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ORIGINAL ARTICLE

Proton Pump Inhibitor Use Among Individuals with Vitamin B12 Deficiency: A Cross-Sectional Study

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ABSTRACT

Background: Vitamin B12 deficiency is a frequent nutritional deficiency that is associated with serious neurological and hematological problems. PPIs (Proton Pump Inhibitors) are commonly prescribed drugs to treat diarrhea of any kind, which can reduce production of stomach acid and decrease B12 absorption. The purpose of the present study was to investigate the prevalence of PPI use in B12 deficient patients and to define the most frequently used PPIs.

Methodology: The subjects of this cross sectional study were 96 vitamin B12 deficient patients of the outpatient department of a tertiary care hospital with laboratory confirmation of vitamin B12 deficiency (<300 pg/mL in adults and <328 pg/mL in children). Data collected through structured questionnaire, which is controlled by the researchers. Data was analyzed using SPSS version 25 software, Chi-square test for categorical variables, p value ≤ 0.05, was considered as statistically significant.

Results: The mean age of participants was 39.96 ± 13.41 years (range: 14–71); 71.9% were female. Over half (53.1%) reported using PPI, and there was a trend towards an association between age group 31-50 (p = 0.054). GERD (80.4%) was the most common gastrointestinal problem. The most common PPIs used were omeprazole (60.8%), esomeprazole (17.6%) and pantoprazole (11.8%). Most (20 mg/day) and 13.7% were taking it for >1 year continuously. Side effects were reported in only 3.9% and 5.8% of patients were intolerant and discontinued therapy. Dietary factors contributed minimally with 88.5% of the participants being non-vegetarian.

Conclusions: PPI use accounted for more than half of the vitamin B12 deficient patients in this study, with omeprazole as the most common PPI used. While the duration of exposure was shorter for most, the potential risk of long-term therapy suggests careful prescribing and monitoring of B12 status in PPI users taking these drugs chronically.

Keywords : Vitamin B12 Deficiency, PPIs, GERD, Drug utilization.

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INTRODUCTION:

Vitamin B12 deficiency is a prevalent nutritional issue with significant health implications[1].It is essential for DNA synthesis, neurological function, and hematopoiesis[2].Additionally it is required as a cofactor for enzymes, serves as a methyl group donor[3] and Tetrahydrofolate synthesis (THF)[4]. Deficiency caused by poor intake, intestinal disorders, or gastric problems can lead to anemia, nerve damage, and elevated homocysteine and methylmalonic acid[5].

One potential factor contributing to B12 deficiency is the use of proton pump inhibitors (PPIs). Proton pump inhibitors (PPIs) are widely used medications, available both by prescription and over-the-counter, primarily for treating acid-related gastrointestinal conditions such as GERD, erosive esophagitis, and Barrett's esophagus[6]. Examples include omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. They work by inhibiting stomach proton pumps to reduce acid production and may also affect gut microbiota and immune responses[7,8] .

Widespread and often inappropriate use of PPIs raises concerns, with studies showing unjustified prescriptions in up to 72% of patients and high off-label use in ICUs. Long-term PPI use has been linked to potential adverse effects, including fractures, dementia, infections, cardiovascular events, and reduced absorption of vitamins—particularly vitamin B12[9]. However,

definitive causal evidence is still lacking, and further research is needed[10].

PPIs impair gastric acid secretion, which is required to release vitamin B12 from food [11]. This reduced bioavailability can lead to deficiency over time. Investigating its prevalence helps confirm and understand the potential mechanisms contributing to this association[12].

A few recent studies (Bakshi 2023, Choudary 2023) report a strong association, and high prevalence (29% to 54%) of PPI use among those who were deficient. However, other studies (e.g., Dinesh 2023) found no such link, indicating the evidence is not conclusive[13].

There has been mixed evidence from previous studies, with some showing a strong association and others showing no association[14], and due to methodological differences and varying treatment durations, dosages and study populations, the results from previous studies are inconclusive. Furthermore, the majority of published work has been devoted to the risk of vitamin B12 deficiency in PPI users, with little evidence available to elucidate the prevalence and utilization trends of PPIs in people with a diagnosis of vitamin B12 deficiency, especially in the local population.

