

# Proton pump inhibitor use and its relation to serum magnesium levels among hemodialysis patients: A single centre study in a South Indian tertiary care hospital

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## Abstract

**Introduction:** Proton pump inhibitors (PPI) are commonly used in clinical practice for various indications such as gastritis, peptic ulcer and gastroesophageal reflux disease. In Observational studies, Hypomagnesaemia has been associated with PPI use in general population. Hypomagnesaemia is a significant predictor of mortality especially in HD patients. There is a lack of data regarding association of PPI with hypomagnesemia in dialysis population.

**Materials and Method:** Study was conducted in Tertiary care hospital using a single-centre observational design on 87 prevalent HD patients on twice weekly and thrice weekly maintenance HD with regular PPI use for >2 weeks. Serum Magnesium (Mg) level was determined using pre dialysis serum samples by colorimetric-kit method. Mean of two consecutive serum Mg levels measured at 6 weeks interval was calculated for further analysis. Clinical, demographic data along with duration of PPI use in months were recorded. Patients on diuretics, chronic diarrhoea and HD for Acute Kidney Injury were excluded. Student t-test was used for comparison between PPI users and non users.

**Results:** 55 patients were on Proton Pump Inhibitors at the time of study. All patients were dialyzed with dialysate Mg of 1.2mg/dL (0.7 mmol/L). Average duration of PPIs use was 6 months (6± 1.45 months). Serum Mg levels among PPI users was 2.5 mg/dL and non-users was 2.4 mg/dL. No correlation was found between serum Mg levels and duration of PPIs use ( $p > 0.8$ ).

**Conclusion:** In our study we did not find any association between hypomagnesemia and PPI use in hemodialysis patients. As our study was single centered, small population with short follow up, further well defined long term Randomized controlled trials on Mg levels with PPI use are needed.

**Keywords:** Hypomagnesemia, Proton pump inhibitor, Chronic kidney disease, Hemodialysis.

## Introduction

Magnesium (Mg) is the 4<sup>th</sup> most common cation in our body, which is a co-factor for enzymatic reactions involved in many functions central to cellular homeostasis.<sup>1</sup>Low serum magnesium levels has been associated with elevated C - reactive protein indicating hypomagnesaemia and low grade inflammation are interactive risk factors.<sup>2</sup>Hypomagnesaemia is a predictor of mortality in HD patients.<sup>3</sup>In Observational studies involving non-dialysis population, PPI use has been associated with hypomagnesaemia.<sup>4</sup> In 2011, United States Food and Drug administration (US-FDA) issued a drug safety communication warning that low magnesium levels may be associated with prolonged use of PPIs. In healthy individuals, serum magnesium is maintained in the normal range by the kidneys, gastrointestinal tract, and bone. Recent observational studies have shown high gastric pH associated with PPI use may alter the Mg transport resulting in a gastrointestinal loss of magnesium. In hemodialysis patients, renal excretion of magnesium is minimal and serum level depends on three main factors: oral magnesium intake, gastrointestinal absorption and dialysate Mg concentration

Intracellular magnesium regulates the activity of TRPM6(transient receptor potential cation channel subfamily M6) along with P<sup>H</sup> whereby a more acidic

milieu causes increase in TRPM6 activity.<sup>5,6</sup> PPI increases the lumen pH by decreasing proton secretion, resulting in decreased TRPM6 activity which decreases magnesium absorption.<sup>7-9</sup>As a matter of fact, long term PPI use is found to increase the intestinal contents of protons in the distal small bowel and significantly decreases basic pancreatic secretions.<sup>10,11</sup> However, since most of the active magnesium reabsorption occurs in the cecum and colon, its effect may dissipate before reaching these locations. Many factors make the Haemodialysis population well suited to study the relationship between PPI use and serum Mg concentration. First, Haemodialysis patients are usually oliguric or anuric, which reduces potential confounding related to renal Mg loss. Furthermore, Haemodialysis patients are typically dialyzed against an ionized Mg concentration of 1.2 mg/dL in the dialysate, such that the dialysate Mg concentration may not be sufficient to raise serum Mg in most instances.<sup>12</sup>

Hence we hypothesised that serum Mg levels are lower in HD patients with PPI use and duration of PPI use correlates with serum Mg levels.

## Materials and Method

This was a hospital based observational study conducted at three dialysis centers attached to Justice K.S Hegde Charitable Hospital in Mangaluru,

Karnataka. 87 adult patients (age > 18years) on maintenance hemodialysis with dialysis vintage of minimum three months were included in the study. All included patients were on regular HD either twice or thrice weekly (four hours/session). Serum magnesium levels were measured on two occasions at six week interval in predialysis sample using calorimetric- kit method and an average of the two readings were taken. The relationship between PPI use and serum Mg concentration was determined in unadjusted analysis and also adjusted for age, gender, cause of ESRD, diabetes, time on HD. Data on PPI use was extracted from the dialysis pharmacy database, and time on PPI was also recorded from dialysis case sheets. Patients on HD for Acute kidney Injury, those who underwent ileostomy or colostomy, those with history of chronic diarrhea were excluded. Informed consent was obtained based on the study's retrospective nature after clearance from institutional ethical committee. Hypomagnesaemia was defined as serum magnesium levels < 1.5 mg/dl.<sup>13</sup>

