ORIGINAL ARTICLE

Relationship Between Long-Term Proton Pump Inhibitor Use and Serum Magnesium Levels: A Cross-Sectional Study

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ABSTRACT

Objective: The objective of this study is to determine the effect of long-term proton pump inhibitor use on serum magnesium levels

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: The study was carried out at the Department of Medicine, Combined Military Hospital, Peshawar, Pakistan, from August 2022 to September 2022.

Materials and Methods: Individuals from both genders were included with a minimum proton pump inhibitor usage of 1 year. Possible confounders, including patients with a history of smoking and alcohol use, GI disorders, hemodialysis dependence, and supplement use, were excluded. Data were summarized as frequencies and mean using a statistical package for social sciences software version 23. Standard deviation was calculated for quantitative variables.

Results: Out of 398 patients included in the study, 72.3% (n=288) were males, and 27.7% (n=110) were females. The mean duration of proton pump inhibitor usage was 3.88±3.79 years. The mean serum magnesium level measured was 0.9548±0.14mmol/L. 2.3% (n=9) individuals had serum magnesium levels <0.7mmol/L, and all of them were using 40mg/day of either of the PPIs, while the remaining 97.7% (n=389) had a serum magnesium level of ≥0.7mmol/L.

Conclusion: This study did not find any statistically significant impact of long-term proton pump inhibitor use on Serum Magnesium levels. Dietary magnesium may have a role in preventing this complication.

Keywords: *Dyspepsia, Magnesium, Omeprazole, Proton Pump Inhibitor.*

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Introduction

Proton Pump Inhibitors (PPIs) were made available in the market in the l1980s80's and have largely replaced the H_2 antagonists in the clinical practice.[1] They are perhaps the most commonly prescribed drug in clinical practice, preceded only by NSAIDs. They have been made available as over-the-counter drugs in many countries worldwide.[2]

PPIs are lipophilic weak bases that cross the parietal cell membrane and enter the acidic parietal cell canaliculus, where they become protonated, producing the activated form of the drug, which binds covalently and blocks the hydrogen-potassium adenosine triphosphatase enzyme system of gastric parietal cells thus irreversibly inhibiting acid secretion. This pump is located on the luminal membrane of the gastric parietal (Oxyntic) cells. It is responsible for pumping potassium into the cell, expelling H^+ ions out into the oxyntic cell canaliculi at a pH of 0.8. An acidic pH is required for the activation of the pepsinogens that digest the proteins.[3] The

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effect of reduced acid secretion is utilized in peptic ulcers, gastroesophageal reflux disease (GERD), Barrett's esophagus, Zollinger-Ellison syndrome, as well as in the eradication of *Helicobacter pylori* as part of combination regimens.[4]

Changing dietary habits in the modern world have led to a rise in the use of PPIs to relieve burning, and people have become more and more dependent on their use.

The side effects of the PPI are not very well studied. Although warnings have been issued from time to time by the US Federal Drug Agency but little has it had any effect on their use in clinical practice.[5] Concerns about side effects that have been described in studies worldwide include infections, impaired absorption of nutrients, dementia, kidney disease, and hypergastrinemia-related side effects. Several mechanisms have been proposed as the basis for their side effects, whether long-term or short-term and most have only been evaluated in observational studies demonstrating only weak associations and a substantial risk of confounding. However, a high probability of causality seems to be established for increased risk of gastrointestinal infections and rebound acid hypersecretion following discontinuation of treatment due to secondary hypergastrinaemia.[6]

