e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 559-562

Original Research Article

Impact of Chronic Proton Pump Inhibitor Therapy on Serum Vitamin D and Calcium Levels: A Cross-Sectional Observational Study

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Received: 01-04-2026 / Revised: 25-05-2026 / Accepted: 12-06-2026
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Conflict of interest: Nil

Abstract

Background: Proton pump inhibitors (PPIs) are widely prescribed for the management of acid-related gastrointestinal disorders. Emerging evidence suggests that prolonged PPI therapy may adversely affect calcium and vitamin D metabolism, potentially increasing the risk of skeletal complications.

Aim: To evaluate serum vitamin D and calcium levels among chronic PPI users and determine their relationship with duration of therapy.

Methods: A hospital-based cross-sectional observational study was conducted among 100 participants comprising 50 chronic PPI users and 50 age- and sex-matched healthy controls. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were measured using chemiluminescent immunoassay, while serum calcium levels were estimated using laboratory autoanalyzer based on spectrophotometric estimation . Group comparisons were performed using independent sample t-tests and chi-square tests. Pearson correlation analysis was used to assess associations between duration of PPI therapy and biochemical parameters.

Results: Mean duration of PPI therapy was 24.34 ± 7.95 weeks. Serum vitamin D levels were significantly lower among PPI users compared with controls (18.4 ± 5.2 vs. 26.7 ± 6.1 ng/mL, $p<0.001$). Serum calcium levels were also significantly reduced in PPI users (7.92 ± 1.07 vs. 8.61 ± 0.52 mg/dL, $p<0.001$). Duration of therapy demonstrated a moderate negative correlation with vitamin D levels ($r = -0.42$, $p = 0.002$) and a weak negative correlation with serum calcium levels ($r = -0.31$, $p = 0.028$).

Conclusion: Chronic PPI therapy is associated with lower serum vitamin D and calcium concentrations. Longer duration of therapy may further exacerbate these deficiencies, highlighting the need for periodic monitoring in long-term users.

Keywords: Proton pump inhibitors, Vitamin D deficiency, Calcium, Hypocalcaemia, Bone health, Osteoporosis.
DOI: 10.25258/ijcpr.18.6.95

Introduction

Proton pump inhibitors (PPIs) have fundamentally transformed the clinical management of acid-related gastrointestinal disorders, including gastroesophageal reflux disease, peptic ulcer disease, and Helicobacter pylori eradication therapy. By irreversibly inhibiting the gastric hydrogen-potassium adenosine triphosphatase (H+/K+ ATPase) enzyme system within parietal cells, PPIs achieve profound and sustained acid suppression. Their efficacy and favourable safety profile have led to extensive long-term use across diverse patient populations.[1]Despite their therapeutic benefits, increasing concern has emerged regarding the long-term safety of chronic PPI therapy. Observational studies have associated prolonged PPI use with adverse systemic outcomes including chronic kidney disease, hypomagnesemia, enteric infections, and impaired micronutrient absorption.[1,6,9] Most notably, skeletal complications and an increased risk of osteoporotic fractures have been reported among long-term users.[2,7,13,15]

Skeletal integrity depends upon maintenance of calcium and vitamin D homeostasis. Vitamin D is metabolized to 25-hydroxyvitamin D [25(OH)D], the major circulating form used for assessment of vitamin D status. Subsequent activation to calcitriol facilitates active intestinal calcium absorption and contributes to bone mineralization.[5,17,18]

The pharmacological induction of chronic hypochlorhydria by PPIs may disrupt this

physiological balance. Gastric acid is essential for ionization and solubilization of dietary calcium salts, particularly calcium carbonate.[4,12,16] Reduced calcium absorption may induce secondary hyperparathyroidism, increase bone resorption, and adversely affect vitamin D metabolism.[4,5,20] Although epidemiological evidence supports an association between chronic PPI use and fracture risk, the direct effects of prolonged therapy on serum vitamin D and calcium levels remain incompletely characterized. Therefore, this study aimed to evaluate serum 25(OH)D and calcium levels among chronic PPI users and assess their relationship with duration of therapy.

Materials and Methods

Study Design and Setting: A hospital-based cross-sectional observational study was conducted over a 12-month period at a tertiary care teaching hospital.

Study Population: The study enrolled 100 adult participants divided into two groups:

- **Group A:** 50 patients receiving continuous PPI therapy for at least 4 months.
- **Group B:** 50 age- and sex-matched healthy controls not receiving acid-suppressive therapy.

Ethical Consideration: The study protocol was reviewed and approved by the Institutional Ethics Committee of Era's Lucknow Medical College and Hospital, Lucknow, prior to commencement of the study. Written informed consent was obtained from all participants before enrolment in the study. Participants were informed regarding the objectives, procedures, potential benefits, and confidentiality of the study. Participation was entirely voluntary, and participants were free to withdraw from the study at any stage without any consequences.

Inclusion Criteria: Participants aged ≥18 years who had not received calcium or vitamin D supplementation during the preceding six months were included.

Exclusion Criteria: Patients with chronic kidney disease, chronic liver disease, malabsorption syndromes, malignancies of bone, Prostate, thyroid and parathyroid gland, post-menopausal osteoporosis, hyperparathyroidism, pregnancy, lactation, or concurrent use of medications affecting bone metabolism were excluded.

Biochemical Assessment: Following overnight fasting, venous blood samples were collected. Serum 25(OH)D concentrations were measured using chemiluminescent immunoassay.

