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Are Proton Pump Inhibitors a Risk Factor for Hypomagnesemia in Patients with Diabetic Kidney Disease

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ABSTRACT

Objective: To compare serum magnesium levels amongst diabetic kidney disease patients using proton pump inhibitors and those not using them.

Study Design: Cross-sectional study.

Place and Duration of Study: Pak-Emirates Military Hospital, Rawalpindi, Pakistan, from May to Jul 2023.

Methodology: Patients with diabetic kidney disease stage 3– 5ND were selected, on regular follow-up in outdoor clinic for at least a month. Exclusion criteria included missing information, use of diuretics or magnesium-containing nutritional supplements or multivitamin tablets, and unwillingness. We recorded data on the use of proton pump inhibitors, including their type, dose, and duration of use. Blood sampling was also done for estimation of serum magnesium, urea, creatinine, sodium, potassium, glycosylated hemoglobin levels and albumin: creatinine levels on spot urinary samples.

Results: This study was done on 94 patients. The mean age of the participants was 62.48 ± 8.32 years. There were 67(77.5%) males and 27(28.4%) females. Proton pump inhibitors were being used by 58(61.7%) patients, and 36(38.3%) were not used.

Conclusion: This study highlights a potential link between hypomagnesemia and proton pump inhibitors in diabetic kidney patients. Care should be exercised by clinicians while dealing with such patients.

Keywords: Cross-Sectional Study, Diabetic Kidney Disease, Hypomagnesemia, Proton Pump Inhibitors, Serum Magnesium.

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INTRODUCTION

Diabetic kidney disease (DKD), a well-documented complication of diabetes mellitus, represents a formidable global health concern. As the prevalence of diabetes continues to rise, the associated burden of DKD escalates, placing a significant strain on healthcare systems worldwide.[1] Among the myriad of challenges presented by DKD, disturbances in electrolyte homeostasis, particularly serum magnesium levels, have gained considerable attention due to their potential impact on disease progression and patient outcomes.[2]

Proton pump inhibitors (PPIs), a class of medications widely prescribed for the management of acid-related gastrointestinal disorders, have come under scrutiny in recent years for their potential to influence electrolyte balance, including serum magnesium concentrations.[2] The utilization of PPIs is pervasive, with millions of individuals relying on them for relief from conditions such as gastroesophageal reflux disease and peptic ulcers.[3] However, emerging research has raised questions about whether PPIs, beyond their intended therapeutic effects, might inadvertently contribute to imbalances in magnesium levels.[4]

Magnesium is crucial for muscle contraction and relaxation, impacting both voluntary movements and involuntary functions like heart and smooth muscle contractions. Its role is particularly significant for cardiovascular health, as proper magnesium levels are essential for the heart and blood vessels.[5] In diabetic kidney disease (DKD), the importance of magnesium is heightened due to renal dysfunction disrupting its homeostasis. Compromised kidneys struggle to regulate magnesium levels, affecting excretion and serum concentrations.[6]

Proton pump inhibitors (PPIs) are widely prescribed medications for acid-related gastrointestinal disorders, helping millions with conditions like gastroesophageal reflux disease and peptic ulcers.[7] However, recent studies have raised concerns about potential side effects, suggesting that PPIs may affect electrolyte balance, including serum magnesium levels.[8] While the exact mechanisms

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behind how PPIs might affect magnesium levels are not yet fully elucidated, there is a growing body of evidence to suggest a possible connection.[9] Understanding this connection is essential, especially in the context of DKD, where magnesium regulation is already intricately linked to disease progression. As individuals with DKD are already at a higher risk of magnesium imbalance, any additional factors contributing to this imbalance must be thoroughly explored and understood.[10]

This research article explores the relationship between PPI use and serum magnesium levels in patients with both diabetes and kidney disease. By examining the potential link between these factors in the context of diabetic kidney disease (DKD), the study aims to provide insights that can inform clinical practices and improve patient management. If a connection between PPIs and magnesium imbalances is confirmed, it could lead to revised clinical guidelines regarding PPI prescriptions, particularly for patients at risk of magnesium deficiency. Additionally, it may highlight the need for regular monitoring of magnesium levels in DKD patients to prevent related complications. Ultimately, this research seeks to advance medical knowledge and improve outcomes for individuals living with diabetic kidney disease.

METHODOLOGY

This cross-sectional study was carried out at the Department of Nephrology, Pak Emirates Military Hospital, Rawalpindi, between May and July 2023. The Ethics Review Committee of the hospital approved the research protocol beforehand, vide letter number A/28/2023. We calculated a sample size requirement for 31 patients in each group (62 in total), assuming an odds ratio of 4.2 for hypomagnesemia amongst patients on PPIs and a frequency of 24.24% for hypomagnesemia amongst patients not on PPIs.[11] All patients were enrolled with their consent. We selected patients with diabetic kidney disease stage 3–5ND who were on regular follow-up in an outdoor nephrology clinic for at least a month. Exclusion criteria included missing information, use of diuretics or magnesium-containing nutritional supplements or multivitamin tablets, and unwillingness.

The recorded data on the use of proton pump inhibitors amongst the study participants, including their type, dose, and duration of use. Blood sampling was also done for estimation of serum magnesium, urea, creatinine, sodium, and potassium, as well as glycosylated hemoglobin levels. Albumin: creatinine levels were also checked on spot urinary samples collected on the same day. Estimated GFR was calculated from serum creatinine levels using the CKD-EPI equation.

Data was analyzed using Statistical Package for Social sciences (SPSS) 23. Frequency and Percentage were calculated for qualitative variables. Mean and SD were calculated for quantitative variables. Independent samples t test and chi square test used. The p value ≤ 0.05 was considered as significant.

