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# Uncovering the Hidden Risks of Proton Pump Inhibitors: A Call for Caution in Long-Term Us

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## ABSTRACT

Therefore, an attempt was made to study a possible relation between proton pump inhibitors (PPIs) in continuing use and magnesium deficiency among the patients in a tertiary care hospital in Rawalpindi. We conducted a cross sectional study at Department of medicine Hayatabad medical complex Peshawar, Pakistan from January 2024 to July 2014. A total of 250 patients over the age of 18 years were enrolled into the study, all being on PPIs for at least one month. For that, we collect data on demographic factors, patient setting, body mass index, type and option of PPI and on suffering hypertension or diabetes mellitus. All participants underwent having their serum magnesium concentrations checked. The information was analyzed using SPSS. Of all, 51.5% (n=156) had hypomagnesemia. Furthermore, patients with the hypomagnesemia group were older on average (48.9 ± 12.3) than those with normal levels of magnesium (38.2 ± 11.4) ($p<0.001$). But multivariate logistic regression showed that duration > 6 months of PPI use (AOR: 58.1; 95% CI: 22.2-152.5; $p < 0.001$), diabetes mellitus (AOR: 23.1; 95% CI: 6.4- 82.6; $p < 0.001$) and hypertension (AOR: 3.2; 95% CI: 1.4-7.1; $p < 0.001$) were associated with low magnesium levels, while use of PPI did not significantly change Diabetes or hypertension and the long time use of PPI, along with advanced age were considered to be major risk factors. It explains the necessity for doctors to be conscious about the harm caused due to PPIs and to prescribe so carefully.

**Keywords:** Proton pump inhibitors, long-term use, adverse effects, medication safety, risk assessment

## INTRODUCTION

In the late twentieth century, using PPIs for gastrointestinal conditions became common, relying on potent, consistent inhibition of the $H^+/K^+$ ATPase enzyme in gastric parietal cells [1,2]. Because PPIs work well to treat GERD, peptic ulcer disease and Zollinger-Ellison syndrome, doctors prescribe them a lot, with many of them dispensed worldwide each year [3,4]. Unfortunately, the unique features that make PPIs effective in medicine have also led to their regular overuse without proper clinical indications or stretching longer than recommended [5,7].

Recent epidemiological studies have raised serious concerns regarding the safety of long-term PPI use, suggesting associations with a spectrum of adverse outcomes including micronutrient deficiencies, gastrointestinal infections, chronic kidney disease (CKD), cardiovascular morbidity, and neurocognitive decline [8,9]. These risks appear particularly pronounced in older adults and individuals with comorbidities, populations often underrepresented in clinical trials but overrepresented in real-world PPI use. Observational studies have demonstrated that prolonged PPI exposure may reduce the absorption of key nutrients—such as magnesium, calcium, and vitamin B12—thereby predisposing patients to complications such as osteoporosis-related fractures, anemia, and electrolyte disturbances [10,11]. Concurrently, acid suppression is hypothesized to impair the gastrointestinal tract's natural defense against ingested pathogens, leading to increased susceptibility to *Clostridioides difficile* infection and community-acquired pneumonia [12,13].

More alarmingly, large-scale cohort studies have identified significant associations between PPI use and incident CKD, myocardial infarction, and dementia, raising the possibility that PPIs exert systemic effects beyond their primary site of action [14,15]. While these associations do not confirm causality, the biological plausibility—rooted in hypotheses involving endothelial dysfunction, gut microbiota dysbiosis, and altered nitric oxide metabolism—supports a growing call for vigilance in long-term PPI prescribing [16].

Despite these concerns, clinical practice continues to reflect a pattern of indiscriminate PPI use, often driven by the perception of safety, ease of access (including over-the-counter availability), and insufficient deprescribing protocols [5,6]. This disconnect between emerging evidence and prescribing behavior underscores the





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urgent need for more rigorous risk-benefit evaluations, patient-specific treatment algorithms, and physician-patient communication regarding potential harms. Moreover, the cumulative healthcare costs and risks associated with chronic PPI therapy necessitate a reevaluation of their place in long-term disease management strategies [17].

