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Association of Long-Term Use of Proton Pump Inhibitors and Histamine-2 Receptor Antagonists with Vitamin B12 Deficiency

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A B S T R A C T

Objective: To determine the association of long-term proton pump inhibitor, use and histamine 2 receptor antagonist with vitamin B12 deficiency.

Methodology: This Case-control Study was executed at the Department of General Medicine, Abbasi Shaheed Hospital, Karachi, from 15th March 2025 to 14th September 2025. The study included adult's participants of both genders, aged between 20 to 70 years. The sample size of 100 vitamin B12-deficient cases and 100 controls were included through non-probability consecutive sampling. Long-term proton pump inhibitor or histamine-2 receptor antagonist use (≥ 2 years) served as the exposure. Data were analysed in SPSS 26 with Chi-square analyses and odds ratios, with p-value was taken to be below 5% as significant.

Results: The mean age of vitamin B_{12}-deficient patients was 61.6 ± 9.4 years, and 56% were females. Mean serum vitamin B_{12} levels were significantly lower in deficient patients (148.9 ± 29.6 pg/ml) compared to controls (466.5 ± 129.2 pg/ml; $p < 0.001$). Long-term PPI use showed an adjusted odds ratio (OR) of 2.156 (95% CI: 0.826–5.626; $p = 0.116$), while H_2RA use had an adjusted OR of 1.264 (95% CI: 0.319–5.015; $p = 0.739$). Diabetes mellitus was significantly associated with vitamin B_{12} deficiency ($p = 0.038$).

Conclusion: This investigation revealed an absence of statistically significant association between prolonged administration of PPI or H_2Ras and the incidence of vitamin B_{12} deficiency within the cohort of assessed patients. Diabetes mellitus, however, was identified as an independent predictor of low vitamin B_{12} levels. These findings emphasize careful and rational use of acid-suppressive medications and highlight the need for periodic vitamin B_{12} monitoring in diabetic and vitamin B_{12}-deficient patients receiving prolonged acid suppression. This null finding is inconclusive rather than confirmation of safety, given the limited sample size and single time-point measurement.

Keywords: Vitamin B12 deficiency, Nutritional deficiency, Drug-induced malabsorption, Proton pump inhibitors, Histamine-2 receptor antagonists

Introduction

The use of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) is one of the most widely used medications in the treatment of acid-related disorders, such as gastro-oesophageal reflux disease and peptic ulcer disease.[1,2,20] These agents work by inhibiting the release of gastrointestinal acid which is an essential phase in the physiological release of dietary vitamin B12 in food proteins as well as the subsequent absorption of this vitamin in the distal ileum [3]. The constant suppression of the acid in the gastrointestinal system can, in turn, break the usual assimilation approach that makes them susceptible to vitamin B12 deficiency. [4]

Over the past several years, clinical and experimental data have indicated that the long-term application of acid-suppressive treatment can have a negative influence on the micronutrient status. Long-term exposure to PPIs or H2RAs has been demonstrated to cause a decrease in circulating vitamin B12 levels especially in older adults or in those with a variety of comorbid conditions.[5,6] In a 2022 systematic review, the evidence that chronic acid suppression reduces serum vitamin B12 levels by interfering with gastric secretion of the nutrient was confirmed.[7] Following population-based studies and meta-analyses indicate that there is a higher risk of deficiency in regular users with odds ratios that are mostly between 1.3 to 1.7 based on the duration and dosage of treatment.[8-10,16] Despite these findings, some contemporary studies have failed to show a consistent relationship, possibly due to methodological differences, heterogeneous definitions of deficiency, and variations in diet and age distribution across study populations [11,12]. Both PPIs and H2RAs share a biologically plausible mechanism by reducing gastric acid secretion, which can hinder the liberation and absorption of vitamin B12 from dietary sources.[13] Persistent deficiency may result in anaemia, neurocognitive decline, and other systemic effects, highlighting its clinical relevance. [14,15,18]

Majority of research studies carried out in the past are carried out in the West where the dietary and drug use patterns as well as health care provisions are very different than that in South Asia.[12] PPIs and H2RAs are commonly employed in Pakistan to long periods of time, with little or no proper oversight. Nevertheless, there is a dearth of evidence on their long-term effect on the vitamin B12 status. In order to address this deficiency in knowledge, the present case-control

investigation was conducted at Abbasi Shaheed Hospital, Karachi, with the objective of elucidating the association between prolonged (> 2 years) administration of PPIs or H_2RAs and the incidence of vitamin B_{12} deficiency in the adult population aged 20 to 70 years.