Magnesium is the 4th most common cation in the body. It is found primarily in the muscles and bones as a constituent of numerous body structures, but it is also essential for enzymes involved in ATP production, hormone synthesis and release, thus playing a key role in regulating numerous physiological functions.[7,8] Despite its importance, it remains one of the least understood elements in human physiology. A daily intake of 3.6mg/kg is required to maintain magnesium balance under normal circumstances. It is mainly absorbed in the jejunum via transcellular or paracellular pathways.[9] Magnesium balance is maintained in the body by renal regulation of magnesium reabsorption.[10] Around 80% of the plasma magnesium is filtered in the glomerulus, and most of the reabsorption occurs in the thick ascending loop of Henle. A normal serum magnesium level is considered between 0.7-1.0 mmol/L. Hypomagnesaemia can be caused by reduced intake, diarrhea or malabsorption or urinary losses, or it can be induced by medications such as cisplatin preparations. Hypomagnesemia may cause tetany, tremor, seizures, muscle weakness, ataxia, nystagmus, vertigo, apathy, depression, irritability, delirium, psychosis, and, most dangerously, cardiac conduction abnormalities. Associated electrolyte abnormalities with low magnesium levels include hypokalemia and hypocalcemia, which are not corrected unless serum magnesium levels are corrected.[4]

The exact mechanism by which PPIs lead to a reduction in intestinal magnesium absorption has not yet been described. Whether all PPIs cause hypomagnesemia or certain agents do, remains a mystery. It is also not known if it is an idiosyncratic reaction. PPIs affect the enzyme and/or the channel functions of the active transport system involved in magnesium absorption either directly or via intestinal pH changes.[11]

An increasing PPI use in our population, over-the-counter availability of these drugs, and abstinence of patients from stopping these drugs and adopting a healthy lifestyle instead with reduced amounts of acid secretion triggers prompted us to carry out a short study for associating long-term PPI use to hypomagnesemia. This has been studied in many studies worldwide, and the association has been highlighted between the two. However, no such study has been done so far in Pakistan. This study will help in generating a good amount of data from this part of the world regarding the side effects of PPI, which have become a compulsory part of every clinical prescription.

This study aims to determine the effect of long-term proton pump inhibitor use on serum magnesium levels.

Materials and Methods

The cross-sectional study was conducted from August 2022 to November 2022. The sample size was calculated using the World Health Organization sample size calculator keeping in view the international prevalence of PPI prescription in the outpatient department. It came out to be 385. Sampling was done using the convenience sampling technique. All the patients visiting the outpatient department of the Combined Military Hospital Peshawar who met the inclusion criteria were

included in the study.

Inclusion Criteria included all patients with a PPI use of more than one year.

Exclusion Criteria excluded patients with intermittent or persistent PPI use of less than a year, patients with a history of smoking, alcoholism, malabsorption, diarrhea, vomiting, or hemodialysis, and patients using magnesium supplements or other drugs that may interfere with magnesium metabolism.

Permission was sought from the hospital ethical review committee prior to the study (reference number 00210/22, dated July 2022). A specialized data collection was developed for the collection of data from individuals that included a consent form for patients who participated in the study. After meeting the criteria mentioned above and informed consent, patients were subjected to blood sampling for serum magnesium levels in the outpatient department by trained laboratory technicians. History was obtained regarding duration, name of the agent, dose, and indication for PPI use. Data were summarized as frequencies and mean. Standard deviation was calculated for quantitative variables.

Results

Three hundred and ninety-eight (398**)** individuals with a mean age of 60±12.47 years were sampled for serum magnesium levels in the outpatient department. Their median age was 60 years. 72.3% (n=288) were males, and 27.7% (n=110) were females. They all were using PPIs for a mean duration of 3.88±3.79 years. The maximum duration of PPI use reported was 22 years, while the mode duration was 1 year (n=127 or 31.9%). The duration of PPI use in the different age groups was studied as well, and the age group 61 to 80 years was found to have the longest duration of use, as depicted in Figure 1.

