

Research Article**Association Between Proton Pump Inhibitor Use and Vitamin B12 Deficiency:
A Cross-Sectional Study****Hassan Liaquat Memon¹, Shabana Lakho², Anum Siddiqui³, Murk Mujahid⁴, Haris
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Abstract

Background: Vitamin B12 deficiency is a common nutritional disorder that can result in neurological and haematological complications. Proton pump inhibitors (PPIs) are widely used in the management of gastrointestinal disorders and may interfere with vitamin B12 absorption by suppressing gastric acid secretion. This study aimed to assess the prevalence and pattern of PPI use among patients with vitamin B12 deficiency and to evaluate the commonly used PPIs, dosage, duration of therapy, and reported adverse effects.

Place and Duration of Study: This study was conducted at United Medical and Dental College, United Hospital Karachi from May 2025 to May 2026

Study Design: Cross-sectional study

Methods: This cross-sectional study included 226 patients with laboratory-

confirmed vitamin B12 deficiency. Vitamin B12 deficiency was defined as a serum vitamin B12 level of <300 pg/mL in adults and <328 pg/mL in children. Demographic characteristics, gastrointestinal symptoms and diagnoses, dietary habits, PPI use, dosage, duration of therapy, and treatment-related adverse effects were collected using a structured questionnaire. Data were analysed using SPSS version 26. Categorical variables were analysed using the chi-square test, and a p-value of ≤0.05 was considered statistically significant.

Results: The mean age of participants was 39.59 ± 13.52 years (range: 15–70 years). Females comprised 70% of the study population, while males accounted for 30%. Of the 226 participants, 120 (53.1%) reported current or previous PPI use. Analysis of PPI use according to age group showed a borderline association in the 31–

50-year age group ($p=0.054$). Gastro-oesophageal reflux disease was the most commonly reported gastrointestinal condition, affecting 180 (80.0%) participants. Among PPI users, omeprazole was the most frequently used PPI (72, 60.0%), followed by esomeprazole (20, 16.67%), pantoprazole (17, 14.72%), and rabeprazole (11, 9.17%). A daily dose of 20 mg was the most commonly reported dosage. Long-term PPI use (>1 year) was reported by 17 (14.17%) participants. Adverse effects were reported by 5 (4.17%) participants, while 7 (5.83%) reported intolerance leading to discontinuation of treatment. Regarding dietary habits, 199 (88.0%) participants reported consuming a non-vegetarian diet.

Conclusion: More than half of the participants with vitamin B12 deficiency reported current or previous PPI exposure, with omeprazole being the most commonly used PPI. Long-term PPI use was reported in a smaller proportion of PPI users. These findings support the importance of periodically reassessing the indication for prolonged PPI therapy and considering vitamin B12 assessment in patients receiving long-term treatment when clinically indicated.

Keywords: Vitamin B12 deficiency; proton pump inhibitors; gastro-oesophageal reflux disease; PPI use; drug utilisation; nutritional deficiency

Introduction

Vitamin B12 (cobalamin) is a water-soluble vitamin that plays an essential role in DNA synthesis, cellular metabolism, myelin formation, and normal neurological and haematological function [1,2]. Vitamin B12 deficiency is an important nutritional and clinical problem that can affect individuals across all age groups. It may result from inadequate dietary intake, impaired

gastrointestinal absorption, autoimmune disorders, gastrointestinal diseases, or medication-related effects [1,3]. Subclinical or marginal vitamin B12 deficiency is relatively common, particularly among older adults and populations with limited consumption of animal-derived foods [4]. Clinical manifestations may include megaloblastic anaemia, fatigue, paraesthesia, peripheral neuropathy, cognitive impairment, and other neurological abnormalities. Importantly, neurological complications may become irreversible if vitamin B12 deficiency remains undiagnosed and untreated [2,5].

The absorption of dietary vitamin B12 is a complex, multistep process that depends on normal gastric, pancreatic, and ileal function [6]. Gastric acid facilitates the release of vitamin B12 from dietary proteins. The released vitamin subsequently undergoes a series of binding and transfer processes before forming a complex with intrinsic factor. The intrinsic factor–vitamin B12 complex is then absorbed in the terminal ileum [6,7]. Consequently, conditions or medications that alter gastric acid secretion may potentially affect the bioavailability and absorption of food-bound vitamin B12. Impaired absorption, in addition to inadequate dietary intake, is an important contributor to vitamin B12 deficiency [3,6]. Proton pump inhibitors (PPIs) are widely used medications for the management of acid-related gastrointestinal disorders. They are commonly prescribed for gastro-oesophageal reflux disease (GORD), peptic ulcer disease, prevention of gastrointestinal complications associated with certain medications, and other acid-dependent conditions. PPIs inhibit the gastric $H^+/K^+-ATPase$ and are generally considered effective and well tolerated [8]. However, their widespread and, in some cases, prolonged use has raised concerns regarding

potential nutritional consequences, particularly their possible effect on vitamin B12 status. By substantially reducing gastric acid secretion, PPIs may impair the release of food-bound vitamin B12 from dietary proteins and thereby potentially reduce its absorption [6,9].

