Serum Vitamin B_{12} (vit B_{12}) and Serum Magnesium Status in Patients with Long Term Proton Pump Inhibitors (PPI) Use: A Cross Sectional Study done at Tripura Medical College and Dr. BRAM Teaching Hospital

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ABSTRACT

Introduction: Proton pump inhibitors are seen to affect the serum vitamin B_{12} and potassium levels. The aim of this study was to determine whether long-term proton pump inhibitor use (more than two years) was associated with an abnormal serum vitamin B_{12} and serum magnesium status in the body.

Material and Methods: This prospective cross-sectional study enrolled 60 proton pump inhibitor (PPI) users, mean age: 50.78 (SD-10.14) years. Demographic data, serum levels of magnesium, vitamin B_{12} and potassium were recorded. The reference level used for serum magnesium, vitamin B_{12} and potassium were (1.8-2.4 mg/dl), (211-911 pg/ml), and (3.5-5.5 mEq/L) respectively.

Results: Among the enrolled 60 PPI users, the prevalence of low serum magnesium and low serum vitamin B_{12} levels were 16 (26.67%) and 4 (6.67%) respectively. Mean PPI use was 5.123 years. From our study it was found that Low serum vitamin B_{12} was associated with PPI use of more than four years whereas, low serum magnesium level was found irrespective of duration of PPI use.

Conclusion: Hypomagnesemia is common in long term PPI use and low vitamin B_{12} is associated with more prolonged use.

Keywords: Food and Drug Administration, Clostridium difficile, Cardiac arrhythmia, Transient receptor potential melastin, Hypokalemia, Achlorhydria.

INTRODUCTION

Proton-pump inhibitor (PPI) drugs (e.g. Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole and Rabeprazole) are potent inhibitors of gastric acid secretion which blocks the hydrogen–potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell.[2] They are widely used for the treatment and prevention of dyspepsia, associated with peptic ulcer disease, esophagitis and gastritis. Although they are well tolerated, they can have serious side effects. PPI therapy, by decreasing gastric acidity, can increase the risk of gastro-intestinal infections like Clostridium difficile enterocolitis.[2] Recent reports reported that the long term use of PPI induces hypomagnesemia.[4-5] On March 2, 2011, the U.S. Food and Drug Administration (FDA) issued a drug safety alert regarding long-time PPI use can cause low levels of serum magnesium.[6]

The postulated mechanism of PPI-induced hypomagnesaemia involves inhibition of intestinal magnesium absorption through transient receptor potential melastin (TRPM) 6 and 7 cation channels.[7] Severe hypomagnesemia can cause tetany, malignant cardiac arrhythmias, generalized seizures, and other metabolic disturbances i.e. hypokalemia and hypocalcemia.[8]

Vitamin B_{12} (cobalamin) is an essential water-soluble nutrient acquired from animal-derived food sources meats, poultry, eggs, fish, shellfish and dairy products. Absorption of Vitamin B_{12} requires peptic enzymes to cleave dietary B_{12} from dietary proteins. This is primarily done by pepsin, which requires gastric acid to activate pepsin from its pepsinogen precursor. Vit B_{12} absorption starts with peptic cleavage in the stomach, at acid pH of food-bound B_{12}, which then binds to salivary R protein[8-11] in the duodenum; pancreatic enzymes release R-protein-bound B_{12}, which binds to IF. The B_{12}–IF complex is absorbed in the terminal part of the ileum after binding to its receptor, cubilin.[12] Absorbed vit B_{12} from ileum is cleaved from IF by cathepsin L and then transported in the blood bound to transcobalamin II. An enterohepatic cycle promotes the conservation of vit B_{12}.[13] Without gastric acid, vit B_{12} would not be cleaved from dietary protein and would not be able to bind with R-proteins, which protect vit B_{12} from pancreatic enzymes. It has been hypothesized that since gastric acidity is essential for vit B_{12} absorption, acid suppression by PPI can lead to malabsorption and ultimately vit B_{12} deficiency from achlorhydria and atrophic gastritis.[14]

Aim of the study was to investigate whether long-term proton pump inhibitor use (more than two years) was associated with an abnormal serum vitamin B_{12} and Magnesium status in body and also to evaluate the duration of PPI use and its association with hypomagnesaemia and low Vit B_{12}.

MATERIAL AND METHODS

This cross sectional study was done over a period of six months at TMC and Dr. B. R. Ambedkar Teaching Hospital after obtaining the ethical approval from institutional ethical committee. A total of 60 patients with long-term PPI use were included in the study after taking written informed consent from them.

Inclusion Criteria

1. Male / female subjects aged 18-65 yrs.
2. On PPI therapy more than two years.
3. Ability to comply with the requirements of the protocol and be available for study visits over six months.

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How to cite this article: Avik Chakraborty, Dulal Chakraborty, Nirmalya Saha, Sannibesh Das. Serum vitamin B_{12} (vit B_{12}) and serum magnesium status in patients with long term proton pump inhibitors (PPI) use: a cross sectional study done at tripura medical college and Dr. BRAM teaching hospital. International Journal of Contemporary Medical Research 2016;3(6):1594-1596.

