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RELATIONSHIP BETWEEN HYPOMAGNESEMIA FOLLOWING CHRONIC USE OF PROTON PUMP INHIBITORS

Original Research

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Acknowledgement: The authors express gratitude to the medical and research staff at Pak-Emirates Military Hospital for their support in data collection and patient follow-ups.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely prescribed for acid-related disorders, with chronic use becoming increasingly prevalent. While generally considered safe, prolonged PPI therapy has been associated with electrolyte disturbances, particularly hypomagnesemia. Magnesium plays a crucial role in neuromuscular function, enzymatic activity, and cellular homeostasis, and its deficiency can lead to significant clinical complications. Despite the growing recognition of PPI-induced hypomagnesemia, limited research has explored this association in community-based populations, necessitating further investigation into the long-term effects of PPIs on serum magnesium levels.

Objective: To evaluate the relationship between hypomagnesemia and chronic PPI use in a community-based population, assessing serum magnesium levels in patients with varying durations of therapy.

Methods: This prospective observational study was conducted at the Department of Medicine, Pak-Emirates Military Hospital (PEMH), Rawalpindi, from July 2023 to June 2024. A total of 310 patients were included in the final analysis, categorized based on PPI use duration: 6–12 months (n=110), 12–24 months (n=136), and more than 24 months (n=64). Patients underwent monthly follow-up for six months, with serial assessments of complete blood count, renal function tests, and serum magnesium levels. Statistical analysis was performed using ANOVA to compare magnesium levels across different duration groups, with a p-value ≤ 0.05 considered significant.

Results: The mean serum magnesium levels at six-month follow-up were significantly lower with increasing PPI duration: 1.48 ± 0.08 mg/dL in the 6–12 month group, 1.31 ± 0.12 mg/dL in the 12–24 month group, and 1.28 ± 0.09 mg/dL in the group using PPIs for more than 24 months ($p<0.001$). The decline followed a linear trend, highlighting a strong association between prolonged PPI use and magnesium depletion.

Conclusion: Chronic PPI use is associated with a progressive decline in serum magnesium levels, with a more pronounced reduction observed in patients with extended therapy durations. These findings emphasize the need for routine magnesium monitoring in long-term PPI users to mitigate potential complications.

Keywords: Chronic disease, community health, drug-related side effects, hypomagnesemia, magnesium deficiency, proton pump inhibitors, renal homeostasis.

INTRODUCTION

Magnesium is an essential cation in the human body, playing a vital role in numerous physiological processes. Approximately 60% of total body magnesium is stored in bones, while the remaining portion is predominantly found in the intracellular compartment. It is crucial for energy production, glycolysis, phosphorylation, cellular membrane stabilization, neuromuscular function, and immune response (1,2). Unlike other electrolytes, magnesium cannot be readily mobilized from bone stores in times of deficiency, making renal reabsorption the primary mechanism for maintaining homeostasis (3). Imbalances in magnesium levels, particularly hypomagnesemia, can result in significant clinical consequences, including neurological deficits, cardiac arrhythmias, muscle weakness, and immune dysfunction (4,5). Drug-induced hypomagnesemia has been increasingly recognized as an important contributor to these imbalances, with diuretics traditionally being implicated in magnesium depletion due to their effects on renal reabsorption (7). In recent years, proton pump inhibitors (PPIs) have also been associated with fluctuations in serum magnesium levels, particularly with prolonged use. These medications, widely prescribed for gastric acid-related disorders, are estimated to be used by approximately 25% of the global population (8). Notably, more than 65% of PPI users are younger than 65 years, suggesting that dietary and lifestyle factors may contribute to their widespread prescription in younger demographics. Additionally, about 25% of individuals on PPIs report chronic use exceeding one year, raising concerns about the long-term metabolic impact of these drugs (9,10).

While hospital-based studies have reported significant reductions in magnesium levels among inpatients using PPIs, there remains a gap in understanding the effects of long-term PPI use on magnesium homeostasis in community-dwelling individuals. Given the increasing prevalence of PPI prescriptions and their potential implications for metabolic health, this study aims to investigate the relationship between chronic PPI use and hypomagnesemia in an outpatient population. By evaluating the extent of magnesium depletion associated with prolonged PPI therapy, this research seeks to provide clinically relevant insights into the risks and necessary monitoring strategies for individuals on long-term PPI treatment.