The potential association between acid-suppressive therapy and vitamin B12 deficiency has therefore been investigated in several studies, although the findings have been inconsistent. A large population-based case-control study reported an association between long-term PPI use and vitamin B12 deficiency, with the risk increasing with longer duration of exposure [10]. Previous observational studies and meta-analyses have also suggested a possible relationship between prolonged acid suppression and impaired vitamin B12 status [11]. However, other studies have reported minimal or no clinically significant differences in vitamin B12 concentrations among PPI users compared with non-users [12]. Differences in study populations, duration and dose of PPI exposure, dietary intake, and definitions used to diagnose vitamin B12 deficiency may contribute to these inconsistent findings.

More recent evidence has continued to demonstrate uncertainty regarding the magnitude and clinical significance of this association. A 2023 systematic review and meta-analysis of 25 s

Methodology

Study Design and Participants

This cross-sectional study included 226 patients with laboratory-confirmed vitamin B12 deficiency. Participants were recruited from the outpatient clinic during the study period. Individuals were eligible for inclusion if they had laboratory evidence of vitamin B12 deficiency according to the predefined study criteria and were willing and able to participate in the study. Written

informed consent was obtained from all participants before enrolment.

Vitamin B12 deficiency was defined as a serum vitamin B12 level of <300 pg/mL in adults and <328 pg/mL in children. Individuals with serum vitamin B12 levels above the predefined thresholds were not included in the study. Patients without laboratory confirmation of vitamin B12 deficiency were excluded.

Sampling

A purposive sampling technique was used to recruit eligible participants. Participants were selected from patients attending the outpatient clinic who fulfilled the predefined eligibility criteria during the study period. A total of 226 participants were included in the final analysis.

Data Collection

Data were collected using a structured, predesigned, interviewer-administered questionnaire. Interviews were conducted after laboratory confirmation of vitamin B12 deficiency. The questionnaire collected information regarding sociodemographic characteristics, medical history, gastrointestinal symptoms and diagnoses, dietary habits, lifestyle factors, and symptoms potentially associated with vitamin B12 deficiency.

Detailed information regarding proton pump inhibitor (PPI) use was also collected, including the name of the PPI, daily dosage, indication for use, frequency of administration, and duration of treatment. Participants were additionally asked about any reported adverse effects associated with PPI use and whether treatment had been discontinued because of intolerance or adverse effects.

Definition of PPI Exposure

PPIs were defined as medications that suppress gastric acid secretion through irreversible inhibition of the gastric hydrogen-potassium adenosine

triphosphatase (H^+/K^+ -ATPase) enzyme in gastric parietal cells. PPI exposure was defined as current or previous use of any PPI reported by the participant.

For the purposes of this study, long-term PPI use was defined as continuous or cumulative use for more than one year.

Statistical Analysis

Data were coded and analysed using the Statistical Package for the Social Sciences (SPSS), version 26. Continuous variables were summarised using means and standard deviations (SD), while categorical variables were presented as frequencies and percentages. The chi-square test was used to assess associations between categorical variables. Fisher's exact test was applied

when the assumptions required for the chi-square test were not met. A two-sided p-value of ≤ 0.05 was considered statistically significant.

Results

226 subjects who had laboratory confirmation of vitamin B12 deficiency were included in the study. The mean age of the participants was 39.59 ± 13.52 years, and ranged between 15–70 years. The study population was predominantly female 70.0% with a male population of 30.0%.

The socio-demographic data of the study sample is presented in Table 1. In general, the study population consisted of mostly female 70.0%. The average age was 39.59 years and SD was 13.52 years.

Table 1. Demographic characteristics of study participants (n=226)

Variable	Value
Age, mean $\pm$ SD (years)	39.59 ± 13.52
Age range (years)	15–70
Female, n (%)	158 (70.0)
Male, n (%)	68 (30.0)

There were 226 participants, 120 (53.1%) of whom were current or past users of a proton pump inhibitor (PPI) and 106 (46.9%) who were not. A borderline association was observed for the age group 31–50 years for PPI use ($p=0.054$).

Table 2. Proton pump inhibitor use among study participants

PPI use	n	%
Current or previous PPI use	120	53.1
No PPI use	106	46.9
Total	226	100.0

The most common gastrointestinal condition reported was gastro-oesophageal reflux disease (GERD) (96 (80.0%) participants). Other gastrointestinal diseases were less common.