In light of the above, this study aims to critically evaluate the adverse outcomes associated with long-term PPI use through a comprehensive review of current literature, highlighting the need for personalized prescribing practices and regular medication reassessment. Understanding the true scope of PPI-related risks is essential for guiding clinical decision-making and ensuring the judicious use of these powerful, yet potentially hazardous, pharmacological agents.

## METHODOLOGY

In the Department of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan from January 2015 to July 2016, researchers studied the impact of chronic use of proton pump inhibitors (PPIs) on hypomagnesemia. Two hundred and fifty people aged 18 years and over taking any PPI for one month or more agreed to participate in the study. The data recorded include Demographic traits, clinical information such as age, gender, weight, patient location (in-hospital or out-patient), duration and type of PPI use as well as illnesses (hypertension and diabetes mellitus, mainly). Regular laboratory testing was used to take a measure of serum magnesium for each participant. Descriptive statistics and multivariate logistic regression were carried out using the SPSS with the results at a p-value less than 0.05 being taken as statistically significant.

## RESULTS

The researchers enrolled 250 patients who met the required criteria. Among the participants, the average age was 43.1 years and females were a slightly larger group (54.8%) than males (45.2%). The largest group of patients were outpatients (60.4%). Patients took PPIs on average for 5.7 ± 3.8 months and in total, 42% used them for more than six months. About 45.6% of patients were treated with omeprazole, 33.2% with pantoprazole, 15.6% with esomeprazole and the remaining 5.6% were treated with PPI formulations other than these three. About one-third of participants had high blood pressure and a fourth had diabetes mellitus.

**Table 1: Demographic and Clinical Characteristics of the Study Population (n=250)**

| Variable | Frequency (%) or Mean ± SD |
|---|---|
| **Age (years)** | 43.1 ± 13.2 |
| **Gender** | |
| **- Male** | 113 (45.2%) |
| **- Female** | 137 (54.8%) |
| **Patient Setting** | |
| **- Outpatient** | 151 (60.4%) |
| **- Inpatient** | 99 (39.6%) |
| **Duration of PPI Use** | |
| **- ≤ 6 months** | 145 (58%) |
| **- > 6 months** | 105 (42%) |
| **Type of PPI Used** | |
| **- Omeprazole** | 114 (45.6%) |
| **- Pantoprazole** | 83 (33.2%) |
| **- Esomeprazole** | 39 (15.6%) |
| **- Others** | 14 (5.6%) |
| **Comorbidities** | |
| **- Diabetes Mellitus** | 70 (28%) |
| **- Hypertension** | 90 (36%) |

### Prevalence of Hypomagnesemia

The hypomagnesemia patients accounted for 129 (51.5%). The serum magnesium level was overall 1.68 ± 0.27 mg/dL in the study group. On average, patients in the hypomagnesemia group were older than the patients in the normal magnesium level group (48.9 ± 12.3 vs 38.2 ± 11.4 years, $p < 0.001$).

**Table 2: Comparison of Serum Magnesium Levels by Patient Characteristics**

| Variable | Hypomagnesemia (n=129) Mean ± SD | Normal Magnesium (n=121) Mean ± SD | p-value |
|---|---|---|---|
| **Age (years)** | 48.9 ± 12.3 | 38.2 ± 11.4 | <0.001 |
| **Duration of PPI Use (months)** | 7.8 ± 4.1 | 3.8 ± 2.6 | <0.001 |

No significant differences were observed in serum magnesium levels among different types of PPIs (p=0.131).