Methodology

This Case-control Study was executed at the Department of General Medicine, Abbasi Shaheed Hospital, Karachi, from 15th March 2025 to 14th September 2025, following approval of the study protocol. The exposure variable was the long-term use of PPI or H_2RAs, defined as continuous intake for at least two years. The deficiency of vitamin B12 was characterized as a serum vitamin B_{12} concentration < 200 pg/ml. All biochemical investigations were performed in the hospital's central diagnostic laboratory using standardized chemiluminescence immunoassay techniques in accordance with Abbasi Shaheed Hospital's quality assurance procedures.

The sample population included individuals who were between the age group of 20 to 70 years of both gender through non-probability consecutive sampling. Participants who had visited outpatient clinics or been admitted to medical wards within the given study period were enrolled in the study. Cases who were identified as having deficiency in vitamin B_{12} and the controls were individuals who presented with normal vitamin B_{12} levels. The research has systematically excluded pregnant women, participants who were taking multivitamin supplements, the already diagnosed cases of vitamin B_{12} deficiency and patients on metformin therapy. Patients with coeliac disease, malabsorption syndromes or other established nutritional deficiency states, and those receiving chemotherapeutic agents, were also excluded.

The sample size was estimated using the WHO sample size calculator based on an expected prevalence of PPI use among vitamin B_{12} deficient of 12 percent compared to 7.2 percent among non-deficient individuals, with 80 percent statistical power and a 95 percent confidence level. The final sample of 200 participants, comprising 100 cases and 100 controls were included.

Data were gathered utilizing a systematically designed proforma subsequent to the acquisition of documented informed consent. The information recorded included demographic characteristics, clinical history, comorbidities, body mass index, smoking status, and details regarding the duration and type of acid-suppressant medication used. All data collection adhered to the departmental ethical protocols and confidentiality standards practiced at Abbasi Shaheed Hospital.

The SPSS version 26 was used to analyse the data. Descriptive statistics were calculated at 95% C.I. The odds ratios were computed to evaluate the strength of association between long-term use of acid-suppressant drugs and vitamin B_{12} deficiency. Categorical variables were compared using the chi-square test, while binary logistic regression was applied to estimate crude and adjusted odds ratios with 95% confidence intervals, with adjustment for age, body mass index, gender, smoking status, diabetes mellitus and hypertension. The p-value was taken to be below 0.05 as significant.

Results

Table I summarizes the baseline and clinical characteristics of the 200 study participants (100 cases and 100 controls). Cases had a higher mean age than controls (61.56 ± 9.42 vs. 58.49 ± 11.48 years) and comparable BMI (25.23 ± 4.79 vs. 25.50 ± 4.66 kg/m²). Mean serum vitamin B_{12} levels were substantially lower among cases (148.89 ± 29.62 vs. 466.52 ± 129.16 pg/mL), while the duration of PPI use (5.41 ± 3.01 vs. 2.72 ± 2.13 years) and H_2 receptor antagonist use (4.39 ± 2.60 vs. 1.78 ± 1.99 years) was longer in cases than controls. Smoking (42.0% vs. 34.0%) and diabetes mellitus (44.0% vs. 31.0%) were more frequent among cases, whereas hypertension was more common among controls (42.0% vs. 35.0%) (Table I).