Table 3. Gastrointestinal conditions reported by participants

Gastrointestinal condition	n	%
Gastro-oesophageal reflux disease	180	80.0
Other gastrointestinal conditions	46	20.0

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Total	226	100.0
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Out of the medication data reported by the participants, omeprazole was the most common PPI reported with 72 (60.0%) participants, followed by esomeprazole with 20 (16.7%), pantoprazole with 17 (14.2%) and rabeprazole with 11 (9.2%). 20mg/day was the most commonly reported dosage regimen. 17 participants (14.2%) used PPI continuously for over one year.

Table 4. Pattern of reported PPI use in 120 patients

PPI / treatment characteristic	n=120	%
Omeprazole	72	60.0
Esomeprazole	20	16.7
Pantoprazole	17	14.2
Rabeprazole	11	9.2
Continuous use >1 year	17	14.2

Some adverse effects and intolerance may occur. 5 (4.2%) participants reported adverse effects associated with PPI treatment. There were also 7 (5.8%) participants who reported intolerance and discontinued PPI therapy.

Table 5. Reported adverse effects and intolerance to PPI therapy

Variable	n=120	%
Reported adverse effects	5	4.2
Intolerance leading to discontinuation	7	5.8

Dietary patterns were considered as a possible cause of vitamin B12 deficiency. Most of the participants said they eat non-vegetarian diet, 199 (88%) participants said non-vegetarian. The remaining 27 (12%) said they follow a Vegetarian diet.

Table 6. Dietary pattern of study participants

Dietary pattern	n	%
Non-vegetarian	199	88

Vegetarian	27	12
Total	226	100.0

A total of >50% of the B12 deficient patients had a history or current use of PPIs. The most common PPI was omeprazole and most common gastrointestinal condition was

GERD. There was a borderline association between the use of PPI and the age group 31–50 years, while most of the participants consumed a non-vegetarian diet

Discussion

In the present study, we assessed the pattern of proton pump inhibitor (PPI) use among 226 patients with laboratory-confirmed vitamin B12 deficiency. Overall, 120 (53.1%) participants reported current or previous PPI use. Although this represents a substantial proportion of the study population, the findings should be interpreted cautiously because all participants had already been diagnosed with vitamin B12 deficiency and no non-deficient control group was included. Therefore, the present study describes the prevalence and pattern of PPI exposure among patients with vitamin B12 deficiency but cannot establish whether PPI use increases the risk of developing vitamin B12 deficiency or demonstrate a causal relationship.

The biological plausibility of a relationship between prolonged PPI use and vitamin B12 deficiency has been described previously. Gastric acid facilitates the release of protein-bound vitamin B12 from food, and suppression of gastric acid secretion may consequently reduce the availability of vitamin B12 for absorption [6,9]. Valuck and Ruscin, in a case-control study of adults aged 65 years and older, reported greater use

of acid-suppressive medications, including PPIs and H2-receptor antagonists, among patients with vitamin B12 deficiency compared with controls [16]. Their findings suggested that prolonged acid-suppressive therapy may represent a potentially modifiable factor among individuals at risk of vitamin B12 deficiency. In contrast to their predominantly older population, participants in the present study had a mean age of 39.59 ± 13.52 years. However, because the current study did not include a non-deficient comparison group, age-specific differences in the relationship between PPI exposure and vitamin B12 deficiency could not be determined.

Mumtaz et al. investigated vitamin B12 status among 1,225 individuals receiving long-term PPI therapy and reported lower vitamin B12 levels among PPI users [17]. Their study also suggested differences in vitamin B12 levels according to the specific PPI used, with lower levels reported among omeprazole users compared with pantoprazole users. In the present study, omeprazole was the most frequently reported PPI, accounting for 72 (60.0%) of the 120 PPI users, followed by esomeprazole, pantoprazole, and rabeprazole. The predominance of

omeprazole may reflect its widespread availability, prescribing patterns, and affordability. However, the present study was descriptive and did not compare vitamin B12 concentrations between users of different PPIs. Therefore, no conclusion can be drawn regarding whether one PPI has a greater effect on vitamin B12 status than another.

Evidence regarding the relationship between PPI therapy and vitamin B12 deficiency remains inconsistent. Den Elzen et al. found no significant differences in vitamin B12 concentration, homocysteine levels, or mean corpuscular volume between elderly PPI users and non-users [18]. These findings contrast with studies suggesting an association between prolonged acid suppression and impaired vitamin B12 status. Differences in age, duration and intensity of PPI exposure, baseline nutritional status, underlying disease, concomitant medications, and definitions used to identify vitamin B12 deficiency may partly explain these discrepancies. In the present study, all participants had laboratory-confirmed vitamin B12 deficiency; therefore, a direct comparison of vitamin B12 status between PPI users and non-users was not possible.

