ISSN : 2350-0743

International Journal of Recent Advances in Multidisciplinary Research

Vol. 11, Issue 11, pp. 10394-10397, November, 2024

RESEARCH ARTICLE

A SYSTEMATIC REVIEW ON PROTON PUMP INHIBITORS INDUCED VITAMIN B12 DEFICIENCY

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ARTICLE INFO

Article History
Received 20th August, 2024
Received in revised form
16th September, 2024
Accepted 27th October, 2024
Published online 30th November, 2024

Keywords:

PPIs, Anaemia, Iron Deficiency, B12 Deficiency.

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ABSTRACT

Background: Drugs known as proton pump inhibitors (PPIs) are frequently prescribed to treat a variety of gastrointestinal disorders, including erosive esophagitis, gastroesophageal reflux disease, and duodenal and stomach ulcers. They are now the most effective medications that lower gastric hydrochloric acid output and have been in use for almost 30 years. Sometimes, in certain patient populations, prolonged use of a proton pump inhibitor (PPI) has been associated with decreased serum levels of vitamin B12 (cobalamin). According to reports, proton pump inhibitors can harm the intestines and alter the gut microbiota, which can impact a number of processes, such as malabsorption. Long-term PPI use can have a number of negative effects, but the most frequent ones are vitamin and mineral deficiencies, recurrent infections, cardiovascular problems, and bone fractures. **Methods**: Previously published articles relating to the topic Proton pump inhibitors and Vitamin B12 deficiency was collected and reviewed. **Observations:** Since continuous PPI medication raises the frequency of vitamin B12 deficiency, particularly in the elderly, the link with vitamin deficiencies has drawn more attention. Conflicting findings were found in a number of investigations that attempted to establish a link between vitamin B12 level and PPI. We thoroughly reviewed observational studies that looked at how long-term PPI side effects affect the absorption of vitamin B12 in this systematic review.

Citation: Megha J.R., Keerthi G S Nair and Shaiju S Dharan. 2024. *"*A systematic review on proton pump inhibitors induced vitamin b12 deficiency*", International Journal of Recent Advances in Multidisciplinary Research,* 11, (12), 10394-10397.

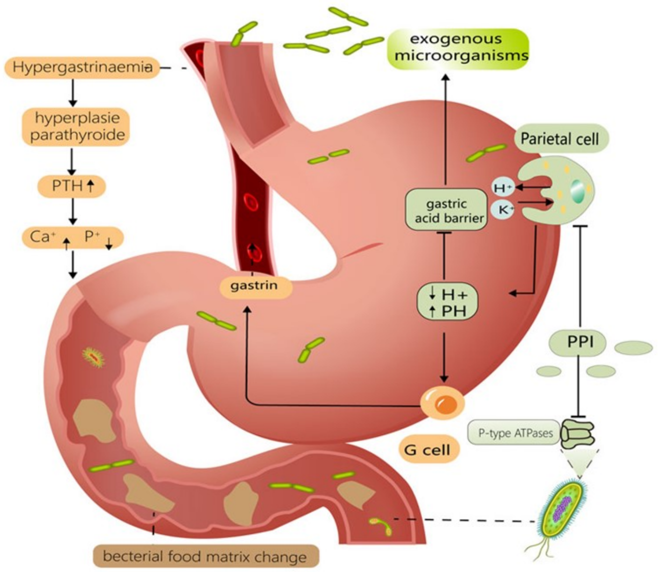
INTRODUCTION

Cobalamin, another name for vitamin B12, is a water-soluble vitamin that is essential as a cofactor for enzymes that produce DNA, myelin, and fatty acids. One The only source of vitamin B12 is food, primarily meat, fish, and dairy products, where it is present in a protein-bound form. The frequency of metabolically verified vitamin B12 deficiency in those over 65 is believed to be between 5 and 15%, making it a reasonably frequent illness among older adults. Pernicious anemia, gastric bypass surgery, total or partial gastrectomy, and inflammatory bowel illness can all result in a B12 shortage. Pernicious anemia, an autoimmune disease that causes vitamin B12 insufficiency, is brought on by autoantibodies against intrinsic factor, which is necessary to bind ingested vitamin B12. Lack of stomach acid during bariatric surgery and gastrectomy reduces the absorption of vitamin B12 from diet. Vitamin B12 deficiency with ileum or ileal/ileocolonic resections of the site of the absorption of the vitamin B12-intrinsic factor complex can be caused by Crohn's disease.