Table I: Baseline and Clinical Characteristics of Study Participants (n=200)

Characteristics		Groups	
		Cases (n=100)	Control (n=100)
Age in years, Mean ± SD		61.56 ± 9.42	58.49 ± 11.48
BMI in kg/m², Mean ± SD		25.23 ± 4.79	25.50 ± 4.66
Vitamin B12 in pg/ml, Mean ± SD		148.89 ± 29.62	466.52 ± 129.16
Duration of PPI Use in years, Mean ± SD		5.41 ± 3.01	2.72 ± 2.13
Duration of H_2 Antagonist Use in years, Mean ± SD		4.39 ± 2.60	1.78 ± 1.99
Gender	Male, *n* (%)	43 (43.0)	45 (45.0)
	Female, *n* (%)	57 (57.0)	55 (55.0)
Residential Status	Urban, *n* (%)	74 (74.0)	71 (71.0)
	Rural, *n* (%)	26 (26.0)	29 (29.0)
Smoking Status		42 (42.0)	34 (34.0)
Diabetes Mellitus		44 (44.0)	31 (31.0)
Hypertension		35 (35.0)	42 (42.0)

Table II compares the long-term use of PPIs and H_2RAs between vitamin B_{12}-deficient and non-, yielding an unadjusted OR of 1.263 (p=0.500) and an adjusted OR of 1.264 (p=0.739). These results indicate that there was no statistically significant association between long-term use of either PPIs or H_2 receptor antagonists and vitamin B_{12} deficiency.

Table III presents the association between patient characteristics and vitamin B_{12} deficiency among long-term PPI users. After multivariable adjustment, age was independently associated with vitamin B_{12} deficiency (adjusted OR = 0.966, 95% CI: 0.938–0.995; p = 0.020), while diabetes mellitus was associated with nearly a twofold higher likelihood of deficiency (adjusted OR = 1.916, 95% CI: 1.037–3.542; p = 0.038). In contrast, BMI (adjusted OR = 1.022, 95% CI: 0.961–1.087; p = 0.491), gender (adjusted OR = 1.063, 95% CI: 0.586–1.929; p = 0.840), smoking status (adjusted OR = 1.396, 95% CI: 0.764–2.549; p = 0.278), and hypertension (adjusted OR = 0.690, 95% CI: 0.379–1.256; p = 0.224) were not significantly associated with vitamin B_{12} deficiency..

Table IV presents the association between patient characteristics and vitamin B_{12} deficiency among long-term H_2 receptor antagonist (H_2RA) users. In the adjusted analysis, age was inversely associated with vitamin B_{12} deficiency (adjusted OR = 0.967, 95% CI: 0.939–0.995; p = 0.023), while diabetes mellitus was independently associated with an increased likelihood of deficiency (adjusted OR = 1.884, 95% CI: 1.022–3.473; p = 0.042). BMI (adjusted OR = 1.024, 95% CI: 0.963–1.088; p = 0.447), gender (adjusted OR = 1.052, 95% CI: 0.581–1.903; p = 0.867), smoking status (adjusted OR = 1.316, 95% CI: 0.727–2.381; p = 0.364), and hypertension (adjusted OR = 0.698, 95% CI: 0.385–1.266; p = 0.236) were not significantly associated with vitamin B_{12} deficiency.

Discussion

This analytical case-control investigation examined the association between extended utilization of PPIs and histamine H_2RAs and the incidence of vitamin B_{12} deficiency in the adult population residing in Karachi, Pakistan. Although participants using acid-suppressive medications for more than two years exhibited lower mean serum vitamin B_{12} levels, the association between long-term therapy and deficiency was not statistically significant after adjusting for confounders. Diabetes mellitus, however, emerged as a significant independent factor associated with lower vitamin B_{12} levels in both medication groups. These findings are augmenting the existing body of evidence that has been compiled to date, which has revealed inconclusive results regarding the impact of chronic acid suppression on vitamin B12 levels. Lam. [3] have reported a notable increase in the likelihood of deficiency among long-term users of proton pump inhibitors (PPIs) and H2 receptor antagonists (adjusted odds ratio 1.65; 95% confidence interval 1.58-1.73), whereas Ruscin. [9] have found no substantial correlation within older demographics,

