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An Approach to Determine the Effect of Proton Pump Inhibitors Intake on Calcium Absorption in Blood



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ABSTRACT

Proton pump inhibitors (PPIs) are one of the most selling and safe over the counter drugs used in many hyper acidic diseases. However, different studies over the past few years while assessing the changes in calcium absorption related to PPI therapy showed apprehension over the association of calcium absorption with PPI intake. This study was carried out to determine the long-time effect of PPI intake (at least for six months) on calcium absorption. In this survey blood test report of serum calcium concentration of 143 (Age ranges from 20-60) patients who have been taking PPI at least for six months due to any acid-related disorder and not been taking calcium supplement was collected from three different hospitals in Bangladesh. The average blood serum calcium concentration (BSCa) of all the patients was found 7.94 mg/dL where female patients possess presumably less average BSCa concentration than the male patients (8.05mg/dL and 7.88 mg/dL respectively). The patient's age ranges from 51-60 years found to have the lowest average BSCa concentration (7.2 mg/dL) among all the patients. Omeprazole, Esomeprazole, Rabeprazole, and Pantoprazole were mostly prescribed PPIs whereas patients taking rabeprazole found to have the lowest level of BSCa concentration. The above data shows a subtle change of blood serum calcium concentration than the normal level (8.5-10.5 mg/dl). However, further study might be necessary to determine whether there is any association in the effect of PPI on calcium.

INTRODUCTION

Proton pump inhibitors are placed in the list of essential medicines and health products by the World Health Organization[1]. Histamine-2 receptor antagonists are replaced by PPIs because of their superior efficacy in the treatment of acid-related disorders[2]. In the treatment of gastroesophageal reflux disease, Helicobacter pylori-induced ulcers, duodenal ulcers, erosive esophagitis, and other pathological hypersecretory conditions, including Zollinger-Ellison syndrome PPIs are widely used[3]. By inhibiting the hydrogen pump H^+/K^+ ATPase irreversibly, PPIs prevent the last and rate-limiting step in acid secretion by parietal cells in the stomach[4]. Rabeprazole, lansoprazole, pantoprazole, esomeprazole, omeprazole, and dexlansoprazole are six FDA approved drugs currently used as PPIs. Variation in the pharmacokinetic parameters such as plasma half-life, routes of administration and drug interactions was the cause of the sequential development of these drugs[5]. Nausea, vomiting, headache, stomach pain, flatulence, and diarrhea are the most common adverse reaction of PPIs. Difficulty breathing, throat tightness, rash, and facial swelling are serious allergic reactions of PPIs[6]. PPIs are associated with a significant increase in the hypocalcemia of the patients[7]. Hypothetically, PPIs increase the risk of osteoporotic fracture by inducing hypochlorhydration, decreased calcium absorption in the intestine, and subsequent negative calcium balance[8]. Since calcium solubility depends on the solution's pH, calcium absorption may also depend on gastric pH. This assumption was supported by a study of 11 achlorhydric subjects who showed impaired absorption of calcium carbonate gelatin capsules in the fasting state but normal absorption of calcium citrate solution. However, when these subjects consumed calcium carbonate capsules with breakfast calcium carbonate absorption was returned to normal[9]. Many research cast serious doubt on the importation of gastric acid and calcium solubility on the subsequent absorption of calcium[10]. The relationship between calcium solubility and absorption was weak; calcium absorption was more closely associated with calcium salt congested food components[11]. The different studies carried out earlier times (Table-1) showed a clear scenario of the intervention of calcium absorption due to PPIs [12-14].

Table No. 1: Studies Assessing Changes in Calcium Absorption Related to PPI Therapy

Study	Subjects	Intervention	Calcium absorption methodology	Result
(Hardy <i>et al.</i> , 1998)	Baseline and again after twice-daily omeprazole 20 mg for 2 months.	Baseline and again after 2 months of omeprazole 20 mg per day	The level of calcium in serum measured weekly at the beginning of dialysis	During omeprazole therapy, lower serum calcium level suggests lower calcium absorption.
(Graziani <i>et al.</i> , 2002)	30 dialysis patients, mean age 57 years.	Baseline and again 20 mg every 8 hours for 3 days after omeprazole.	Postprandial increment of calcium level in serum.	Lack of serum calcium increase with omeprazole therapy suggests decreased calcium absorption.
(O'Connell <i>et al.</i> , 2005)	Postmenopausal women, mean age 76 years	7 days of placebo daily and 20 mg of omeprazole daily for 7 days	Fasting serum ^{45}Ca isotope level 5 hours after intake of 500 mg ^{45}Ca carbonate	Calcium absorption decreased from 9% to 4% following omeprazole therapy ($p < .05$)

Our study was designed to determine the effect of PPIs therapy on the serum calcium level.