4. Willing to participate in the study.

Exclusion Criteria

1. Subjects aged < 18 and >65 yrs.
2. Patients on vitamin B_{12} and magnesium supplementation over last six months.
3. Strict vegetarian.
4. Diseases which interferes vitamin B_{12} absorption i.e. Achlorhydria, Hypochlorhydria, Pernicious anemia, Gastrectomy, Chronic pancreatitis, Malabsorption syndrome, Small intestinal bacterial overload, Short bowel syndrome, Crohn's disease, Celiac sprue, etc.
5. Drugs which interferes vitamin B12 and magnesium level on body i.e. Diuretic, Metformin, Potassium, Chloramphenicol, Angiotensin converting enzyme inhibitors, beta blockers, Digitalis, Gentamycin, Amphotericin B, Cisplatin etc.

Calculation of Sample Size:

$n = 4\,p\,q\,/L^2$

Where p = Prevalence = 13% (Prevalence as per the study, "Association of Proton pump inhibitor with Hypomagnesaemia: A cross sectional study at a Tertiary care Hospital of Anand District."[1]

q = (100-p) =87 %, L = Allowable error (absolute) = 9 %

By the formula, $n = 4\,p\,q/L^2$

Calculated sample size = 55.

Extra 10% sample added to compensate any incomplete data

So, final sample size = 60.

STATISTICAL ANALYSIS

All relevant data so collected were entered in the master chart and analyzed using IBM SPSS Statistics 20. Results obtained were based on descriptive statistics.

RESULT

Of the 60 participants, male were 30 (50%) and female 30 (50%). Age >45 years were 45 (75%) and <45 years were 15 (25%). Mean age was 50.78 years. The prevalence of participants with low serum magnesium and low serum vit B_{12} levels were 16 (26.67%) and 4 (6.67%) respectively. The prevalence of PPI users with low serum magnesium and low serum vit B_{12} levels in younger (<45 years) were 2 (12.5%) and 0 (0%) respectively and among older (>45 yrs) were 14 (87.5%) and 4 (100%) respectively (table-1). Mean PPI use was 5.123 years.

DISCUSSION

In 2011, Cundy T et al. reported 30 cases of severe hypomagnesaemia in patients on PPI therapy.[15] In 2008, Agarwal et al. reported a 43-year-old man, on high-dose omeprazole for reflux esophagitis for 3 years developed symptomatic hypomagnesaemia and hypocalcaemia and withdrawal of PPI therapy led to normalized level in 6 wks and symptoms in 12 wks.[16] In 2008, Cundy et al. reported 2 patients with severe hypomagnesaemia and hypocalcaemic seizures, and who were on long-term PPI therapy.[17] In 2006, Epstein et al. reported two patients on PPI therapy presented with tetany due to hypomagnesaemic hypoparathyroidism, and withdrawal of the PPI normalized the metabolic abnormalities.[18] In 1980, Steinberg WM et al. reported the effect of cimetidine on the uptake of protein-bound cyanocobalamin, the excretion of radio-active cyanocobalamin decreased from 2.3% to 0.2% after a morning dose of cimetidine300 mg.[19] In 1994, Macuard et al. reported that treatment of healthy subjects with omeprazole 20 mg or 40 mg daily for 2 weeks resulted in decreased vitamin B_{12} absorption as measured by a modified Schilling test. Cyanocobalamin absorption was reduced from 3.2% to 0.9% in those who received 20 mg omeprazole, and from 3.4% to 0.4% in those who received 40 mg omeprazole.[20]

In our cross-sectional study, prolonged acid suppression due to proton pump inhibitor use was associated with significantly low S. Magnesium level among 16 patients (26.67%) and low serum vit B_{12} level in 4 patients (6.67%). All age groups of patients using long term PPI were equally involved with low serum Mg level, suggesting that age is not a factor influencing S. Mg level in chronic PPI users (figure-1). Whereas, low S. Vit B_{12} levels are found in older aged patients with chronic PPI use.

From our study it was found that Low serum vitamin B_{12} was

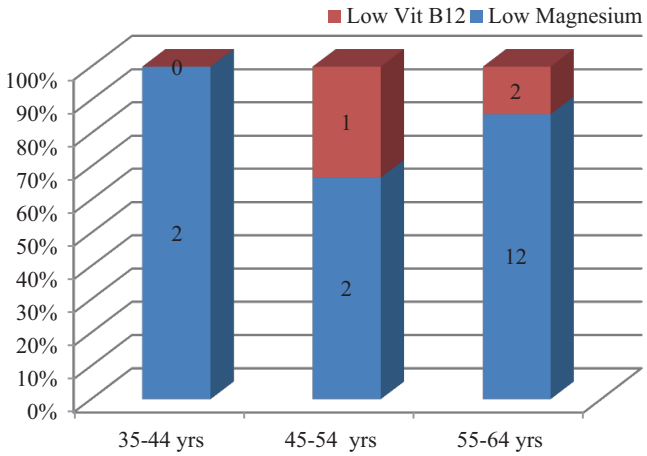

Figure-1: Age Distribution of low serum magnesium and low serum vitamin B_{12} level