Those who follow a strict vegetarian diet or consume little meat or dairy products may also experience a B12 deficit. Long-term PPI use has been linked to a higher risk of vitamin and mineral deficiencies, which has sparked concerns. As acid-suppressing drugs, proton pump inhibitors are widely used by most people worldwide, and most patients take them for at least a year without a clear reason. These medications, which were created to treat and prevent acid-mediated upper gastrointestinal disorders, are increasingly being utilized for purposes where their advantages are less clear. Out of 700 medications, proton pump inhibitors have also been shown to harm the gut and alter its microbiota, which can impact several processes such as malabsorption, autoimmune disorders, and other microscopic issues. Furthermore, patients who take proton pump inhibitors (PPIs) for an extended period of time have reduced absorption of vitamin B-12 and decreased release of stomach acid. According to observational studies, the prevalence of PPI usage has grown over time, with 7% to 15% of patients using these drugs at any given time. For individuals 70 years of age or older, the prevalence rises to 40%.

PPIs are the preferred treatment for acid-mediated upper gastrointestinal (GI) disorders like erosive esophagitis and peptic ulcer disease, but they are also being used more frequently for less obvious indications and for uncertain periods of time. About 25% of all patients who receive a PPI will continue to use them for at least a year.Given the length of time, several research provide results that differ from what was anticipated. Nevertheless, omeprazole and pantoprazole did not lead to vitamin B12 insufficiency when the course of treatment lasted more than four years and regular monitoring was ignored[2]. There were no discernible variations in the vitamin B12 levels of patients with peptic ulcer disease who had been taking PPIs for more than a year, according to a cross-sectional study[9]. There was no difference in vitamin B12 levels between older participants who had been taking PPI for more than three years and their non-PPI-using counterparts, according to another study.

PPIS' MECHANISMS OF ACTION ON SERUM LEVELS OF TOTAL VITAMIN B-12: PPIs function by inhibiting the activity of gastric H+K+- ATPase which pumps H+ ions from the gastric parietal cells into the gastric lumen, where they combine with Cl− ions to generate HCL-2 (Fig I).



Esomeprazole, lansoprazole, and omeprazole are typical PPI medication examples [6]. The function of stomach acid in the digestion of foods containing vitamin B-12 is linked to the impact of PPIs on vitamin B-12 status. As previously mentioned, gastric acid facilitates the conversion of pepsinogen to pepsin, which liberates vitamin B-12 from dietary proteins. When PPIs are used, the stomach's ability to release vitamin B-12 from meals is compromised, which lowers the amount of vitamin B-12 the body absorbs [6]. After two weeks of omeprazole treatment, *Marcuard et al*. observed a significant decrease in stomach acid output and protein-bound vitamin B-12 absorption in men (aged 22–50 years, n = 10). The brief treatment length was cited as the reason why serum total vitamin B-12 concentrations were not immediately impacted [5]. These results are in line with those of *Schenk et al.*, who demonstrated that in adults (ages 22–52 years, 5 men and 3 women), the absorption of protein-bound vitamin B-12 was considerably reduced following 9 days of omeprazole treatment, while the absorption of unbound vitamin B-12 remained unhindered [12]. Several investigations have established the link between PPI and vitamin B12. Numerous hypotheses were put up to explain how they interacted to cause vitamin B12 insufficiency. The most widely recognized explanation for vitamin B12 absorption is that the stomach mucosa, which contains parietal cells and oxyntic glands, must remain intact [5].

VITAMIN B12 INSUFFICIENCY AND THE TREATMENT DURATION OF PPIs: *Jung et al.* conducted a recent systematic review and meta-analysis to assess the relationship between the development of vitamin B-12 deficiency and long-term (≥10 mo) usage of acid-lowering medications (PPIs and H2RAs; precise dosages not stated). One observational research and four case-control studies—which included over 19,000 controls and over 4200 cases of vitamin B-12 deficiency—were found to satisfy the analysis's inclusion requirements [4]. The Jung meta-analysis examined the duration of acid-lowering medication use as a factor; the study found no correlation between vitamin B-12 deficiency and short-term (less than 12 months) acid-lowering agent use[4]. A study conducted by *B Termanini et al.* suggests that, Serum vitamin B12 levels significantly decline with prolonged omeprazole medication, although folate levels do not. These results imply individuals with Zollinger-Ellison syndrome treated with H(+)-K(+)-ATPase inhibitors should have serum vitamin B12 levels monitored. Furthermore, our data suggest the prospect that other individuals treated persistently with H(+)-K(+)-ATPase inhibitors may acquire B12 insufficiency [1]. The findings of a study by *Hasime Qorraj-Bytyqi et al.* show a significant correlation between using PPIs for 12 months and lower vitamin B12 and iron body stores, as well as a higher prevalence of HHcy in PPI users. Iron and vitamin B12 levels are impacted by long-term PPI treatment. However, there were no appreciable differences between PPI users and non-users, with only 3.8% and 2.9% of the individuals, respectively, receiving the later diagnoses of hypoferremia and vitamin B12 deficiency at the end of the trial [11].