### Statistical Analysis

Continuous data was presented as mean  $\pm$  standard deviation, or median and interquartile range as appropriate. Continuous variables were compared using Student's t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data, and chi square test for categorical variables. A multivariate linear regression model was used to determine the independent effect of PPI on Mg levels after adjusting for age, gender, race, diabetic status, cause of ESRD, time on HD and dialysate Mg. Among PPI users, a Cox proportional hazard model was used to determine whether time on PPI was predictive of serum Mg level. Statistical significance is defined as a p value

of <0.05. All statistical analysis was done in SPSS version 20.

### Results

Eighty seven Patients on maintenance HD for ESRD were included in the study. The baseline characteristics of studied population are displayed in Table 1 and Table 2. Among population studies 68 were male and 19 were females. A large proportion of patients were on PPI (63%). Number of patients above 65 years were 28, among them 18 were on regular PPI use. More than 50% of patients were on Pantoprazole, Other PPI used were Rabeprazole, and Esomeprazole. Diabetes Mellitus was the most common cause of ESRD in our population followed by Systemic Hypertension. All patients were dialysed against dialysate Mg concentration of 1.2mg/dL (0.7mmol/L). 55 patients were on regular PPI use at the time of study, mean duration on PPI was around 6 months (6 $\pm$ 1.45 months). Patient demographics and the dose of PPI used are as shown in the Table 1.

As shown in Table 1, among PPI users, mean serum magnesium level was 2.5 $\pm$ 0.49 mg/dL in comparison to non PPI users (mean 4 $\pm$ 0.27 mg/dL). There was no correlation between serum magnesium levels and PPI use in unadjusted analysis and after adjusting for patient age, gender, cause of ESRD and duration on HD.

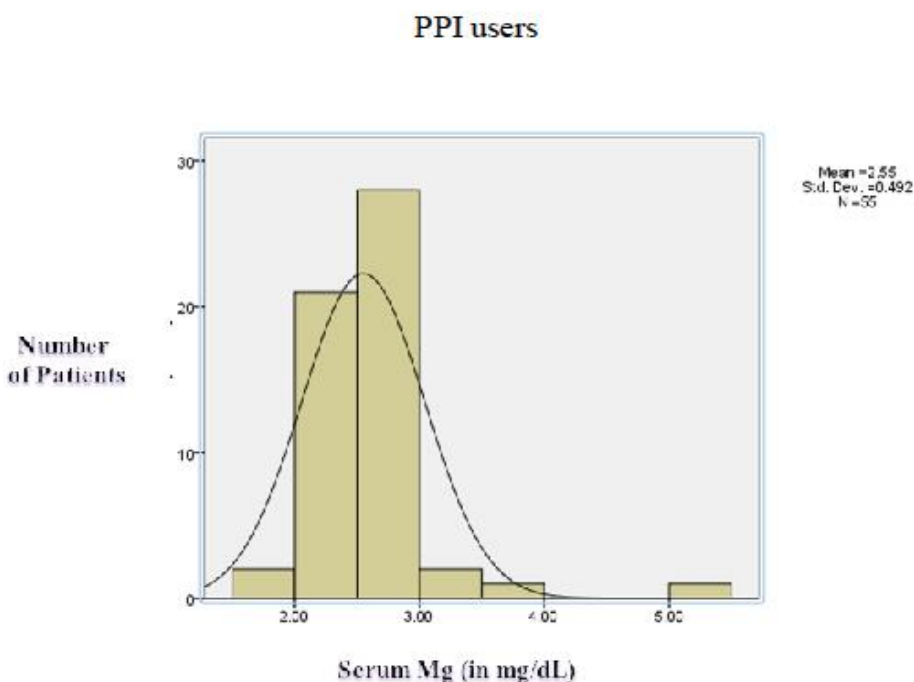
Hypomagnesemia, defined as a serum magnesium level < 1.5 mg/dL.<sup>13</sup> All individuals included in the study were observed to have normal serum magnesium levels. No significant difference in Serum Mg levels were noted among PPI users and non-users. All patients had serum Mg levels > 1.6 mg/dL. All PPIs were used in standard doses available in market. Since potency of all PPI is considered equipotent, analysis was not done for individual drugs.