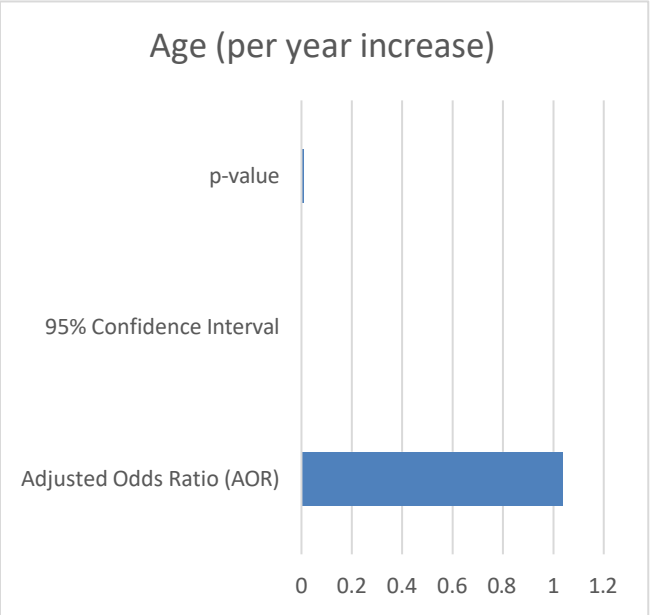
### Predictors of Hypomagnesemia

After looking at other variables, we found that long-term use of PPIs (over six months) greatly affected the risk of hypomagnesemia (AOR: 58.1 and 95% CI: 22.2–152.5). People experiencing diabetes mellitus and hypertension were more likely to have less magnesium in their blood.

**Table 3: Multivariate Logistic Regression Analysis of Factors Associated with Hypomagnesemia**

| Variable | Adjusted Odds Ratio (AOR) | 95% Confidence Interval | p-value |
|---|---|---|---|
| **PPI Use > 6** | 58.1 | 22.2 – 152.5 | <0.001 |

| | | | |
|---|---|---|---|
| **months** | | | |
| **Diabetes Mellitus** | 23.1 | 6.4 – 82.6 | <0.001 |
| **Hypertension** | 3.2 | 1.4 – 7.1 | <0.001 |
| **Age (per year increase)** | 1.04 | 1.01 – 1.07 | 0.012 |




The high prevalence of hypomagnesemia (51.5%) in patients with chronic PPI use is further highlighted by these findings. Prolonged use beyond 6 months, older age and diabetes mellitus and hypertension were significant risk factors. However, there were no significant differences by type of PPI in the risk of hypomagnesemia.

## DISCUSSION

This shows a high prevalence (51.5%) of hypomagnesemia in patients taking PPIs chronically at odds with growing evidence for disruption of magnesium homeostasis by long term PPI therapy. Concordance with the majority of previous work has also shown that prolonged PPI use, particularly longer than 6 months, significantly increases the risk of hypomagnesemia through intraluminal absorption of magnesium ions. Magnesium is clinically important because it plays a critical role in several physiological processes, including regulation of neuromuscular function and cardiac rhythm and this adverse effect is of great clinical importance.

Like elderly patients, with multiple comorbidities and polypharmacy, are also at increased risk of developing hypomagnesemia which is associated with advancing age in the present study. Furthermore, diabetes mellitus and hypertension were independent predictors of hypomagnesemia. Each condition is associated with a change in renal magnesium handling and may itself contribute to PPI induced magnesium wasting. These findings indicate that clinicians should prescribe PPIs with increased vigilance in patients who have these comorbidities and that serum magnesium should be monitored regularly.

However, the type of PPI had no significant effect on magnesium levels, suggesting that hypomagnesemia is probably not a drug specific issue, but a class effect. It emphasizes the necessity for consistent watchfulness irrespective of the medicine used for the PPI. Although PPIs are widely used to treat acid related gastrointestinal disorders, there is a lack of awareness of its potential to cause hypomagnesemia.

This study's cross-sectional design limits the ability to infer causality and future prospective studies are needed to confirm these associations. However, our findings graphically illustrate the need for cautious PPI prescribing with short course therapy and magnesium monitoring in high risk populations. Informational education of healthcare professionals and patients about these hidden risks may improve patient safety and outcomes.

## CONCLUSION

This study ultimately shows that there is a large prevalence of hypomagnesemia associated with chronic PPI use, particularly in the geriatric and diabetic or hypertensive patients. The risk of this increases substantially with prolonged PPI therapy greater than six months. Healthcare providers should take note of these potential adverse effects associated with PPI use and apply guarded prescribing and constant vigilance of serum magnesium when treating vulnerable patients to prevent the hitherto unseen risks of prolonged PPI use.

