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*Original research article*

# Association between long-term proton pump inhibitor use and deficiency of vitamin B12 and magnesium in Gharbia, Egypt: a retrospective study

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## ABSTRACT

Proton pump inhibitors (PPIs) are widely prescribed for acid-related disorders, but prolonged use has been implicated in nutrient malabsorption. Therefore, this study aimed to evaluate the association between long-term PPI use and deficiency of vitamin B12 and magnesium. Medical records for 312 adult patients with documented PPI use between January 2020 and January 2025 were reviewed. These patients were recruited from Tanta University Hospital and its affiliated centers in Gharbia Governorate, Egypt. Participants were stratified by PPI duration: <3 months, 3–6 months, 6–12 months, and >1 year. Serum vitamin B12 and magnesium were compared across groups. Multivariate regression was performed, adjusting for age, gender, comorbidities, and concomitant medications. Statistical significance was set at $p<0.05$. The results demonstrate that mean age was 58.7±12.4 years; 55% were male. Mean vitamin B12 levels significantly declined with longer PPI use (421.3 pg/mL in <3 months vs. 271.9 pg/mL in >1 year, $p<0.001$), as did magnesium levels (2.03 mg/dL vs. 1.69 mg/dL, $p<0.001$). Regression analysis confirmed that age, duration of PPI use, certain concomitant medications, and comorbidities were independent predictors of deficiency. Participants using PPIs for over 1 year had 11.6 times higher odds of B12 deficiency and 12.8 times higher odds of magnesium deficiency, with corresponding 95% CI, after adjustment. Altogether, long-term use of PPIs is significantly associated with deficiencies in both vitamin B12 and magnesium levels among patients in Gharbia Governorate, Egypt. The risk of deficiency increased with age and length of use, regardless of PPI type or sex of user.

**Keywords:** vitamin B12 deficiency, proton pump inhibitors, magnesium, long-term use

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## 1. Introduction

Proton Pump inhibitors (PPIs) are widely used among most of the world's population as acid-suppressing medications, and most patients who receive PPIs do so for the long term without a clear indication.[1] PPIs have also been reported to cause adverse gut microbiota changes affecting several mechanisms, including malabsorption, autoimmune changes, and other microscopic complications.[2]

Vitamin B12 absorption is a complex process that requires gastric acid for the release of cobalamin from dietary proteins and its subsequent binding to intrinsic factor.[3] PPIs, by reducing gastric acid secretion, may impair this process, leading to decreased vitamin B12 absorption.[4] Moreover, PPIs seem to affect the gastrointestinal absorption of magnesium. Hypomagnesemia has recently been recognized as a side effect of PPIs. Low magnesium levels may cause symptoms from several systems, some of which are potentially serious, such as tetany, seizures, and arrhythmias.[5,6]

Several studies have reported that PPIs such as omeprazole, if used for more than 6 months, can cause clinical manifestations of vitamin B12 deficiency, including neurotoxicity and cognitive decline by oxidative stress mechanisms.[7-9]

Patients who take PPI for a long period experience decreased gastric acid secretion and decreased vitamin B12 and magnesium (Mg) levels. This statement is supported by systematic reviews, meta-analyses, and population-based studies in which data account for the increased risk of vitamin B12 and Mg deficiency in patients who take PPIs for more than 1 year, [10-14] in contrast to other studies that denied vitamin B12 defieciency.[15,16] As the exact effect is unclear, this study aimed at observing the effect of long-term PPIs use retrospectively.

## 2. Materials and Methods

### 2.1 Study design

This was a retrospective, cross-sectional, observational multicenter study conducted at multiple healthcare institutions affiliated with Tanta University Hospital, including Bassyoun Hospital, Kafr El-Zayat Hospital, and El Mahalla El-Kobra Hospital in the Gharbia Governorate, Egypt. Detailed medical records of the patients were collected from January 2020 to January 2025.

### 2.2 Study population and inclusion criteria

All adult patients (≥18 years) who had documented use of PPIs during the specified study period, with available medical records with sufficient demographic, clinical, and laboratory data, were eligible for inclusion. The study population was stratified into groups based on the duration of PPI therapy: <3 months, 3–6 months, 6–12 months, and >1 year.