	All (n= 60)	Low magnesium(n=16)	Low vitamin B_{12} level(n=4)
Age in years	50.78(SD-10.14)	55.63(SD-7.182)	58.75(SD-5.50)
Male	30(50%)	8(50%)	4(100%)
Female	30(50%)	8(50%)	0
Height	1.5570(SD-0.0558)	1.56(SD-0.6)	1.57(SD-0.012)
Weight	58.75(SD-7.53)	57.62(SD-7.6)	64(SD-2.3)
BMI	24.18(SD-2.26)	23.44(SD-2.33)	25.98(SD-1.36)
Duration of PPI	5.12(SD-2.81)	5.43(SD-3.52)	10
Magnesium	1.84(SD-0.18)	1.6(SD-0.13)	1.95(SD-0.058)
Vitamin B_{12}	436(SD-184.1)	464(SD-220.53)	207(SD-1.16)
SD - Standard Deviation. BMI - Body mass index.			

Table-1: Demographic data of long term PPI users in relation with low serum magnesium and low serum vitamin b12 level.

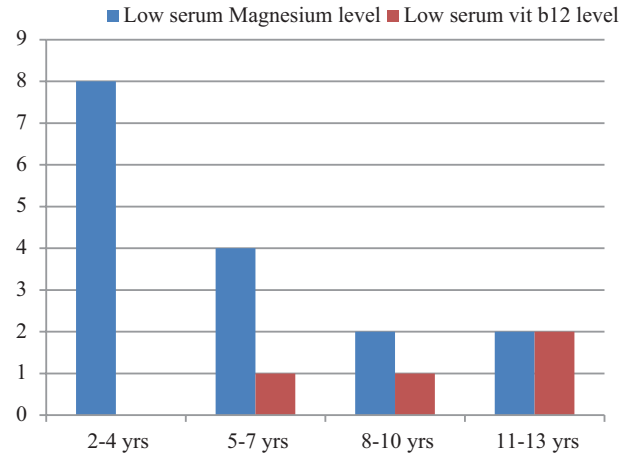

Figure-2: Duration of PPI with low serum magnesium and low serum vitamin B_{12} level.

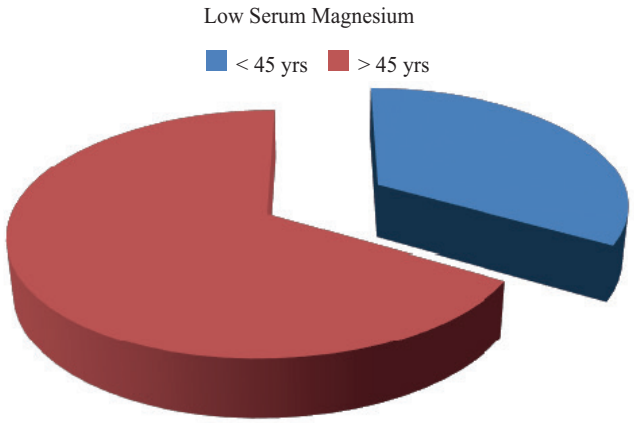

Figure-3: Low Serum Magnesium in reference to age in Chronic PPI users.

associated with PPI use of more than four years whereas, low serum magnesium level was found irrespective of age and duration (figure-2). Hence, Hypomagnesemia was common in long term PPI use and low vitamin B_{12} was associated with more prolonged use.

Here, among 60 participants age >45 years were 45 (75%) and <45 years were 15 (25%).Hypomagnesemia was found in 2 (<45 yrs) and 14 (>45 yrs) among all long-term PPI users (figure-3).

CONCLUSION

Our cross-sectional study revealed significantly lower serum Mg level and serum Vit B_{12} level in long term PPI users and it implies that long-term use of PPIs could be associated with subclinical Mg and vit B_{12} insufficiency or deficiency status. Hypomagnesaemia was seen irrespective of duration and age of long term PPI use, however low vit B_{12} was found in older individuals after more prolonged use. Our study also revealed that since different types of PPIs were involved with hypomagnesaemia, collectively we could conclude that it was a class effect of all types of PPIs. Future studies that include non PPI users as a control group and other prospective studies that include pre-treatment and post-treatment S. Mg and S. Vit B_{12} levels when initiating PPI therapy will provide more direct evidence for the association of PPIs with s. Mg and s. vit B_{12} levels and shall clarify its underlying mechanism(s) involved. Limitations of our study were: Sample size was small, duration of study was short, and serum levels of magnesium and vit B_{12} were not recorded prior to the study.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 07-04-2016; **Published online**: 07-05-2016