Long-term PPI use may be associated with a higher risk of vitamin B12 deficiency, particularly in men between the ages of 18 and 40, according to a study by *Mumtaz et al.* Minimizing adverse effects requires using PPIs for the shortest amount of time at the lowest effective dose. These side effects have the potential to have a therapeutic influence, while their causal relationship is still under investigation [8]. Pelluri et al. in a case report regarding Pantoprazole induced Vitamin B12 Deficiency suggests that, Vitamin and mineral shortages that affect the metabolism of calcium, iron, magnesium, vitamin B12, and vitamin C have been linked to PPIs [9]. According to another study by *Valuck RJ et al.*, elderly patients with vitamin B12 insufficiency had a considerably higher likelihood of using H2RA/PPI for durations longer than 12 months. This is a relevant issue because patients are increasingly taking acid-suppressive drugs for extended periods of time to prevent recurrent symptoms of gastroesophageal reflux disease (GER), to prevent potential complications from GER, like Barrett's esophagus and peptic stricture, and to prevent NSAID-induced gastropathy. Despite being widely regarded as incredibly safe, evidence indicates that H2RAs and PPIs may actually increase the malabsorption of food-bound vitamin B12. Compared to younger populations, older patients already have a higher risk of vitamin B12 insufficiency and may have borderline vitamin

B12 status at baseline. Therefore, with additional factors that can affect vitamin B12 absorption, including the usage of H2RA/PPI, older people may be more susceptible to developing vitamin B12 shortage. The most recent 2021 cohort study looked at the protective effect of fortified foods on vitamin B12 levels in 3299 older individuals living in the community (1216 PPI users, 2083 non-PPI users). [2]According to the study's findings, those who took higher PPI dosages (≥30 mg/d) for longer than six months were substantially more likely to have high MMA levels, lower holotranscobalamin (holoTC), and a greater prevalence of vitamin B12 deficiency (21% versus 15% in controls; $p = 0.001$).

Participants who consumed unfortified foods had a much higher prevalence of vitamin B12 insufficiency than those who used crystalline forms of vitamin B12. Additionally, the author came to the conclusion that older people with chronic, higher doses of PPI benefited from eating fortified foods [(12)]. The aforementioned studies highlight how important it is to consider PPI dosage when examining its relationship to vitamin B-12 status. To show how PPI usage impacts long-term vitamin B12 status and whether it is recommended to regularly evaluate vitamin B12 status in PPI users, the effects of PPI ingestion over a longer time period are also required.

DIAGNOSIS OF VITAMIN B12 DEFICIENCY: Vitamin B12 insufficiency has never been easily diagnosed in a lab. The two main components of diagnostic testing are the measurement of blood indicators that build up as a result of vitamin B12 deficiency and the measurement of circulating vitamin B12 levels. Serum vitamin B12 and holoTC measure circulating vitamin levels, while vitamin B12 deficiency raises MMA and homocysteine levels[(2)].The absence of a gold standard test to measure vitamin B12 levels in order to diagnose deficiency is a drawback of laboratory diagnosis. Diagnosing B12 deficiency based solely on serum B12 levels leaves many cases undiagnosed.

The more specific of the two markers of B12 deficiency, homocysteine (Hcy), and MMA, is elevated MMA. Elevated MMA suggests a vitamin B12 deficiency [(22)]. A recent study found that holoTC is a good initial test to identify vitamin B12 insufficiency. Further study is required to decide whether to use holoTC as the first-line test or in conjunction with a metabolic marker before developing a standard diagnostic strategy with relevant cut-off values.