### 2.3 Exclusion criteria

- Patients with known vitamin B12 or magnesium supplementation before or during PPI therapy.
- History of gastrointestinal surgeries (e.g., gastric bypass, bowel resection).
- Known malabsorption syndromes (e.g., celiac disease, Crohn's disease).
- Use of proton pump inhibitors for less than 4 weeks.
- Patients with active malignancy, end-stage liver disease, or terminal illness.
- Incomplete or missing laboratory or demographic records.

### 2.4 Data collection

A structured data extraction sheet was used to collect relevant information from the electronic medical records and patient charts using a purposive sampling method. The following variables were collected:

- Demographics: age, sex, body mass index, and smoking status.
- Clinical history and comorbidities.
- PPI use: type, dose, and duration.
- Medication history.
- Laboratory data: serum levels for vitamin B12 and magnesium.

### 2.5 Outcome measures

The primary outcomes were the association between vitamin B12 deficiency and hypomagnesemia in relation to duration of PPI use. Secondary outcomes included the impact of confounding factors such as age, comorbidities, and concurrent medications.

### 2.6 Statistical analysis

All data were entered into and analyzed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). The following statistical procedures were employed:

- Continuous variables were presented as mean ± standard deviation (SD).
- Categorical variables were expressed as frequency and percentage.

Comparative Analysis:

- One-way ANOVA was used to compare continuous variables across PPI duration groups.
- Chi-square or Fisher's exact test was used for categorical comparisons.
- Multivariable logistic regression was conducted to identify independent predictors of vitamin B12 deficiency and hypomagnesemia. Variables included age >65, sex, PPI duration >1 year, PPI type, comorbidities, and use of interfering drugs.
- Odds ratios (OR) with 95% confidence intervals (CI) and p-values were reported.
- A P-value of $< 0.05$ was considered statistically significant for two-tailed tests.

## 3. Results

### 3.1 Baseline characteristics of the study participants

A total of 312 participants were included in the study. The mean age was 58.7 ± 12.4 years, with a nearly balanced gender distribution: 55.1% were males and 44.9% were females. The average body mass index (BMI) was 27.9 ± 3.6 kg/m². The most prevalent comorbidities were diabetes mellitus (DM) (34.9%), followed by chronic kidney disease (CKD) (13.1%). In terms of PPI use, esomeprazole was the most prescribed agent (34.6%), followed by omeprazole (28.5%), lansoprazole (20.8%), and pantoprazole (16.0%). Among esomeprazole users, the most frequent dosage was 20 mg (15.4%), while omeprazole was most used at 20 mg (17.0%). Lansoprazole was primarily administered at 30 mg (10.3%), and pantoprazole was most often prescribed at 20 mg (9.0%), as shown in Table 1.

### 3.2 Duration of PPI use among participants

Classification of participants according to duration of PPI use revealed that approximately 56% of participants had been on PPIs for more than six months, and nearly 29% had prolonged use beyond one year, as presented in Table 2.

### 3.3 Association between duration of PPI use and deficiency

Table 3 shows a significant association between duration of PPI use and degree of deficiency. Mean vitamin B12 levels significantly declined with longer PPI use (421.3 pg/mL in <3 months vs. 271.9 pg/mL in >1 year, $p<0.001$), as did Mg levels (2.03 mg/dL vs. 1.69 mg/dL, $p<0.001$).

### 3.4 Predictors of vitamin B12 and magnesium deficiency

Table 4 shows that PPI duration, age, comorbidities (DM, CKD), and drug use (metformin, diuretics) all have statistically significant relationships with both vitamin B12 and Mg levels, where these relationships were weak for Mg and strong for vitamin B12. The β coefficients for all these predictors are negative, indicating that these predictors are associated with decreased levels of B12 and Mg. However, male sex does not have a statistically significant relationship with either B12 or Mg levels.

### 3.5 Adjusted odds ratios for deficiency by PPI duration and type

Participants using PPIs for over 1 year had 11.57 times higher odds of B12 deficiency and 12.8 times higher odds of magnesium deficiency, after adjustment. This demonstrates a strong, dose-response-like association.