Awareness of PPI use in this population is important to recognize potentially modifiable risk factors, to ensure appropriate long-term prescribing and to help monitor vitamin B12 levels in those on long-term PPI therapy. Thus, this study was conducted to assess the prevalence of PPIs use among patients with B12 deficiency, and to establish the most commonly used PPIs agents.

Methodology: This cross-sectional study was conducted in Out Patient Department (OPD) of Liaquat National Hospital, Karachi, Pakistan after obtaining approval from Liaquat National Hospital Ethical Review Committee (ERC App No. 1087-2024-LNH-ERC). All subjects had written informed consent before enrolment.

Adults 18 years and above, who had laboratory confirmation of vitamin B12 deficiency and were attending the OPD during the study period were included in the study. Vitamin B12 deficiency was taken to be serum vitamin B12 level below 300 pg/mL for adult which is based on the laboratory reference value of Liaquat National Hospital. Those with normal serum vitamin B12 (VitB12) levels were ruled out of the study.

Proton pump inhibitors were labeled as irreversible inhibitors of gastric hydrogen-potassium adenosine triphosphatase (H^+/K^+-ATPase) enzyme in the parietal cells leading to inhibition of gastric acid production. Long-term use of PPI was considered as continuous or cumulative use for over six months.

A purposive sampling method was used for selecting the participants. To ensure that the required sample size of 96 was achieved, Open Epi version 3.01 was used with the assumption that 47.1% of vitamin B12 deficient individuals take proton pump inhibitors (PPI) for at least 6 months, and with a 95% confidence level and 10% margin of error.

Structured and predesigned interviewer administered questionnaires were used to collect data. Each participant was personally interviewed and the questionnaire was completed from their responses after confirmation of vitamin B12 deficiency in the lab. The questionnaire gathered details of socio-demographic data, medical history, dietary and lifestyle practices, gastrointestinal history, PPI usage (type, dosage, duration, indication), adverse effects, and symptoms of vitamin B12 deficiency.

SPSS 25 software was used for data entry and analysis. The quantitative data were presented as mean ± standard deviation (SD) and categorical data were presented as frequencies and percentages. The associations between categorical variables were evaluated with either Chi-square or Fisher's exact test as appropriate. The p value of <0.05 was taken as statistically significant.

RESULTS: A total of 96 participants who had laboratory confirmation of vitamin B12 deficiency were analyzed. Table 1 shows the demographic characteristics of the study participants.

Table 1. Baseline Characteristics of Study Participants (N = 96)

Variable	Category	n (%)
Age (years)		
	Mean ± SD	39.96 ± 13.41
	≤30	28 (29.2)
	31–50	42 (43.8)
	>50	26 (27.1)
Gender		
	Male	27 (28.1)
	Female	69 (71.9)

SD, standard deviation.

Footnote*:* Data are presented as frequency (%) unless otherwise indicated.

The clinical features of the study subjects such as dietary habits, previous gastrointestinal surgery, and gastrointestinal disorders are summarized in Table 2.

Table 2. Demographic and Clinical Characteristics of Participants (N = 96)

Variable	Category	n (%)
Vegan diet		
	Yes	11 (11.5)
	No	85 (88.5)
Animal product intake		
	Daily	16 (18.8)
	Several times/week	38 (44.7)
	Weekly	24 (28.2)
	Rarely	6 (7.1)
	Never	1 (1.2)
Previous GI surgery		
	Yes	8 (8.3)
	No	88 (91.7)
Gastrointestinal disorder		
	Yes	56 (58.3)
	No	40 (41.7)

GI, gastrointestinal.

The most frequent gastrointestinal disorder among the subjects with the disorder was gastroesophageal reflux disease. A little over half of the study population mentioned taking PPIs, and omeprazole was the most commonly prescribed one (Table 3).

Table 3. Clinical Characteristics and Pattern of Proton Pump Inhibitor Use Among Participants (N = 96)

Section	Category	n (%)
Gastrointestinal disorders		
	GERD	45 (80.4)
	Gastritis	6 (10.7)
	Peptic ulcer disease	3 (5.4)
	H. pylori infection	2 (3.6)
PPI utilization		
	Users	51 (53.1)
	Non-users	45 (46.9)
PPI characteristics		
	Omeprazole	31 (60.8)
	Esomeprazole	9 (17.6)
	Pantoprazole	6 (11.8)
	Rabeprazole	5 (9.8)
	20 mg daily	28 (54.9)
	Once daily	24 (47.1)

GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

DISCUSSION:

The current research assessed the prevalence of Proton Pump Inhibitor (PPI) usage in individuals with vitamin B12 deficiency. There was a significant exposure burden because over half (53.1%) of participants reported using PPIs regularly or occasionally. This result is consistent with earlier research showing a significant relationship between chronic PPI use and decreased vitamin B12 absorption; most of which has been attributed to reduced gastric acid production necessary for the release of protein-bound vitamin B12 from food sources[15].
Gender distribution in the study revealed a higher proportion of female participants (71.9%), among whom PPI use was also more prevalent than males. Although this may reflect gender differences in health-seeking behavior and higher reported prevalence of gastrointestinal complaints such as gastro esophageal reflux disease (GERD) among women, further studies are needed to confirm whether female gender is an independent risk factor for PPI-associated B12 deficiency.

The age group most affected by PPI use was 31–50 years, showing a marginally significant association ($p = 0.054$). This contrasts with the anticipation that long-term PPI use and age-related decline in gastric acid secretion would predispose older adults to higher rates of deficiency[16]. One possible explanation is that middle-aged individuals are more frequently prescribed PPIs for chronic conditions such as GERD, which was the predominant gastrointestinal disorder in this study (80.4%)[17].

Omeprazole was the most frequently used PPI (60.8%), followed by esomeprazole (17.6%) and pantoprazole (11.8%). This is congruous with global prescribing trends, where omeprazole remains the first-line agent due to its availability and cost-effectiveness[18].(WHO,2021).A 2023 multinational study by Haastrup et al., analyzing > 2 million prescriptions found omeprazole accounted for 44.6% of initial PPI prescriptions, closely matching observed frequency of this study followed by esomeprazole (26.1%) and Pantoprazole (14.2%). The most common dose was 20 mg once daily, which is considered standard therapy, although prolonged use beyond one year was also reported in a significant subset of participants. Mumtaz et al. (2022), in a cohort study, reported a significant association between prolonged PPI use (more than 12 months) and the prevalence of Vitamin B12 deficiency (OR ≈ 0.56; 95% CI: 0.444–0.707).

They also noted that young males were especially susceptible, with significantly greater probability of developing B12 deficiency after long-term treatment, as indicated by an odds ratio of approximately 10.38. However, the current findings of the research come in contrast that most of the people in the study period exhibited a comparatively short period of exposure to PPI. Only 13.7% reported ongoing use of more than one year, and 17.6% reported intermittent long-term use, but this might not have been enough to significantly affect Vitamin B12 status.

Of course, only a few PPI users reported adverse effects (3.9%) and only 5.8% stopped taking the drug because of intolerance. This helps highlight the well tolerated profile of PPIs which, paradoxically, leads to their overuse and long term use without routine clinical re-evaluation.

Other dietary factors also contribute to B12 deficiency, but in this study, most of the subjects (88.5%) were non-vegetarians and very few subjects were following a vegan diet (11.5%). This further supports the findings that the observed deficiency was likely due to the PPI use instead of the diet alone.

Overall, the study findings reinforce the importance of judicious prescribing of PPIs, especially for long-term therapy. Vitamin B12 monitoring should be closely observed in chronic PPI users, especially those with other risk factors like gastrointestinal disorders and/or dietary deficiency. On the other hand, patient

education on the hazards of unnecessary long term usage should be warranted.

CONCLUSION:

In the present study, PPI use was seen to be high in patients with vitamin B12 deficiency, of which omeprazole is the most frequently used followed by esomoprazole and pantoprazole. Most of the participants used products for a relatively short period; however, there is concern about the potential effects of long-term use. Large-scale studies to further elucidate the long-term relationship between the use of PPIs and B12 deficiency are necessitated.

Strengths and Limitation: One of the strengths of the study was that a detailed evaluation of the utilization of PPI was performed, including the type of PPI, dose level, frequency of use, duration of therapy. However, the cross-sectional design precludes causal inference, vitamin B12 deficiency was assessed using serum vitamin B12 levels alone without functional biomarkers (methylmalonic acid or homocysteine), and the single-center design with a relatively small sample size may limit the generalizability of the findings.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Author Contributions:

FA: Leading the project and compiled the data

HY, FB. HA, GR: Data Collection

FA: Data Analysis and discussion writing

FR, HF, GM: Results and conclusion

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