## REFERENCES

1. Dutta, A. K., Jain, A., Jearth, V., Mahajan, R., Panigrahi, M. K., Sharma, V., ... & Bhatia, S. (2023). Guidelines on optimizing the use of proton pump inhibitors: PPI stewardship. Indian Journal of Gastroenterology, 42(5), 601-628.
2. Setia, A., Challa, R. R., Vallamkonda, B., Viswanadh, M. K., & Muthu, M. S. (2024). Clinical Implications of Proton Pump Inhibitors and Vonoprazan Micro/Nano Drug Delivery Systems for Gastric Acid-Related Disorders and Imaging. Nanotheranostics, 8(4), 535.
3. Lata, T., Trautman, J., Townend, P., & Wilson, R. B. (2023). Current management of gastro-oesophageal reflux disease—treatment costs, safety profile, and effectiveness: a narrative review. Gastroenterology report, 11, goad008.
4. Rückert-Eheberg, I. M., Nolde, M., Ahn, N., Tauscher, M., Gerlach, R., Güntner, F., ... & Baumeister, S. E. (2022). Who gets prescriptions for proton pump inhibitors and why? A drug-utilization study with claims data in Bavaria, Germany, 2010–2018. European journal of clinical pharmacology, 78(4), 657-667.
5. Targownik, L. E., Fisher, D. A., & Saini, S. D. (2022). AGA clinical practice update on de-prescribing of

proton pump inhibitors: expert review. Gastroenterology, 162(4), 1334-1342.
6. Rossi, A., Perrella, L., Scotti, S., Olmastroni, E., Galimberti, F., Ardoino, I., ... & Casula, M. (2024). Approaches to Deprescribing Proton Pump Inhibitors in Clinical Practice: A Systematic Review. Journal of Clinical Medicine, 13(20), 6283.
7. Awad, A., Al-Tunaib, A., & Al-Saraf, S. (2024). Physicians' perceptions and awareness of adverse effects of proton pump inhibitors and impact on prescribing patterns. Frontiers in Pharmacology, 15, 1383698.
8. Maideen, N. M. P. (2023). Adverse effects associated with long-term use of proton pump inhibitors. Chonnam medical journal, 59(2), 115.
9. Iolascon, A., Andolfo, I., Russo, R., Sanchez, M., Busti, F., Swinkels, D., ... & from EHA-SWG Red Cell and Iron. (2024). Recommendations for diagnosis, treatment, and prevention of iron deficiency and iron deficiency anemia. Hemasphere, 8(7), e108.
10. Sanam, S. (2024). Pharmacokinetic Drug Interactions of Multivitamins and Proton-pump Inhibitors (Doctoral dissertation, © University of Dhaka).
11. Choudhury, A., Jena, A., Jearth, V., Dutta, A. K., Makharia, G., Dutta, U., ... & Sharma, V. (2023). Vitamin B12 deficiency and use of proton pump inhibitors: a systematic review and meta-analysis. Expert review of gastroenterology & hepatology, 17(5), 479-487.
12. Di Bella, S., Sanson, G., Monticelli, J., Zerbato, V., Principe, L., Giuffrè, M., ... & Luzzati, R. (2024). Clostridioides difficile infection: history, epidemiology, risk factors, prevention, clinical manifestations, treatment, and future options. Clinical Microbiology Reviews, 37(2), e00135-23.
13. Gallo, A., Pellegrino, S., Pero, E., Agnitelli, M. C., Parlangeli, C., Landi, F., & Montalto, M. (2024). Main Disorders of Gastrointestinal Tract in Older People: An Overview. Gastrointestinal Disorders, 6(1), 313-336.
14. Kean, E. A., & Adeleke, O. A. (2024). Geriatric drug delivery—barriers, current technologies and the road ahead. Journal of Drug Targeting, 32(10), 1186-1206.
15. Szklarz, M., Gontarz-Nowak, K., Matuszewski, W., & Bandurska-Stankiewicz, E. (2022). Can Iron Play a Crucial Role in Maintaining Cardiovascular Health in the 21st Century?. International Journal of Environmental Research and Public Health, 19(19), 11990.
16. Morris, N., & Nighot, M. (2023). Understanding the health risks and emerging concerns associated with the use of long-term proton pump inhibitors. Bulletin of the National Research Centre, 47(1), 134.
17. Targownik, L. E., Fisher, D. A., & Saini, S. D. (2022). AGA clinical practice update on de-prescribing of proton pump inhibitors: expert review. Gastroenterology, 162(4), 1334-1342.
18. Holland, E., Matthews, K., Macdonald, S., Ashworth, M., Laidlaw, L., Cheung, K. S. Y., ... & Fraser, S. D. (2024). The impact of living with multiple long-term conditions (multimorbidity) on everyday life–a qualitative evidence synthesis. BMC Public Health, 24(1), 3446.