METHOD:

This was a cross-sectional survey-based study conducted prospectively for over 12 months (June 2018 to June 2019) in three different hospitals in Dhaka city. Data were collected from a total of 380 patients among whom 143 were included in the study who met the criteria of this study. The following criteria were considered to be included as a participant in this study.

- The patient must have been taking PPI at least for six months.
- The patient must not be taking any calcium supplements within the last six months.
- Patients must not be suffering from any severe bone-related diseases before taking PPI.

The questionnaire was particularly designed to collect the patient's detailed medical history and was written most efficiently to avoid unnecessary semantic confusion. Finally, laboratory reports of the patients were also collected containing the blood serum calcium level. Verbal consent was also obtained from the eligible participants before the interview and collecting

the laboratory test report. The objective of the study was well clarified to the participants and they were also assured that their identity would not be divulged in any situation.

RESULTS AND DISCUSSION:

In this study data of 143 patients' age ranges from 20-60 years have been collected. Among which highest number of both male and female patients was within the age range 40-49 years (Figure-1).

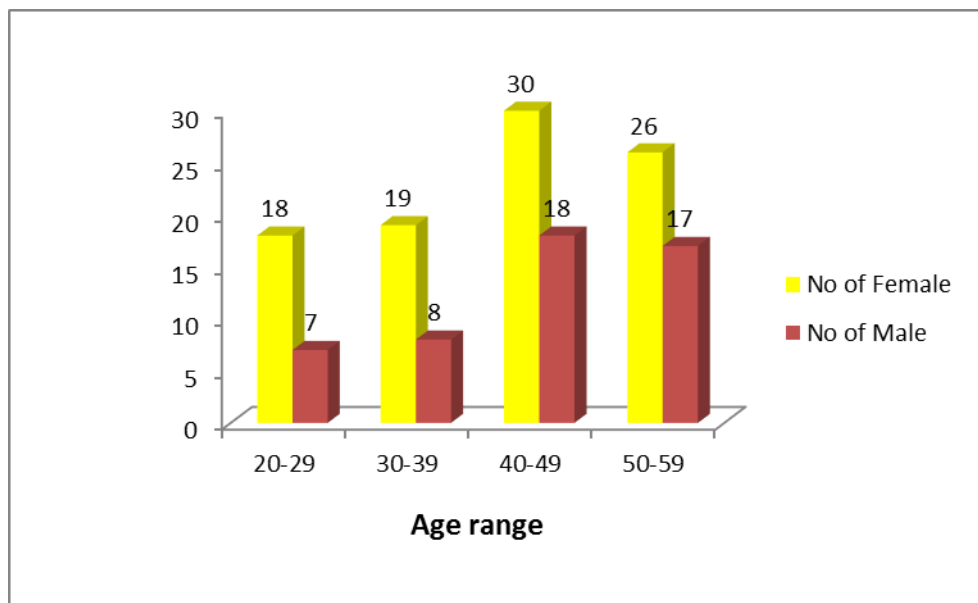


Figure No. 1: Number of patients in the different age range

Here data of serum calcium concentration was collected of all the patients and the average blood serum calcium concentration found was 7.94mg/dL which was lower than the lower limit of normal serum calcium concentration (Figure-2).