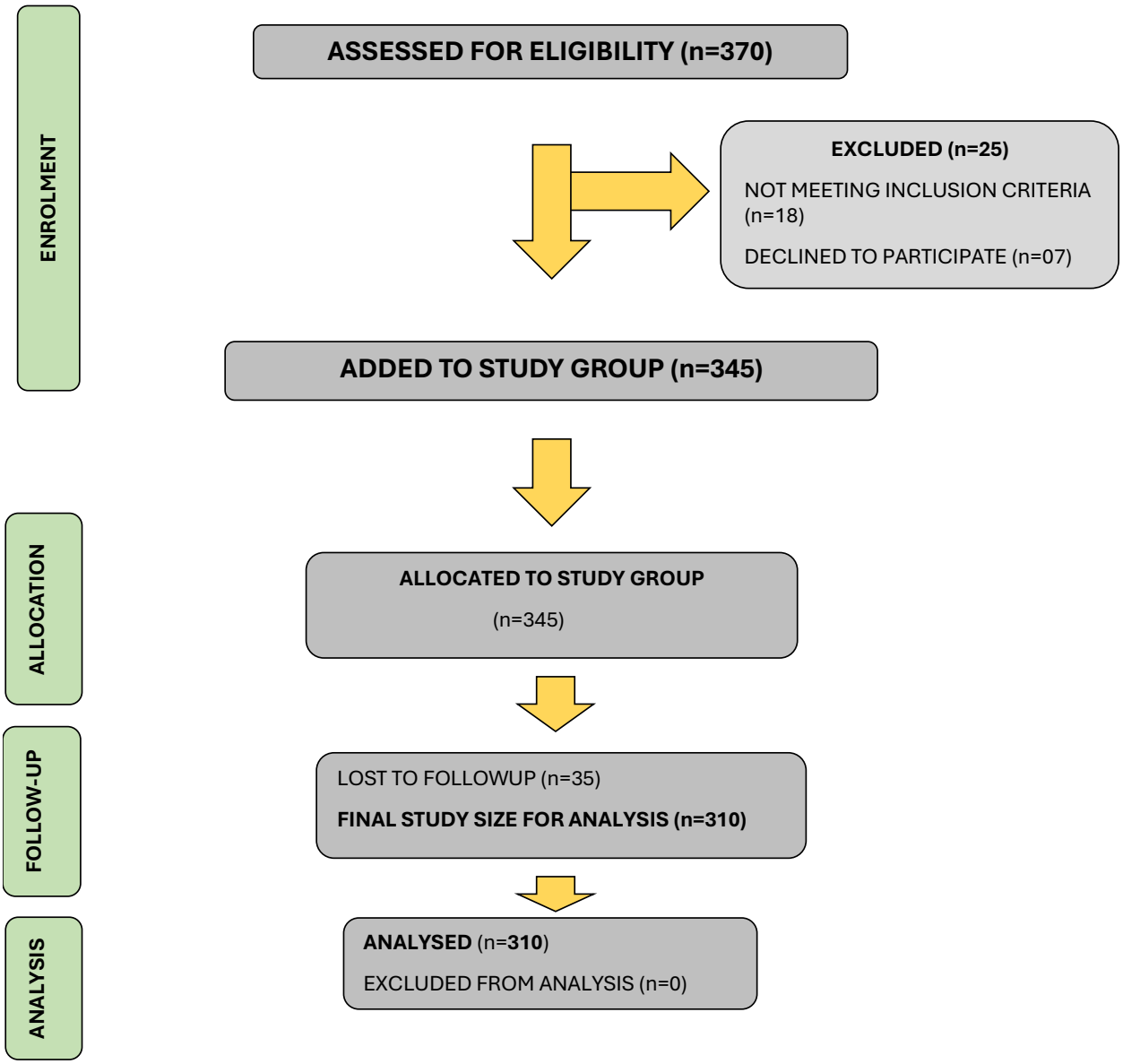
METHODS

This prospective observational study was conducted at the Department of Medicine, Pak-Emirates Military Hospital (PEMH), Rawalpindi, from July 2023 to June 2024, following approval from the institutional ethical review board. The sample size was determined based on a 95% confidence interval, a 5% margin of error, and a population proportion of 25% reported for chronic proton pump inhibitor (PPI) use (11). Using the WHO sample size calculator, the minimum required sample was calculated to be 288 patients; however, to ensure a robust dataset, 310 participants were included in the final analysis, adhering strictly to the study's inclusion criteria. Patients of both genders, aged 18 to 75 years, presenting to the outpatient department with chronic oral PPI use (defined as uninterrupted intake for more than six months) were included (11). Exclusion criteria comprised patients requiring frequent intravenous PPI therapy (>1 time per week) due to advanced peptic ulcer disease, individuals with interruptions in PPI use exceeding two weeks, those with advanced cardiac, renal, or respiratory diseases, patients lost to follow-up, and individuals on medications known to influence serum magnesium levels, such as diuretics, long-term steroids, calcium channel blockers, and insulin. Additionally, patients unable to provide a clear history of PPI use or those unwilling to participate were excluded from the study.

Following recruitment, all eligible participants provided written informed consent before data collection. Each patient was assigned a four-digit anonymized code to maintain confidentiality throughout the study. Data were gathered at baseline and during subsequent follow-ups at one-month, three-month, and six-month intervals. A consultant medical specialist conducted detailed history-taking, which included demographic information (age, weight, gender), comorbid conditions, indication for PPI use, and concurrent medications. The duration of PPI use was categorized into three groups: 6–12 months, 12–24 months, and more than 24 months. Laboratory investigations, including a complete blood count, renal function tests, and serum magnesium levels, were performed at baseline and at each follow-up visit. Participants were required to present fresh laboratory reports at each scheduled visit, ensuring consistency in data collection. Given the high likelihood of loss to follow-up in outpatient studies, patients were counseled regarding the importance of adherence to scheduled visits. Monthly follow-ups were conducted when patients visited the institute for medication collection, where history-taking and laboratory evaluations were repeated.