Out of 398 individuals, 98% (n=390) individuals were using PPIs for dyspepsia, 1% (n=4) were using them for gastroesophageal reflux disease, and 1% (n=4) for gastritis (Figure 2). had No previous comorbid conditions were reported by 60% (n=239) of the participants. Solely, diabetes mellitus was reported by 18.8% (n=75) of the individuals, whereas 23.1% (n=92) had both diabetes mellitus and hypertension, 6.3% (n=25) had diabetes mellitus, hypertension, and ischemic heart disease combined. Hypertension alone was found in 16.6% (n=66), while 7% (n=28) had hypertension with ischemic heart disease. Only 4.3% (n=17) had ischemic heart disease alone. Omeprazole was being used by 96.5% (n=384) of patients, while 3.3% (n=13) were using pantoprazole, and only 1 individual was using esomeprazole. A dose of 40 milligrams per day of either of the drugs was being used by 83.9% (n=334) of individuals, while 16.1% (n=64) took 20 milligrams per day of either of the drugs. Among the participants of the study, 20.8% (n=83) individuals were ≤50 years of age, while 79.2% (n=315) had age >50 years. The mean Serum magnesium level measured was 0.954±0.14 mmol/L. Only 2.3% (n=9) individuals had serum magnesium less than 0.7mmol/L, and all of them were using 40mg/day of either of the PPIs, while the remaining 97.7% (n=389) had serum magnesium ≥0.7mmol/L (Figure 3).

Discussion

Most of the participants of the study were in the elderly age group. Elderly people often have a sedentary lifestyle and low gastrointestinal motility, which frequently causes dyspepsia. With our dietary habits switching to more refined food products and a sedentary lifestyle brought about by the industrial age, the use of proton pump inhibitors has become widespread. Any new onset dyspepsia beyond the age of 55 years must be investigated with an esophagogastroduodenoscopy (OGD), but it is sometimes delayed in our setup because of limited resources and the high burden of the disease.[12] A trial of PPIs is generally preferred over going for OGD. The lack of drug regulatory mechanisms in Pakistan and open access to drugs for the masses has led to self-medication and misuse of many drugs, including PPIs. A study conducted at Aga Khan University Hospital Karachi in the year 2021 showed that 66.2% of the patients visiting the outpatient department of the hospital were using PPIs without any labelled indication for it.[13] The mean duration of PPI use was around 3 years, indicating that their use has been on the rise in recent years. A study conducted at Post Graduate Medical Institute, Lahore, by Hassan G et al. highlighted that PPIs were overused while prescribing drugs to discharged patients from the hospital without a clear indication.[14] A Hungarian study by Matuz M et al. pointed out that an