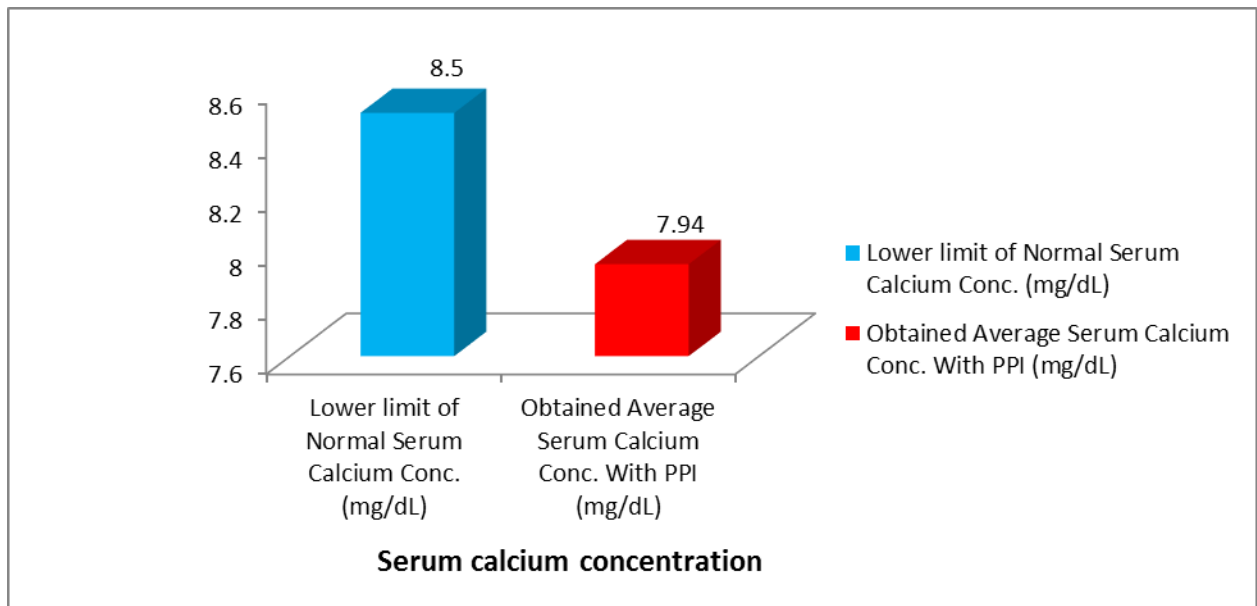


Figure No. 2: Comparison of normal serum concentration to the average value

The data showed that four different types of PPIs were taken by the patients which were Omeprazole, Esomeprazole, Rabeprazole, and Pantoprazole respectively. Omeprazole was the leading prescribing PPI with 67.6% of patients found to have been taking the drug (Table-2).

Table No. 2: Number of patients taking each type of PPI

PPI	Number of Patients taking PPI in %	Number of Patients
Omeprazole	67.6	96
Esomeprazole	14.4	20
Rabeprazole	13.1	7
Pantoprazole	4.9	19

The serum calcium level of the patients taking all four types of PPI was found to be lower than the normal level of serum calcium. Among these four drugs, patients taking Rabeprazole were found to have the lowest serum level of calcium (7.78mg/dL). Whereas patients taking omeprazole found to have less intervention due to PPI with highest level serum calcium level(Figure-3) nevertheless the average serum calcium levels of all four PPIs were quite close to each other and lower than the normal level of serum calcium.