**Table 1: Characteristics of population studied**

Demographic variable	PPI users (n=55)	PPI non-users (n=32)
1. Age (Mean) in years	58.2 $\pm$ 12.56	58.6 $\pm$ 11.59
2. Gender		
Male (%)	44 (80)	24 (75)
Female (%)	11 (20)	08 (25)
3. Serum Mg (Mean) mg/dL	2.5 $\pm$ 0.49	2.4 $\pm$ 0.27
4. Time on HD (in months)	40 $\pm$ 5.26	23 $\pm$ 3.13
5. Dose of PPI used		
Omeprazole	40 mg	-
Pantoprazole	40 mg upto 80mg	-
Rabeprazole	20mg upto 40mg	-

**Table 2: Causes of CKD**

	PPI users (N=55)	PPI non- users (N=32)
a. Systemic Hypertension	15	08
b. Diabetes Mellitus	25	11
c. Glomerulonephritis	06	04
d. Polycystic Kidney Disease	00	03
e. Others	09	06

**Fig. 1: Histogram of serum Mg levels among PPI users**

### Discussion

In our Observational study, involving patients on maintenance HD, we did not find hypomagnesemia in either PPI users or non-users. We found serum Magnesium levels were within normal limits in all the patients. In our study, patients with diabetes were unequally distributed in both PPI users and non-users, Residual renal function in our patients was negligible as eGFR was < 10mmol/L. Since PPIs are used off label and few observational data have shown hypomagnesemia among PPI users, our findings are to be taken with caution Fig. 1 shows Histogram of serum Mg levels among PPI users and non-users

In our study, we measured total serum Magnesium levels and did not consider ionized magnesium levels. But in HD patients, a lower ionized fraction could possibly due to a higher fraction of complexed magnesium (phosphates, citrate, sulphates), but low serum albumin levels could also lead to a higher fraction of ionized magnesium, thus opposing this effect significantly.<sup>14,15</sup> Thus, we opine that, the ionized

magnesium fraction in dialysis patients seems to be always variable. In HD and peritoneal dialysis (PD) patients, both total and ionized magnesium concentrations are often slightly elevated above the normal level and have been shown to be dependent on residual renal function. As all our patients were on HD with eGFR < 10 mL/kg/m<sup>2</sup> who are usually anuric or oliguric, serum Mg levels were not adjusted to residual renal function.<sup>16</sup>

As young erythrocytes have a higher magnesium concentration than older cells, one might expect that patients on dialysis would be having higher red blood cell magnesium concentration.<sup>17</sup> But in fact, the average magnesium level of erythrocytes was found to be consistently higher in several previous studies on dialysis patients compared with healthy volunteers.<sup>18-20</sup> Hence, a change in serum Mg levels in PPI users may not cause clinically significant hypomagnesemia as evident in our study. But majority of the reported cases of hypomagnesemia were in non-dialysis patients on PPI use for more than 8-9 years. However in our study,

the average duration of PPI use was only six months. It is also possible that chronic PPI use may decrease the intestinal magnesium absorption and still net change in serum magnesium levels may be prevented by compensatory magnesium efflux from the bone.

In case of gastrointestinal absorption, passive reabsorption (paracellular) regulated by the enterocyte tight junction proteins claudin-16 and claudin-19 which are responsible for approximately 90% of the absorption.<sup>21</sup> Passive intestinal absorption of Magnesium is dependent on low affinity and concentration. On the other hand, an active transcellular process is mediated by transport channels, and by TRPM6 and TRPM7, which are present in the apical membranes of the enterocytes.<sup>22</sup> Magnesium excretion is regulated tightly by TRPM6 in the renal distal convoluted tubules. The PPI inhibits H<sup>+</sup>/K<sup>+</sup>-ATPase activity, resulting in reduced excretion of protons into the intestine, this effect impairs TRPM6 mediated Mg<sup>2+</sup> absorption stimulated by extracellular protons.<sup>23</sup> It is possible that rare genetic variants in magnesium transport channels or cell junction proteins might account for the observed reports of profound hypomagnesaemia which may not be applicable to general populations.

There are few case reports of symptomatic hypomagnesemia in hospitalised and out patients who were on long term PPI<sup>24-27</sup>

Misra et al in their cross-sectional study on 155 patients on HD found correlation between hypomagnesaemia and PPI use but did not reach statistical significance.<sup>28</sup> John Danziger et al in his large scale observational study with PPI alone did not find significant correlation, but hypomagnesaemia was noted from patients with concurrent PPI and diuretics. Sakaguchi et al reported higher all-cause and cardiovascular mortality in HD patients in the lowest magnesium level (< 2.3 mg/dL).<sup>29</sup> Akio Nakashima et al in their study used serum magnesium levels < 2 mg/dL to define hypomagnesaemia<sup>30</sup> and found correlation between level of hypomagnesaemia and use of PPI, but in our study we defined hypomagnesaemia as < 1.6 mg/dL as there is no adequate evidence that higher cut off with regards to magnesium levels needs to be considered in patients on HD. Hypomagnesaemia increases all cause mortality and is an independent predictor of cardiovascular morbidity and mortality with levels < 1.7 mg/dL.<sup>30</sup> It is still not clear that considering higher cut off levels has role in clinical prediction of mortality risk.

Although the study had limitations such as being single centred, small study population and observational study design. It is the first study in India to address relation between PPI use and serum Mg levels in patients on maintenance HD. Our study provides reasonable data for lack of association of short term PPI use and hypomagnesemia in HD patients.

## Conclusion

In Our study, we did not find any correlation between Hypomagnesemia and PPI use. Long term, well defined observational studies are required further confirmation.

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