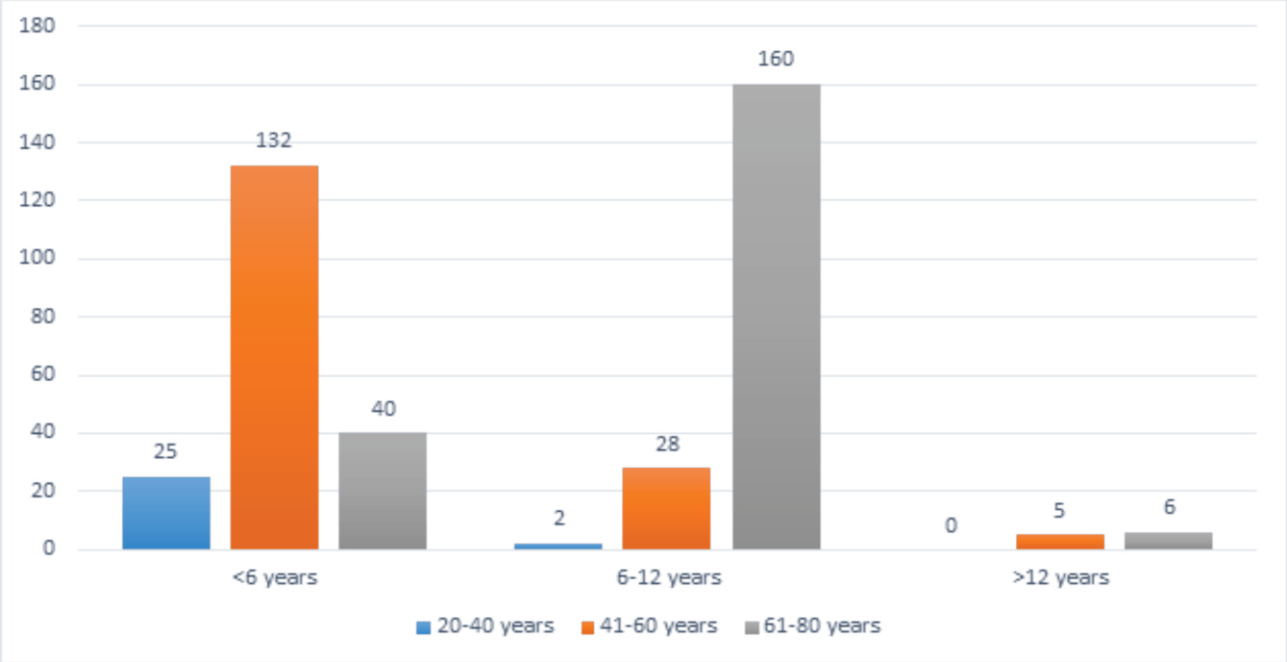

Fig 1: Duration of use of PPI in different age groups (n=398)

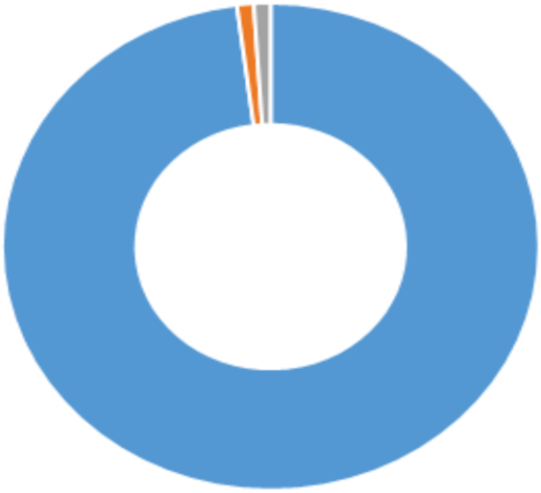

Fig 2: Indications of PPI use n (%)

increasing proportion population is getting exposed to PPI.[15] The longest use of PPI was seen in the middle age group hinting at the impact of changes in dietary patterns in our society and the introduction of PPIs into clinical practice.

Most of the participants enrolled had underlying conditions such as diabetes mellitus, hypertension, ischemic heart disease, chronic kidney disease, or a combination of these. This trend may suggest that PPI has become a part of the routine prescription from clinicians. Some of these conditions are also known to have an independent effect on serum magnesium levels. Almost all the precipitants of the study were using omeprazole, the first drug in the PPI class, introduced back in 1988 and is easily available in pharmacies.[16]