Table II: Comparison of Long-Term Proton Pump Inhibitor and H_2 Receptor Antagonist Use Between Vitamin B_{12} Deficient and Non-Deficient Groups (n=200)

Outcomes	Groups					
	Cases (n=100)	Control (n=100)	Unadjusted OR (95% CI)	P-Value	Adjusted OR (95% CI)	P-Value
Long Term PPI use	14 (14.0)	8 (8.0)	1.872 0.748-4.684	0.175	2.156 0.826-5.626	0.116
Long term H_2 Antagonist Use	5 (5.0)	4 (4.0)	1.263 0.329-4.848	0.500	1.264 0.319-5.015	0.739

Table III: Association of Patient Characteristics with Vitamin B_{12} Deficiency Among Long-Term Proton Pump Inhibitor (PPI) Users

Predictor	Unadjusted Odd Ratio (95% CI)	P-value	Adjusted Odd Ratio (95% CI)	P-value
Age (years)	0.971 (0.944 – 0.999)	0.040	0.966 (0.938 – 0.995)	0.020
BMI (kg/m^2)	1.010 (0.952 – 1.071)	0.743	1.022 (0.961 – 1.087)	0.491
Gender	0.929 (0.530 – 1.629)	0.798	1.063 (0.586 – 1.929)	0.840
Smoking Status	1.481 (0.829 – 2.646)	0.185	1.396 (0.764 – 2.549)	0.278
Diabetes Mellitus	1.764 (0.986 – 3.158)	0.056	1.916 (1.037 – 3.542)	0.038
Hypertension	0.736 (0.414 – 1.308)	0.296	0.690 (0.379 – 1.256)	0.224

Table IV: Association of Patient Characteristics with Vitamin B_{12} Deficiency Among Long-Term Histamine-2 Receptor Antagonist (H_2RA) Users

Predictor	Unadjusted Odd Ratio (95% CI)	P-value	Adjusted Odd Ratio (95% CI)	P-value
Age (years)	0.972 (0.945 – 0.999)	0.044	0.967 (0.939 – 0.995)	0.023
BMI (kg/m^2)	1.012 (0.954 – 1.074)	0.681	1.024 (0.963 – 1.088)	0.447
Gender	0.917 (0.524 – 1.605)	0.762	1.052 (0.581 – 1.903)	0.867
Smoking Status	1.409 (0.794 – 2.501)	0.241	1.316 (0.727 – 2.381)	0.364
Diabetes Mellitus	1.745 (0.977 – 3.115)	0.060	1.884 (1.022 – 3.473)	0.042
Hypertension	0.745 (0.421 – 1.320)	0.313	0.698 (0.385 – 1.266)	0.236

suggesting that the association may be contingent upon demographic variables and health status. On the

same note, Nieber [1] and Mouchaileh [7] have highlighted that despite being biologically plausible, the clinical significance of the vitamin B 12 deficiency caused by acid suppression is not consistent across populations and that the magnitude of risk could be determined by age, diet, length of use, and underlying nutrition condition. Other studies found stronger association (i.e., Dinesh. [6]) and Sridharan [5]) and positive correlations, especially in cases when acid-suppressive therapy was in concomitants with metformin or other drugs that could influence nutrient absorption, which suggests that the depletion of vitamin B 12 is probably multifactorial. In the current investigation, the adjusted odds ratio of using long-term PPI was 2.156 and H_2RAs 1.264.

Though these odds ratios indicated a direction of greater risk, the p-values indicate the significance insignificance may be due to the smaller sample, unexamined exposure to the medication, or countermeasures by the body that offset absorption impairment. The biological explanation of these facts is quite clear: gastric acid helps to release vitamin B 12 out of diet proteins and bind it to intrinsic factor that is necessary to be absorbed in the distal ileum [4,10].