To minimize bias in data handling, completed history proformas were submitted to a designated resident physician who was responsible for data entry but remained uninvolved in the final statistical analysis. Data were compiled into a Microsoft Excel sheet and subsequently analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0. Descriptive statistics were used to summarize demographic data, with means and standard deviations reported for continuous variables and frequencies with percentages for categorical data. The primary outcome variable was the mean serum magnesium level after chronic PPI use, with subgroup comparisons based on the duration of drug intake. The ANOVA test was applied to compare serum magnesium levels at one-month, three-month, and six-month intervals among the different PPI usage groups. A p-value of ≤0.05 was considered statistically significant.

FIGURE-1: PHASES OF THE STUDY



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RESULTS

A total of 370 patients were screened for eligibility. Eighteen patients did not meet the inclusion criteria, while seven declined participation due to concerns regarding follow-up. Of the 345 patients who were initially enrolled, 35 were lost to follow-up, resulting in a final sample size of 310 patients for analysis. The mean age of the participants was 49.48 ± 5.52 years, and the mean weight was 76.39 ± 5.26 kg. Gender distribution revealed that 109 (35.2%) participants were male, whereas 201 (64.8%) were female. The major indications for PPI use included chronic dyspepsia in 110 (35.5%) patients, non-erosive gastroesophageal reflux disease in 95 (30.6%) patients, concomitant preventive therapy for non-steroidal anti-inflammatory drugs (NSAIDs) in 80 (25.8%) patients, and peptic ulcer disease in 25 (8.1%) patients. The duration of chronic PPI use ranged from 6 to 12 months in 110 (35.5%) patients, 12 to 24 months in 136 (43.9%) patients, and exceeded 24 months in 64 (20.6%) patients.

Mean serum magnesium levels were analyzed at one-month, three-month, and six-month follow-ups. At the one-month follow-up, mean serum magnesium levels were 1.51 ± 0.13 mg/dL in patients who had used PPIs for 6–12 months, 1.50 ± 0.08 mg/dL in those with 12–24 months of use, and 1.34 ± 0.09 mg/dL in patients with more than 24 months of use ($p<0.001$). At three months, mean serum magnesium levels declined to 1.48 ± 0.09 mg/dL in the 6–12 month group, 1.47 ± 0.11 mg/dL in the 12–24 month group, and 1.33 ± 0.12 mg/dL in the group with more than 24 months of use ($p<0.001$). By the six-month follow-up, mean serum magnesium levels remained at 1.48 ± 0.08 mg/dL in the 6–12 month group, declined to 1.31 ± 0.12 mg/dL in the 12–24 month group, and further decreased to 1.28 ± 0.09 mg/dL in patients who had used PPIs for more than 24 months ($p<0.001$).