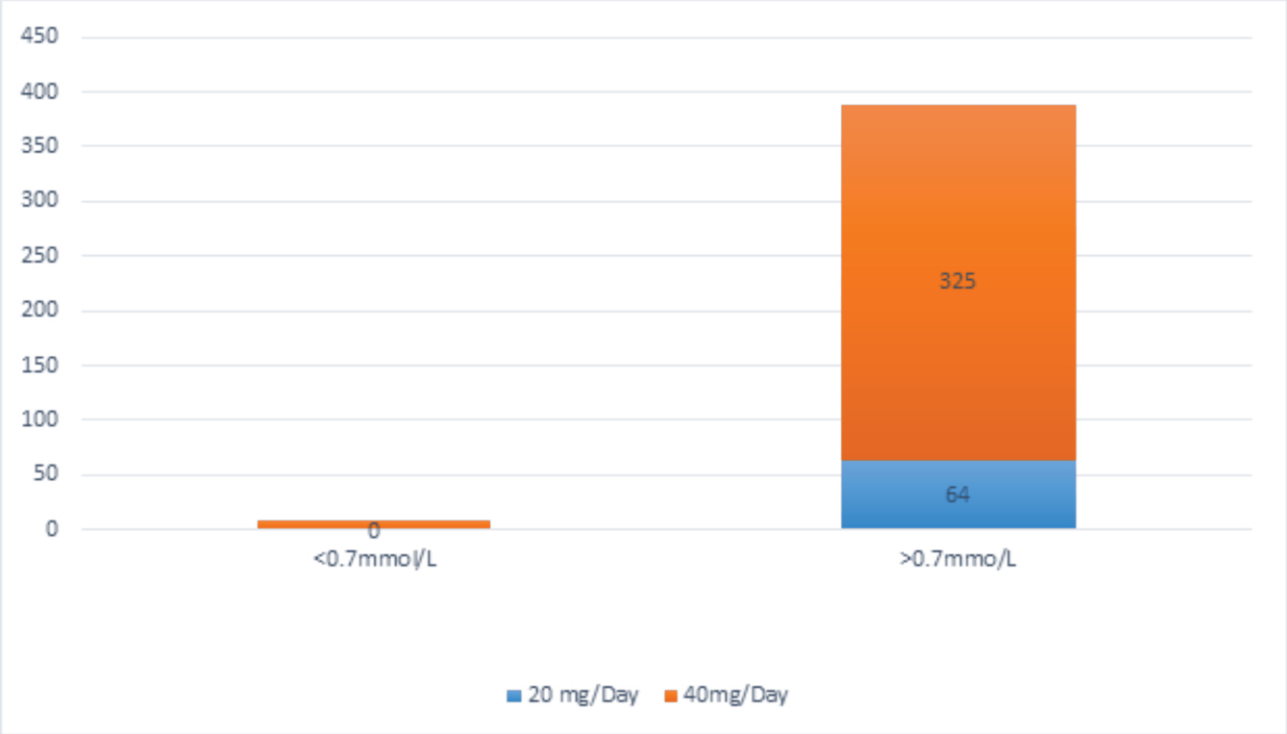

Fig 3: Frequency of Serum magnesium level (mmol/L) in individuals using PPI (40mg/day)

The mean serum magnesium level was 0.954 mmol/L, and only 9 participants had a serum magnesium level below 0.7 mmol/L to be labeled as hypomagnesemia. These participants were using 40mg/day of a PPI drug, a relation that was not found statistically significant. A meta-analysis conducted by Liao S et al. from a number of reputable databases, comprising a total of 15 studies including 129,347 participants, failed to draw a definite relationship between PPI use and hypomagnesemia and concluded that further research is still needed.[17] Similarly, Ala I Sharara et al. from Lebanon have reported that in the absence of known precipitating factors, chronic PPI use has not been found to be associated with hypomagnesemia.[18]

Some studies have reported that people using either low or middle dosing (20-40 mg/day) of PPI develop hypomagnesemia.[19] Srinutta et al. did a meta-analysis that comprised cross-sectional studies, case-control studies, and a cohort study, with a total of 131,507 patients and found that PPI users had 1.83 times more risk of developing hypomagnesemia as compared to the non-user group.[20] In the setting of our study, we may assume that a low incidence of hypomagnesemia can be related to the dietary habits and water content of magnesium of the Khyber Pakhtunkhwa province population and warrants further probing.[9]

Limitations

Our study was conducted at a single center which does not represent the entire population of the region. Most of the participants included in the study were males. Moreover, due to lesser or non-availability of other drugs in the PPI class, including esomeprazole, pantoprazole, rabeprazole, and lansoprazole, we cannot say for sure that hypomagnesemia cannot occur with other medications.

Conclusion

This study did not find the effect of long-term PI use on Serum Magnesium levels. PPI use has been on the rise in our population for the last 2 decades. It has exposed our population to the side effects of the treatment as well. Patients are more familiar with the use of these drugs. Patients have a tendency to self-medicate due to over-the-counter availability without a prescription.

Recommendations

We recommend that patients should be educated on a regular basis regarding the adverse drug reactions

of these drugs, and pharmacies should not be allowed to issue them on a non-prescription basis.

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