Inhibition of this process by PPIs and H_2RAs may consequently cause deficiency, though this may not be as significant in a population with sufficient dietary intake of vitamin B 12 or with shorter periods of treatment. Interestingly, diabetes mellitus also exhibited a substantial correlation with vitamin B 12 deficiency without metformin therapy, which is consistent with the results of Dinesh *et al.* [6] and Al-Hamdani *et al.* [12,19,21] who found that diabetes itself with its mechanisms as gastrointestinal dysmotility, inflammation, and neuropathic changes is able to change nutrient absorption. The current findings, therefore, support the idea of paying more attention to B 12 in diabetic patients, despite the absence of using metformin.

The largest population-based study, by Lam *et al.* [3], analysed 25,956 vitamin B_{12}-deficient cases against 184,199 controls and reported a modest but significant risk for two or more years of PPI use (adjusted OR 1.65; 95% CI 1.58 to 1.73) and H_2RA use (OR 1.25; 95% CI 1.17 to 1.34). In the present series the point estimates were directionally consistent and in fact larger (adjusted OR 2.156 for PPIs and 1.264 for H_2RAs), but the wide confidence intervals that crossed unity (95% CI 0.826 to 5.626 and 0.319 to 5.015, respectively) indicate that a sample of 200 participants was underpowered to confirm an effect of the magnitude reported in cohorts two to three orders of magnitude larger. The present findings are therefore better described as inconclusive than as contradicting the existing evidence. Comparable variability is evident across recent work: Jung *et al.* [4] catalogued chronic PPI and H_2RA use among recognised causes of drug-induced vitamin B_{12} deficiency, while Ito *et al.* and Mir *et al.* [10,11] documented measurable reductions in serum B_{12} during prolonged acid suppression, including in Zollinger-Ellison syndrome. Conversely, Ruscin *et al.* [9] reported no consistent association in older adults, mirroring the present negative result. The significant independent association of diabetes mellitus with vitamin B_{12} deficiency observed here is consistent with the polypharmacy analysis of Al-Hamdani *et al.* [12] and the quality-improvement data of Whitney and Hoag [14], both of which linked metabolic disease and concomitant acid suppression to lower serum B_{12}.

Although the study has a solid design, as well as incorporates both PPI and H 2 RA users, it is also limited in several ways. The sample size used might not have been large enough to pick smaller effect sizes, medication exposure was retrospective, and dietary intake, socioeconomic status, and genetic factors were not assessed. Also, functional biomarkers like methylmalonic acid or homocysteine were absent, which hindered the determination of subclinical deficiency [11,18]. In addition, serum vitamin B_{12} was measured at a single time point; concentrations were not compared before and after the initiation of acid-suppressive therapy, so the design cannot establish a temporal or causal sequence between drug exposure and the observed fall in vitamin B_{12}. However, the results have practical significance due to the widespread and often long-term use of PPIs and H_2RAs in Pakistan, which is not always justified by clinical reasons [8,12,17]. Doctors must not overlook the possible nutritional implications of chronic acid inhibition and should consider regular screening of vitamin B 12 particularly in the geriatric population, those with diabetes or people on several drugs [7,13,14,21]. The subsequent multicentre, prospective investigations in bigger cohorts, extended follow-up, incorporation of functional biomarkers and dietary information are justified to elucidate dose response relationship and offer evidence-based recommendations on the safe and rational application of acid-suppressive therapy [10,15].

Conclusion

This investigation revealed an absence of statistically significant association between prolonged administration of PPI or H_2Ras and the incidence of vitamin B_{12} deficiency within the cohort of assessed patients. Diabetes mellitus, however, was identified as an independent predictor of low vitamin B_{12} levels. These findings emphasise careful and rational use of acid-suppressive medications and highlight the need

for periodic vitamin B_{12} monitoring in diabetic and vitamin B_{12}-deficient patients receiving prolonged acid suppression. The absence of a statistically significant association should not be interpreted as evidence that acid-suppressive therapy is free of risk to vitamin B_{12} status, since the adjusted odds ratios pointed towards a higher risk and the limited sample size and single time-point measurement may have masked a true effect. These results should therefore be regarded as inconclusive rather than reassuring, and they reinforce rather than weaken the case for judicious prescribing and periodic vitamin B_{12} monitoring in long-term users of acid-suppressive therapy.

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