Table 1: Demographic Data And Clinical Characteristics (N=310)

VARIABLE	
MEAN AGE (YEARS)	49.48±5.52
MEAN WEIGHT (KG)	76.39±5.26
GENDER DISTRIBUTION	
• MALE	109 (35.2%)
• FEMALE	201 (64.8%)
INDICATON FOR PPI USE	
• CHRONIC DYSPEPSIA	110 (35.5%)
• NON-EROSIVE REFLUX DISEASE	95 (30.6%)
• CONCOMITANT PREVENTIVE THERAPY WITH NSAIDs USE	80 (25.8%)
• PEPTIC ULCER DISEASE	25 (8.1%)
DURARTION OF CHRONIC PPI USE	
• MORE THAN 6 MONTHS BUT LESS THAN 12 MONTHS	110 (35.5%)
• MORE THAN 12 MONTHS BUT LESS THAN 24 MONTHS	136 (43.9%)
• MORE THAN 24 MONTHS	64 (20.6%)

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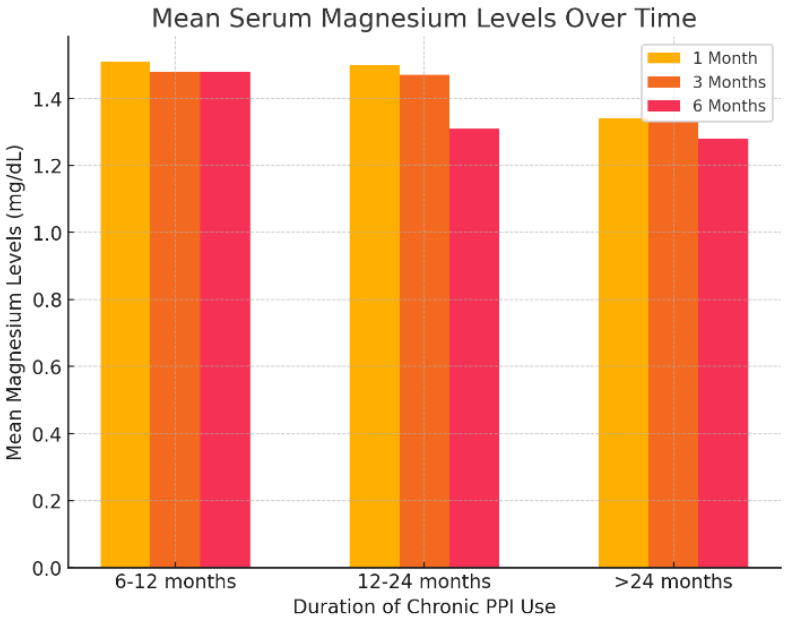
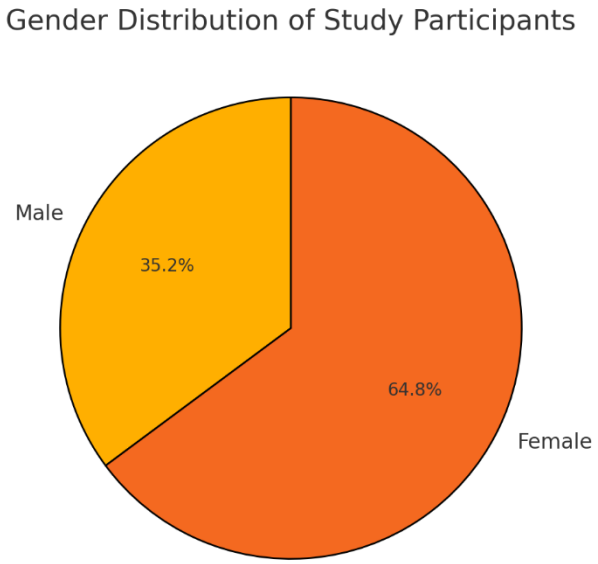
Table 2: Chronic PPI Use Duration And Magnesium Levels (N=310)