MANAGEMENT: All patients with unexplained anemia and/or neurological symptoms, as well as those who are at risk of developing vitamin B12 deficiency, such as the elderly and those with intestinal disorders, should be evaluated for vitamin B12 deficiency. In situations that remain unclear, it is recommended that the first analysis be the measurement of plasma cobalamins, which should be followed by the measurement of plasma methylmalonic acid. There is growing evidence that plasma holotranscobalamin (holoTC), a physiologically active cobalamin, may be better than plasma cobalamins. As a result, holoTC measurement is now being used in clinical settings. Either injections every two to three months or a daily dose of 1 mg vitamin B12 can guarantee effective treatment once the diagnosis of vitamin B12 deficiency has been verified.

PREVENTIVE MEASURES

- Every patient using a PPI should have their current indications for usage reviewed and documented on a frequent basis. The patient's primary care physician ought to be in charge of this review.
- Every patient who does not have a clear indication for a chronic PPI should be given the opportunity to try deprescription medication.
- The majority of patients with a chronic PPI usage indication who now take twice-daily doses ought to be evaluated for switching to once-daily PPIs.
- PPI withdrawal should typically not be considered for patients with complex gastroesophageal reflux disease, such as those who have a history of severe erosive esophagitis, esophageal ulcers, or peptic strictures.
- Patients with idiopathic pulmonary fibrosis, Barrett's esophagus, or eosinophilic esophagitis should not be considered for a deprescribing experiment.
- Before being deprescribed, PPI users should have their risk of upper gastrointestinal bleeding evaluated using an evidence-based approach.
- PPIs should not be deprescribed for patients who are at high risk of upper gastrointestinal hemorrhage.
- Patients who stop taking PPIs for an extended period of time should be informed that rebound acid hypersecretion may cause temporary upper gastrointestinal discomfort.
- Both dose titration and abrupt discontinuation are options when administering PPIs.
- The decision to stop using PPIs should not be motivated by worries about PAAEs, but only by the fact that there is no indication for their usage.PPI discontinuation is not always indicated by the existence of a PAAE or a history of one in a current PPI user. Similarly, the existence of underlying risk factors for the occurrence of a PPI-related adverse event shouldn't be a stand-alone reason to stop taking PPIs[(20)].

CONCLUSION

A vitamin B12 deficit may arise after long-term, high-dose PPI use. A vitamin B12 shortage can cause mild anemia or serious neurological impairments. Elevated homocysteine levels, which are strongly linked to vascular and neurodegenerative deficiencies, are a laboratory indicator of deficiency. It may also raise the chance of developing cardiovascular disease. Therefore, it is important to pay close attention to the diagnostic indicators of vitamin B12 deficiency in order to confirm the shortage before any clinical symptoms appear. A timely identification of vitamin deficiency is essential when giving long-term PPI, particularly in older patients who are more vulnerable. To track the negative effects of long-term PPI use, further study is necessary to examine PPI-induced vitamin B12 insufficiency, especially randomized clinical trials. Additionally, more prospective studies on the clinical effects of vitamin B12 insufficiency caused by proton pump inhibitors would be helpful. Therefore, we recommend that doctors use PPIs sparingly, stop using them when they are not needed, and be alert about PPI-induced vitamin deficiencies.

FUNDING: No funding.

DECLARATION OF COMPETING INTEREST: None declared.

ACKNOWLEDGMENTS

All components of the work are the only author's responsibility.

