion, this study highlights the high prevalence of pain among patients undergoing hemodialysis and its association with mineral imbalances, particularly elevated phosphorus, and low calcium levels. Understanding these relationships is crucial for improving pain management strategies and overall patient outcomes in this vulnerable population. Enhanced monitoring, patient education, and a multidisciplinary approach are essential to address the complex interplay between mineral levels and pain in individuals with chronic kidney disease.

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