Vitamin D status was categorized as:

Deficient: <20 ng/mL

Insufficient: 20–30 ng/mL

Sufficient: >30 ng/mL[11,18]

Total serum calcium was measured using an automated clinical chemistry analyser based on spectrophotometric (colorimetric) estimation following the manufacturer's standard operating procedure. Results were reported in mg/dL

Statistical Analysis: Data was analysed using SPSS version 25. Continuous variables were expressed as mean ± SD. Independent sample t-tests were used for intergroup comparisons. Categorical variables were analysed using chi-square tests. Pearson correlation coefficients were calculated to evaluate relationships between duration of therapy and biochemical parameters. A p-value <0.05 was considered statistically significant.

Results

Table 1: Baseline Demographic Characteristics

Variable	PPI Users (n=50)	Controls (n=50)	p-value
Age (years)	36.4 ± 15.2	38.6 ± 14.5	0.466
Male sex, n (%)	28 (56%)	25 (51%)	0.68
Female sex, n (%)	22 (44%)	24 (49%)	—
BMI (kg/m²)	24.0 ± 2.7	24.8 ± 2.8	0.34
Mean Daily sunlight exposure.(hr/day)	1.3	1.4	0.433
Duration of therapy (weeks)	24.34 ± 7.95	NA	—

The two groups were comparable in baseline demographic characteristics. Mean age was 36.4 years in PPI users versus 38.6 years in controls. BMI of both the groups was comparable 24 vs 24.8 kg/m². Mean daily sunlight exposure did not differ significantly (1.3 vs 1.4 hours/day). Gender distribution in both the groups was similar. with males constituting 56% of the PPI group and 51% of controls. The mean duration of PPI therapy among users was 24.34 ± 7.95 weeks.

Table 2: Biochemical Profile

Parameter	PPI Users	Controls	p-value
Serum 25(OH)D (ng/mL)	18.4 ± 5.2	26.7 ± 6.1	<0.001
Vitamin D deficient	31 (62%)	18 (36%)	χ^2 p<0.001
Vitamin D insufficient	15 (30%)	16 (32%)	
Vitamin D sufficient	4 (8%)	16 (32%)	
Serum calcium (mg/dL)	7.92 ± 1.07	8.61 ± 0.52	<0.001

Table 2 summarizes the biochemical profile of both groups. Mean serum 25-hydroxyvitamin D levels were significantly lower among chronic PPI users compared with controls (18.4 ± 5.2 ng/mL vs. 26.7 ± 6.1 ng/mL, p<0.001). Vitamin D deficiency was observed in 62% of PPI users compared with 36% of controls, whereas sufficient vitamin D levels were present in only 8% of PPI users compared with 32% of controls. The overall distribution of vitamin D status differed significantly between the groups (χ^2 test, p<0.001). Similarly, mean serum calcium levels were significantly lower in the PPI group than in controls (7.92 ± 1.07 mg/dL vs. 8.61 ± 0.52 mg/dL, p<0.001).

Table 3: Correlation Analysis

Variable	Pearson r	p-value
Duration vs Vitamin D	−0.42	0.002
Duration vs Calcium	−0.31	0.028

Table 3 depicts the correlation between duration of PPI therapy and biochemical parameters. A statistically significant moderate negative correlation was observed between duration of PPI use and serum vitamin D levels (r = −0.42, p = 0.002), indicating lower vitamin D concentrations with increasing duration of therapy. In addition, a weak but significant negative correlation was found between duration of PPI therapy and serum calcium levels (r = −0.31, p = 0.028), suggesting that prolonged PPI exposure may contribute to a gradual decline in calcium homeostasis.

Discussion

The present study demonstrated significantly lower serum vitamin D and calcium concentrations among chronic PPI users compared with healthy controls. Furthermore, increasing duration of PPI therapy was associated with worsening vitamin D status and lower calcium levels.

These findings are consistent with observations reported by Ito and Jensen, who demonstrated associations between long-term PPI therapy and micronutrient deficiencies resulting from impaired gastrointestinal absorption.[1] Similar findings have been reported by Schinke et al., who highlighted adverse effects of chronic acid suppression on bone metabolism and mineral homeostasis.[3]

The significantly lower serum calcium concentrations observed in PPI users support the hypothesis that chronic acid suppression impairs calcium absorption. Heaney et al. demonstrated that gastric acidity is essential for optimal dissolution and absorption of calcium salts, particularly calcium carbonate.[4] Similar conclusions have been reached by O'Connell et al. and Hansen et al.[12,16]

The moderate negative correlation between therapy duration and serum vitamin D levels suggests a cumulative effect of chronic acid suppression. Prolonged hypochlorhydria may impair nutrient bioavailability and contribute to secondary hyperparathyroidism, ultimately affecting bone mineralization.

The clinical significance of these findings is considerable. Vitamin D deficiency and hypocalcaemia are recognized risk factors for osteopenia, osteoporosis, and fragility fractures. Previous studies by Yang et al., Targownik et al., Corley et al., and Eom et al. demonstrated increased fracture risk among long-term PPI users.[2,7,13,14] The biochemical alterations observed in the present study may partially explain these epidemiological findings.

Strengths of this study include inclusion of a matched control group and evaluation of both biochemical markers and therapy duration. However, the cross-sectional design limits causal inference. Additionally, parathyroid hormone, magnesium concentrations, and bone mineral density measurements were not assessed.

Conclusion

Chronic proton pump inhibitor therapy is associated with significantly lower serum vitamin D and calcium concentrations. Longer duration of therapy appears to exacerbate these alterations, suggesting a cumulative adverse effect on calcium–vitamin D homeostasis. Routine monitoring of vitamin D and calcium status should be considered in patients receiving prolonged PPI therapy, particularly those at increased risk of osteoporosis and fracture. Prospective longitudinal studies incorporating bone mineral density, magnesium status, and parathyroid hormone measurements are

warranted to further clarify the skeletal consequences of long-term PPI use.

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