RESULTS

This study was done on 94 patients. The mean age of the participants was 62.48±8.32 years. There were 67(77.5%) males and 27(28.4%) females. Proton pump inhibitors were being used by 58(61.7%) patients and 36(38.3%) were not used. There was not statistically significant difference seen between Proton pump inhibitors used and Proton pump inhibitors not used according to age (*p* value = 0.565), DM duration (*p* = 0.488) and Gender (*p* value= 0.086) Shown in Table-I.

Table-I: Comparison between serum magnesium and use of Proton Pump Inhibitors (n=94)

Parameters	Study Groups		*p*-value
	Group A (using PPI) (n= 58)	Group B (Not using PPI) (n= 36)	
Age in years (Mean ±SD)	62.85±8.20	61.81±8.85	0.565
Mean Duration of Diabetes (years)	12.35±6.25	11.46±8.41	0.488
Gender, n (%) Male (n=67) Female(n=27)	45(77.6%) 13(22.4%)	22(61.1%) 14(38.9%)	0.086

DISCUSSION

The present study aimed to investigate the potential association between proton pump inhibitor (PPI) use and lower serum magnesium levels in patients with diabetic kidney disease (DKD). Our findings contribute to the growing body of literature concerning the intricate interplay between PPIs, magnesium homeostasis, and DKD.

Koyyada *et al.,* in a study done on the prevalence and impact of proteinuria-associated hypomagnesemia in chronic kidney disease patients, found that age and gender were independently associated with renal damage.[12] Our study population exhibited a typical distribution with regard to age and

gender, consistent with the epidemiology of DKD and its prevalence among middle-aged and elderly individuals, with a slight male predominance. The median duration of diabetes of 12 years aligns with the chronic nature of the disease and the potential for DKD development over time, as shown by a study done by Biyik *et al*.[13]

In a study done by Srinutta *et al.,* did not find any plausible difference in magnesium levels in patients using PPI undergoing percutaneous coronary intervention.[14] The prevalence of PPI use in our cohort (56.80%) underscores the widespread utilization of these medications, which are commonly prescribed for gastrointestinal conditions. Veronese *et al.,* showed in their study that magnesium levels were significantly altered in chronic renal failure patients undergoing hemodialysis.[15] Notably, the median duration of PPI use among our study participants was 6 years, reflecting the chronicity of therapy in this patient population. The prolonged exposure to PPIs has implications for magnesium homeostasis, given the cumulative effect of these medications on mineral absorption and renal excretion, as shown by Sakaguchi *et al.,* in their study.[16]

Ashique *et al.,* conducted a study among hemodialysis patients and did not find any significant relationship between PPI users and hypomagnesemia.[17] The primary outcome of interest of the study was the occurrence of hypomagnesemia in patients with DKD, particularly in relation to PPI usage. Encouragingly, only a small proportion (3.20%) of our study participants exhibited hypomagnesemia. Importantly, all three patients with hypomagnesemia were using PPIs, suggesting a potential link between PPI therapy and altered magnesium levels. While the observed prevalence of hypomagnesemia is relatively low, it raises concerns about the clinical significance of this association, especially considering the potentially detrimental effects of magnesium imbalance on DKD progression and associated complications. Abdul-Hameed *et al.,* recommended regular monitoring of magnesium levels among chronic PPI users, showing that PPI, along with diuretics, was associated with significantly high hypomagnesemia.[18]

Lateef *et al.,* found an increased incidence of over mortality and cardiovascular mortality among patients with hypomagnesemia on chronic PPI.[19] In this study, comparison of serum magnesium levels between patients using PPIs and those not using them revealed noteworthy trends. Although no statistically significant difference was observed in the mean serum magnesium levels between the two groups, the correlation analysis revealed a positive relationship between the duration of PPI usage and serum magnesium levels. This correlation, with a coefficient of 0.316 and a *p*-value of 0.039, suggests that longer exposure to PPIs may contribute to lower serum magnesium levels, indicating a dose-response relationship, which may lead to an increase in all-cause mortality, particularly cardiovascular mortality in chronic kidney disease patients. Zaslow *et al.,* found hypomagnesemia as a risk factor and accelerator for vascular aging in diabetes and chronic kidney disease patients.[20]

As an overview, the study offers valuable insights into the potential relationship between PPI usage and lower serum magnesium levels in patients with diabetic kidney disease. The association between prolonged PPI usage and decreased serum magnesium levels, coupled with the presence of hypomagnesemia exclusively in PPI users, raises intriguing possibilities for further investigation. Clinicians should be vigilant regarding the potential implications of PPI therapy on magnesium balance in patients with DKD, and future research endeavors should delve deeper into the mechanisms underlying this relationship. These findings underscore the need for judicious use of PPIs in individuals with DKD, warranting a balanced assessment of the benefits and risks of these medications in the context of magnesium homeostasis and overall renal health.

CONCLUSION

This study highlights a potential link between prolonged PPI use and decreased serum magnesium levels in DKD patients. Clinicians should consider magnesium balance when prescribing PPIs to DKD patients, and further research is needed to understand the underlying mechanisms.

LIMITATION OF STUDY

The relatively small sample size and the single-center nature of the study could impact the generalizability of our findings. Additionally, our cross-sectional design precludes us from establishing a causal relationship between PPI use and hypomagnesemia. Longitudinal studies with larger cohorts are warranted to confirm these findings and elucidate potential mechanisms underlying the observed association.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

ARA & MHKS: Data acquisition, data analysis, critical review, approval of the final version to be published.

UZ & MAS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MWK & MA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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