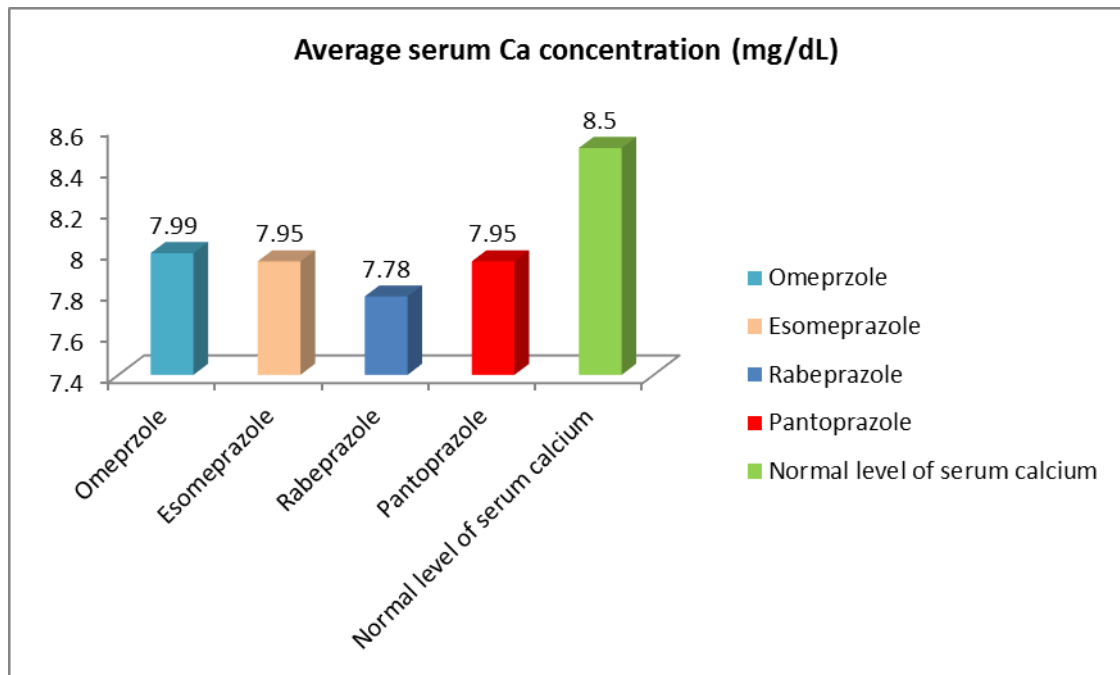


Figure No. 3: Average serum calcium concentration with different PPI intake

From Figure 4 it is evident that the average serum calcium concentration of the patients taking PPI was gradually decreasing along with the growing age of the patients. Patients between 50-60 years of age found to have the lowest level of serum calcium concentration (7.2 mg/dL). This change might well be regarded due to the intake of PPI or the growing age of the patients can also be a potential reason for this change.

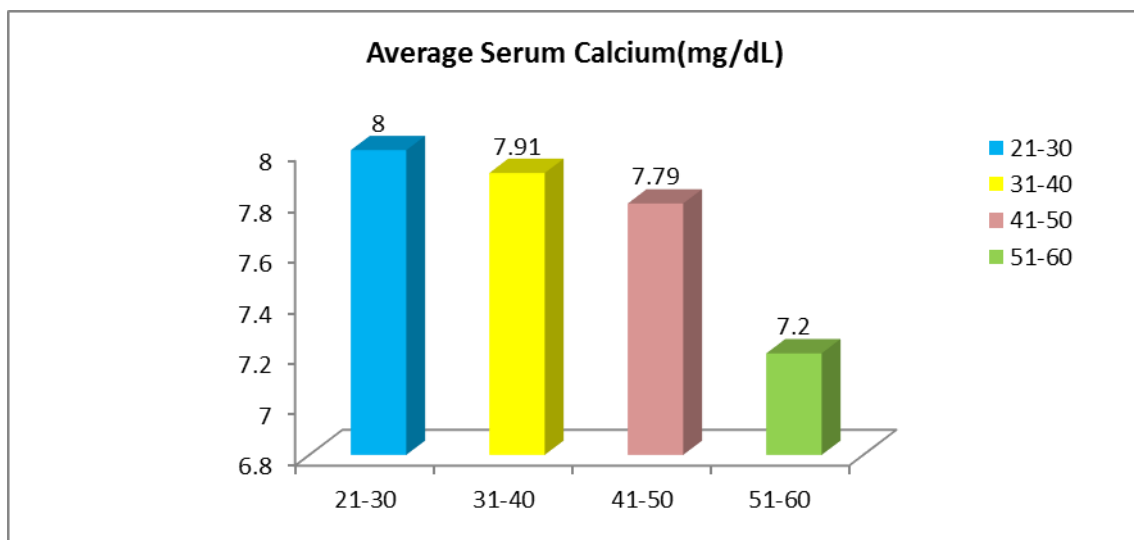


Figure No. 4: Average serum calcium concentration of patients with a different age range

Many studies have been carried out to assess the effect of PPI on calcium absorption, which has already been mentioned in table-1. Analyzing the result of this study it is also evident that there might be a subtle interference of calcium absorption due to the intake of PPI for a longer period as the reduced level of calcium was found in patients of different age groups who have been taking PPI for a long period in acid-related disorders.

CONCLUSION

Proton pump inhibitors have been extensively used as a potent gastric acid inhibitor for a long period in many hyper acidic conditions. Considering the previous study a survey has been conducted to demonstrate the current condition of patients of Bangladesh. From the above result, it is evident that PPI could be a prominent factor in calcium absorption impairment. However, the further controlled study could be noteworthy on this issue as the obtained results cannot completely be considered due to some methodological limitations.

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