**Table 1.** Baseline demographic and clinical characteristics of study participants.

| Variable | Value (n = 312) |
|---|---|
| **Age (years), mean ± SD** | 58.7 ± 12.4 |
| **Sex** | Male: 172 (55.1%)<br>Female: 140 (44.9%) |
| **BMI (kg/m²), mean ± SD** | 27.9 ± 3.6 |
| **Comorbidities** | |
| DM | 109 (34.9%) |
| CKD | 41 (13.1%) |
| Mg (mg/dL), mean ± SD | 1.89 ± 0.22 |
| Vitamin B12 (pg/mL), mean ± SD | 347.2 ± 81.3 |
| **PPI Use** | |
| Esomeprazole | 108 (34.6%) |
| 20 mg | 48 (15.4%) |
| 40 mg | 42 (13.5%) |
| 80 mg | 18 (5.8%) |
| Omeprazole | 89 (28.5%) |
| 20 mg | 53 (17.0%) |
| 40 mg | 36 (11.5%) |
| Lansoprazole | 65 (20.8%) |
| 30 mg | 32 (10.3%) |
| 60 mg | 24 (7.7%) |
| 90 mg | 9 (2.9%) |
| Pantoprazole | 50 (16.0%) |
| 20 mg | 28 (9.0%) |
| 40 mg | 22 (7.0%) |

Data are presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. BMI: Body Mass Index; DM: Diabetes Mellitus, HTN: Hypertension, CKD: Chronic Kidney Disease, Mg: Magnesium, PPI: Proton Pump Inhibitor.

**Table 2.** Classification of participants according to duration of PPI use.

| Duration of PPI Use | Mean duration ± SD | Number (n) | Percentage (%) |
|---|---|---|---|
| <3 months | 1.5 ± 0.87 | 62 | 19.9% |
| 3–6 months | 4.5 ± 0.87 | 74 | 23.7% |
| 6–12 months | 9.0 ± 1.73 | 86 | 27.6% |
| >1 year | 18.0 ± 3.46 | 90 | 28.8% |

Data are presented as mean ± SD, absolute frequencies (n) and corresponding percentages (%), PPI: Proton Pump Inhibitor.

**Table 3.** Association between duration of PPI use and deficiency.

| Duration of PPI use | B12 level (pg/mL) | Participants with B12 deficiency | Mg level (mg/dL) | Participants with Mg deficiency |
|---|---|---|---|---|
| <3 months | 421.3 ± 89.6 | 4 (6.5%) | 2.03 ± 0.17 | 3 (4.8%) |
| 3–6 months | 388.1 ± 81.2 | 10 (13.5%) | 1.96 ± 0.19 | 8 (10.8%) |
| 6–12 months | 329.4 ± 77.5 | 23 (26.7%) | 1.83 ± 0.22 | 17 (19.8%) |
| >1 year | **271.9 ± 69.3*** | **39 (43.3%) *** | **1.69 ± 0.20*** | **36 (40.0%) *** |
| p-value | **<0.001** | **<0.001** | **<0.001** | **<0.001** |

Data are presented as mean ± standard deviation (SD) for continuous variables and as number (percentage) for categorical variables. PPI: Proton Pump Inhibitor; Mg: Magnesium. Vitamin B12 deficiency was defined as serum B12 < 200 pg/mL; Magnesium deficiency was defined as serum magnesium < 1.7 mg/dL. Statistical comparisons were performed using one-way ANOVA followed by pairwise post hoc comparisons for continuous variables and the Chi-square test for categorical variables. *: statistically significant (p-value < 0.05) comparing <3 months vs. >1 year in pairwise comparisons.

**Table 4.** Multivariable linear regression models for vitamin B12 and magnesium.

| Predictor | β Coefficient (B12) | p-value | β Coefficient (Mg) | p-value |
|---|---|---|---|---|
| **PPI duration** | –6.42 | **<0.001** | –0.014 | **<0.001** |
| **Age** | –0.91 | **0.038** | –0.005 | **0.041** |
| **Male** | –12.5 | 0.174 | –0.021 | 0.133 |
| **DM** | –31.8 | **0.002** | –0.062 | **0.003** |
| **CKD** | –45.2 | **<0.001** | –0.089 | **<0.001** |
| **Metformin** | –28.6 | **0.004** | –0.031 | **0.029** |
| **Diuretic** | –19.4 | **0.018** | –0.056 | **0.002** |

Data are presented as β coefficients with corresponding p-values from multivariable linear regression models. PPI: Proton Pump Inhibitor; Mg: Magnesium; DM: Diabetes Mellitus; CKD: Chronic Kidney Disease. Statistical significance was defined as $p < 0.05$. Negative β values indicate an inverse association between the predictor and the dependent variable (vitamin B12 or magnesium level).