REFERENCES

1. B Termanini, Fathia Gibril, Sutliff VE, Yu F, Venzon D, Jensen RT. Effect of Long-Term Gastric Acid Suppressive Therapy on Serum Vitamin B12 Levels in Patients with Zollinger-Ellison Syndrome. The American Journal of Medicine. 1998 May 1;104(5):422–30.
2. Carabotti M, Annibale B, Lahner E: Common pitfalls in the management of patients with micronutrient deficiency: keep in mind the stomach. Nutrients. 2021, 13:10.3390/nu13010208
3. Chappell L, Brown SA, Wensel TM. Evaluation of Vitamin B12 Monitoring in Patients on Concomitant Metformin and Proton Pump Inhibitors. INNOVATIONS in pharmacy. 2020 Oct 28;11(4):5.
4. Elaine Parker, MD . Proton Pump Inhibitor Use Contributing to Vitamin B12 Deficiency. Proceedings of UCLA Health . 2022;Volume 26(2022).
5. HIRSCHOWITZ BI, WORTHINGTON J, MOHNEN J. Vitamin B12 deficiency in hypersecretors during long-term acid suppression with proton pump inhibitors. Alimentary Pharmacology & Therapeutics. 2008 Jun;27(11):1110–21.
6. Ito T, Jensen RT: Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010, 12:448-57. 10.1007/s11894-010-0141-0
7. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Internal Medicine Journal. 2015 Apr;45(4):409–16.
8. Marcuard SP. Omeprazole Therapy Causes Malabsorption of Cyanocobalamin (Vitamin B_12). Annals of Internal Medicine. 1994 Feb 1;120 (3):211.
9. Miller JW. Proton Pump Inhibitors, H2-Receptor Antagonists, Metformin, and Vitamin B-12 Deficiency: Clinical Implications. Advances in Nutrition. 2018 Jul 1;9(4):511S518S.
10. Mumtaz H, Ghafoor B, Saghir H, Tariq M, Dahar K, Ali SH, et al. Association of Vitamin B12 deficiency with long-term PPIs use: A cohort study. Annals of Medicine and Surgery. 2022 Oct;82:104762.
11. Pelluri R, Shafiya Begum S, Sowmya N. A Case Report onPantoprazole Induced VIT.B12 Deficiency. Indian Journal of Pharmacy Practice. 2015 Jan 28;Volume 9(1):63–4.
12. Podgajna M, Mielnik M, Szudy-Szczyrek A, Kuśmierczuk K, Hus M. Chronic use of PPIs as a potential cause of anemia: case reports and review of the literature. Acta Haematologica Polonica. 2020 Jun 16;51(2):108–11.
13. Porter KM, Hoey L, Hughes CF, Ward M, Clements M, Strain J, et al. Associations of atrophic gastritis and proton-pump inhibitor drug use with vitamin B-12 status, and the impact of fortified foods, in older adults. The American Journal of Clinical Nutrition. 2021 Jun 16;114(4):1286–94.
14. Qorraj-Bytyqi H, Hoxha R, Sadiku S, Bajraktari IH, Sopjani M, Thaçi K, et al. Proton Pump Inhibitors Intake and Iron and Vitamin B12 Status: A Prospective Comparative Study with a Follow up of 12 Months. Open Access Macedonian Journal of Medical Sciences. 2018 Mar 12;6(3):442–6.
15. Rahamn MR, Uddin Ahmed QM, Rahim MA, Sami CA, Ahmad HI, Hasan MN. Correlation of Long-Term Proton Pump Inhibitors (PPI) Use with Iron and Vitamin B12 Deficiency Anaemia. Bangladesh Med. J., 50(1), 27–32.
16. Ruscin JM, Page RL, Valuck RJ. Vitamin B12 Deficiency Associated with Histamine2-Receptor Antagonists and a Proton-Pump Inhibitor. The Annals of Pharmacotherapy. 2002 May;36:812–6.
17. Schenk BE, Festen HP, Kuipers EJ, Klinkenberg-Knol EC, Meuwissen SG. Effect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin. Aliment Pharmacol Ther 1996;10(4):541–5
18. Stabler SP, Lindenbaum J, Allen RH. Vitamin B-12 deficiency in the elderly: current dilemmas. The American Journal of Clinical Nutrition. 1997 Oct 1;66(4):741–9.
19. Swarnakari KM, Bai M, Manoharan MP, Raja R, Jamil A, Csendes D, et al. The Effects of Proton Pump Inhibitors in Acid Hypersecretion-Induced Vitamin B12 Deficiency: A Systematic Review (2022). Cureus. 2022 Nov 19;
20. Targownik LE, Fisher DA, Saini SD. AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review. Gastroenterology. 2022 Feb;162(4).
21. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. Journal of clinical epidemiology [Internet]. 2004 [cited 2019 Dec 30];57(4):422–8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15135846
22. Van Vlaenderen J, Christiaens J, Van Winckel M, De Bruyne R, Vande Velde S, Van Biervliet S: Vitamine B12 deficiency in children: a diagnostic challenge. Acta Gastroenterol Belg. 2021, 84:121-4. 10.51821/84.1.753
23. Wolffenbuttel BHR, Wouters HJCM, Heiner-Fokkema MR, van der Klauw MM. The Many Faces of Cobalamin (Vitamin B12) Deficiency. Mayo Clinic Proceedings: Innovations, Quality & Outcomes [Internet]. 2019 Jun [cited 2019 Nov 16];3(2):200–14
24. W.P. Den Elzen, Y. Groeneveld, W. de Ruijter, et al., Long-term use of proton pump inhibitors and vitamin B12 status in elderly individuals, Aliment. Pharmacol. Ther. 27 (6) (2008 Mar 15) 491–497

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