	DURATION OF CHRONIC PPIs USE			
	MORE THAN 6 MONTHS BUT LESS THAN 12 MONTHS (n=110)	MORE THAN 12 MONTHS BUT LESS THAN 24 MONTHS (n=136)	MORE THAN 24 MONTHS (n=64)	p VALUE
MEAN MAGNESIUM LEVELS IN PATIENTS (MG/DL)				
• AT ONE MONTH FOLLOW-UP	1.51±0.13	1.50±0.08	1.34±0.09	**<0.001**
• AT 03 MONTH FOLLOW-UP	1.48±0.09	1.47±0.11	1.33±0.12	**<0.001**
• AT 06 MONTH FOLLOW-UP	1.48±0.08	1.31±0.12	1.28±0.09	**<0.001**





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DISCUSSION

This study is the first in the demographic region to assess magnesium levels following chronic proton pump inhibitor (PPI) use in a community setting. While previous research has primarily focused on acute declines in magnesium levels during critical illness, the gradual decline associated with prolonged PPI use has received limited attention. Hypomagnesemia as a consequence of chronic PPI therapy was first recognized nearly two decades ago and is now an established adverse effect of prolonged use (12). While short-term therapy has also been linked to reductions in magnesium levels, long-term studies stratified by dosing duration remain limited (13). Although the decline in magnesium levels may initially appear mild, its impact extends beyond hypomagnesemia alone, as studies have highlighted concomitant reductions in calcium, phosphorus, potassium, and sodium levels. These disturbances often occur in parallel, particularly when serum magnesium levels drop below 1.6 mg/dL, with severity increasing as levels fall below 1.2 mg/dL (14). This highlights the necessity of routine magnesium monitoring in patients receiving prolonged PPI therapy. The findings demonstrated a significant association between PPI use and declining magnesium levels. While levels were already lower than normal in patients with 6–12 months of continuous use, the most pronounced declines were observed in those receiving therapy for more than 24 months. The decline in magnesium levels followed a linear pattern, reinforcing the need for long-term monitoring in patients on chronic PPI therapy. Interestingly, while no major differences in serum magnesium levels were found between genders, a higher proportion of females were affected, reflecting increased PPI use among women in the study population (16). This aligns with previous reports suggesting gender-based differences in prescribing trends, although the underlying reasons remain unclear.

One of the critical challenges in defining chronic PPI use is the lack of universal consensus on an appropriate duration threshold. Existing studies have used varying timeframes, ranging from 8 weeks to 12 months, to categorize PPI therapy as chronic. A systematic review concluded that while an 8-week duration is sufficient for treatment-related follow-ups, a research-based definition of chronic use should be set at more than 6 months to observe significant effects (18). This study adhered to this approach, ensuring that only prolonged users were included to establish a more robust association between PPI use and hypomagnesemia. The study has several strengths, including its prospective design and rigorous exclusion of confounding factors such as diuretics, insulin, steroids, and calcium channel blockers. This enabled a more precise evaluation of the direct impact of PPI use on magnesium levels. However, limitations exist, including the single-center setting, which may restrict generalizability. Future research incorporating multi-center studies with larger sample sizes could provide a more comprehensive understanding of this association. Further investigations analyzing the interaction of PPIs with additional factors influencing magnesium levels, such as dietary intake and renal function variations, would enhance clinical understanding and improve risk stratification in patients requiring long-term PPI therapy (19,20).

Given the significant findings, routine monitoring of magnesium levels in patients on chronic PPI therapy is warranted, especially in those receiving treatment for more than 24 months. Implementing standardized monitoring protocols and reassessing the necessity of prolonged therapy could mitigate the risk of electrolyte disturbances and associated complications in long-term PPI users.

CONCLUSION

Chronic use of proton pump inhibitors is associated with a progressive decline in serum magnesium levels, with the extent of reduction increasing in correlation with the duration of therapy. This study reinforces the importance of monitoring magnesium levels in long-term PPI users to prevent potential complications arising from electrolyte imbalances. Given the widespread use of PPIs, these findings highlight the need for clinical vigilance in assessing the necessity of prolonged therapy and implementing appropriate monitoring strategies to mitigate risks associated with chronic use.

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