**Table 5.** Adjusted odds ratios for deficiency by PPI duration and type.

| Duration/ Type | Reference | aOR for B12 deficiency (95% CI) | p-value | aOR for Mg deficiency (95% CI) | p-value |
|---|---|---|---|---|---|
| 3–6 months | < 3 months | 1.94 (0.56–6.74) | 0.295 | 2.38 (0.59–9.51) | 0.221 |
| 6–12 months | < 3 months | 5.29 (1.69–16.55) | **0.004** | 4.89 (1.40–17.09) | **0.013** |
| >1 year | < 3 months | 11.57 (3.84–34.9) | **<0.001** | 12.76 (3.94–41.32) | **<0.001** |
| Esomeprazole/ Omeprazole | Pantoprazole/ Lansoprazole | 1.42 (0.95–2.13) | 0.086 | 1.39 (0.94–2.10) | 0.094 |

Data are presented as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI) and p-values, derived from multivariable logistic regression models. PPI: Proton Pump Inhibitor; Mg: Magnesium. Models were adjusted for age, gender, diabetes mellitus, chronic kidney disease, metformin use, and diuretic use. A p-value < 0.05 was considered statistically significant.

## 4. Discussion

Proton pump inhibitors (PPIs) are one of the preferred treatments for many gastric diseases, especially gastric acid-related diseases.[17] However, emerging evidence suggests that long-term PPI use may be associated with adverse effects, including deficiencies in essential nutrients such as vitamin B12 and magnesium.[3-7] Our retrospective study aimed to evaluate these associations in a cohort of patients from the Gharbia Governorate, Egypt.

Our study indicates that PPI use is associated with reduced vitamin B12 levels, with a more pronounced effect observed in >1-year users. This aligns with previous clinical studies and meta-analyses, which indicate that using PPIs for 12 months reduced vitamin B12 levels.[10-15,18]

This long-term pronounced effect may be explained by the dose-dependent reductive effect. Swarnakari et al. demonstrated a dose-dependent reduction of cyanocobalamin absorption in healthy volunteers on short-term omeprazole therapy for two weeks.[19] Further, Khan et al. reported an increased risk for vitamin B12 deficiency due to long-term PPI use in patients with Zollinger-Ellison syndrome,[20] similar to our results showing a 10.3 times increased risk between long-term PPI usage and vitamin B12 insufficiency. Another study determined a significant decline in serum vitamin B12 levels with increasing duration of PPI use.[21] Furthermore, Buendgens et al. reported that long-term PPI use was linked to an increased incidence of vitamin B12 deficiency (odds ratio: 1.7; 95% CI: 1.6–1.7).[22]

In contrast Den Elzen et al. reported no association between long-term PPI use and vitamin B12 status.[16] Another study that enrolled 250 adults, of which 200 subjects were PPI users, reported that PPI use for 12 months did not result in clinically significant iron and/or vitamin B12 deficiency.[23]

The proposed mechanism for PPI-induced vitamin B12 deficiency is that pepsinogen is converted to pepsin by gastric acid to release vitamin B12 from food proteins. A lack of gastric acid due to PPI use will reduce the digestive capacity to release vitamin B12 from foods and thus reduce the amount of vitamin B12 that is absorbed in the body.[24-26]

Our results showed that old age was more likely to cause vitamin B12 insufficiency among PPI users, suggesting that age-related factors may influence the risk differently across populations. This is matched with previous studies, which reported that vitamin B12 deficiency is frequently reported in elderly patients.[21,27] One of them reported that even vitamin B12 supplementation does not prevent this decline in older persons taking long-term PPI.[21]