Hirschowitz et al. evaluated patients with acid hypersecretory conditions receiving prolonged lansoprazole therapy and reported reductions in serum vitamin B12 levels, with functional abnormalities observed in some patients during long-term treatment [19]. These findings are relevant because serum vitamin B12 concentration alone may not identify all cases of functional deficiency. In the present study, vitamin B12 deficiency was defined using serum vitamin B12 concentrations, while functional biomarkers such as methylmalonic acid and homocysteine were not assessed. Future studies incorporating these biomarkers may

provide a more comprehensive assessment of vitamin B12 status and help clarify the clinical significance of PPI exposure.

Duration of PPI exposure may also be an important factor. Termanini et al. reported reduced serum vitamin B12 levels among patients receiving long-term omeprazole therapy for Zollinger-Ellison syndrome, with greater reductions observed with longer treatment duration [20]. In the present study, 17 (14.2%) of the 120 PPI users reported continuous PPI use for more than one year. Although this represented a relatively small proportion of PPI users, the finding highlights the importance of documenting the duration of acid-suppressive therapy when evaluating patients with vitamin B12 deficiency.

A systematic review and meta-analysis by Jung et al. also reported an association between long-term acid-suppressive therapy and vitamin B12 deficiency [21]. However, substantial heterogeneity was observed in the definitions of both medication exposure and vitamin B12 deficiency across the included studies. Such methodological differences make direct comparison between studies difficult and emphasise the need for well-designed prospective studies using standardised definitions and objective biomarkers.

Gastro-oesophageal reflux disease (GERD) was the most frequently reported gastrointestinal condition in the present study, affecting 180 (80.0%) participants. This may partly explain the relatively high prevalence of PPI exposure because GERD is a common indication for acid-suppressive therapy. Importantly, however, PPI use may reflect the presence of an underlying gastrointestinal condition rather than being an independent determinant of vitamin B12 deficiency. The high prevalence of GERD in this population therefore represents a

potential confounding factor that should be considered when interpreting the findings. Most participants, 199 (88.0%), reported consuming a non-vegetarian diet, while 27 (12.0%) reported a vegetarian diet. Although dietary intake is an important determinant of vitamin B12 status, the present study did not quantify dietary vitamin B12 intake or assess the nutritional composition of individual diets. Therefore, dietary pattern alone cannot be used to determine the contribution of inadequate vitamin B12 intake to the observed deficiency.

Strengths and Limitations

The present study provides descriptive information regarding PPI exposure, specific PPI types, dosage, duration of use, and reported adverse effects among patients with laboratory-confirmed vitamin B12 deficiency. However, several limitations should be considered. First, the cross-sectional design prevents assessment of temporality and causality. Second, the study used purposive sampling, which may introduce selection bias and limit the generalisability of the findings. Third, information regarding PPI use, dosage, and duration was self-reported and may therefore be affected by recall bias. Fourth, no non-deficient control group was included, preventing estimation of the relative risk or odds of vitamin B12 deficiency associated with PPI exposure. Fifth, functional biomarkers such as methylmalonic acid and homocysteine were not measured. Finally, potentially important confounding factors, including gastrointestinal disorders, dietary intake, comorbidities, and concomitant medications, may have influenced vitamin B12 status and PPI use.

Despite these limitations, the study provides useful information regarding the pattern of PPI exposure among patients with vitamin B12 deficiency. More than half of the participants reported current or previous PPI

use, and omeprazole was the most frequently reported PPI. These findings support the importance of periodically reassessing the indication, dose, and duration of PPI therapy, particularly when prolonged treatment is being considered. However, the findings should not be interpreted as evidence that PPI therapy caused vitamin B12 deficiency.

Future prospective studies involving appropriate non-deficient control groups, objective medication exposure data, detailed dietary assessment, and functional biomarkers of vitamin B12 status are needed to better clarify the relationship between prolonged PPI therapy and vitamin B12 deficiency.

Conclusion

More than half of the patients with laboratory-confirmed vitamin B12 deficiency in this study reported current or previous PPI use, with omeprazole being the most frequently reported PPI. Gastro-oesophageal reflux disease was the most commonly reported gastrointestinal condition, and a smaller proportion of PPI users reported continuous treatment for more than one year.

The findings highlight the importance of periodically reassessing the indication, dose, and duration of PPI therapy, particularly in patients receiving prolonged treatment or those with vitamin B12 deficiency. However, because this was a cross-sectional study conducted exclusively among patients with vitamin B12 deficiency and without a non-deficient control group, the findings cannot establish a causal relationship between PPI use and vitamin B12 deficiency. Further prospective studies with appropriate control groups and functional biomarkers of vitamin B12 status are warranted.

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Ethical Approval and Consent: Ethical approval was obtained from the relevant institutional ethics committee, and written informed consent was obtained from all participants.

Conflict of Interest: The authors declare no conflict of interest.

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