Our study identified a significant association between long-term PPI use and hypomagnesemia. Patients on prolonged PPI therapy exhibited lower serum Mg levels. Several systematic reviews and meta-analyses prove the association between PPI use and the development of hypomagnesemia.[10-14,28-30] A previous study reported that hypomagnesemia was encountered with both low and high-dose PPI. However, a more pronounced effect was achieved with high doses.[28]

The mechanisms that explain lower serum Mg levels observed in PPI users are not clear. This effect may be related to variant alleles of transient receptor potential membrane melastatin 6 and 7 (TRPM6/ TRPM7), which are associated with malabsorption of Mg, as the change of intestinal PH could influence active transport channels and TRPM6 channels, where the binding and absorption of magnesium take place, leading to hypomagnesemia in these individuals.[31] Another review showed that Mg absorption in the small intestine depends on passive paracellular diffusion. Consequently, two factors are essential to consider: Mg availability and tight junction permeability. Both factors are potentially compromised by PPI treatment.[32]

On the other hand, a previous study reported that long-term PPI use was not associated with changes in serum Mg levels.[33] Another study retrospectively observed the change in serum Mg levels in 2400 patients treated with different doses of PPIs with or without diuretics, the results revealed that magnesium levels remained unchanged.[34] This discrepancy makes the association between the PPIs and risk of hypomagnesemia unclear, as concluded in a meta-analysis by Liao et al.[35] This raises the need for further research to clarify the relationship between PPI use and Mg levels.

Our study revealed no difference between PPI types in their potential to cause nutrient deficiencies. This result is matched with previous studies that observed a non-significant difference between PPI types in the incidence of hypomagnesemia.[36,37] In contrast to our results, an earlier study indicated that all PPI types were associated with hypomagnesemia, with esomeprazole having the lowest risk, and pantoprazole the highest.[38] Aydın et al. also stated that omeprazole users had significantly lower magnesium levels compared to users of other PPI types.[39]

Sex was not found to be significantly linked to either B12 or Mg deficiencies. The results regarding sex as a contributing factor for deficiency are conflicting. A previous study matched our results, indicating that PPI increases risk for B12 deficiency in both males and females with no significant difference.[40] On the other hand, another study showed that female sex is a risk factor for deficiency,[41] in contrast to others showing that male sex is linked to deficiency.[18,42]

Metformin was found to be an independent predictor for vitamin B12 and Mg deficiencies. The underlying mechanism for these deficiencies is not fully clear. Regarding proposed mechanisms for metformin-induced vitamin B12 deficiency it may involve: (1) interference with binding of the Intrinsic factor (IF)-vitamin B12 complex to the cubilin receptor on enterocytes of the ileum; (2) interaction with the cubilin endocytic receptor; (3) alteration in small intestine motility leading to bacterial overgrowth and subsequent inhibition of IF-vitamin B12 complex absorption; (4) reduced IF secretion by gastric parietal cells.[43] However, long-term metformin use was proposed to

downregulate TRPM6 gene expression in intestine and kidney, which translated into an inverse correlation with Mg levels.[44]

The associations between long-term PPI use and deficiencies in vitamin B12 and Mg have significant clinical implications. Healthcare providers should be vigilant in monitoring these nutrients for all long-term users, with special concern given to the high-risk populations, such as the elderly, individuals with CKD, and those on concomitant medications like diuretics and metformin. Alternative treatment strategies, including the use of less powerful acid-lowering therapy with H2-receptor antagonists or step-down therapy, may be appropriate for some patients to mitigate the risk of nutrient deficiencies.

The limitations of this study are its retrospective design, which means limited control over confounding variables, which may be unrecorded; causality cannot be established, recall bias, incomplete records, in addition to relying solely on serum levels for outcome assessment. However, the strengths lie in having collected data for a relatively large sample size over a long time period, which cannot easily be achieved in prospective studies.

## 5. Conclusion

Long-term use of PPIs is significantly associated with deficiencies in both vitamin B12 and magnesium levels among patients in the Gharbia Governorate, Egypt. The risk of deficiency increased with age and duration of use, regardless of PPI type or sex of user. These findings align with a growing body of international research highlighting the potential adverse effects of prolonged PPI therapy and support the need for biochemical monitoring for high-risk patients and judicious prescription of prolonged PPI therapy in clinical practice.

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## Conflicts of Interest

The authors declare no conflict of interest.

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