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Retrospective Study of Proton Pump Inhibitors Induced Vitamin B12 Deficiency and Their Management.

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Abstract

Aim and Objectives: We undertook this study aiming to investigate the association between PPIs use for 2 years and potential changes in iron and vitamin B12 status and to study the efficiency of treatment. **Methods:** Retrospective case-control study was conducted within a sample of 240 people of the Indian population aged 18 and older from the Tirupur government hospital. **Results:** Statistical analyses revealed a significant change that vitamin B12 deficiency was more likely among users of gastric acid inhibitors in young people and in women on the basis of gender. **Discussion:** A study based on a sample of 240 adult patients about assessing the appropriate use of PPIs among the Indian population indicate significant changes in VitaminB12. **Conclusion:** We conclude that there is a significant association between long-term PPI use and vitamin B12 deficiency, which is stronger among young age groups and among women and can be managed by proper drug treatment.

Keywords

Gastric acid inhibitors, proton pump inhibitors, vitamin B12 deficiency, Treatment.

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INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent suppressors of gastric acid secretions. At normal doses, acid production decreases by 80% to 95 %(1). These drugs are among the most frequently prescribed drugs in the world and are usually used in the long-term treatment of various acid peptic disorders including gastroesophageal reflux disease (GERD), peptic ulcers and hyper secretory states such as Zollinger-Ellison syndrome (1,2). Most Commonly used proton pump inhibitors are Pantoprazole, Omeprazole, Esomeprazole, Lansoprazole and Rabeprazole.

TABLE 1. FDA-Approved Indications for Proton Pump Inhibitor Therapy[3]
Treatment of gastroesophageal reflux disease Healing of erosive esophagitis Maintenance treatment for healed erosive esophagitis.
Treatment of gastric and duodenal ulcers.
Treatment and prophylaxis for NSAID-induced ulcers.
Treatment of Helicobacter pylori infection in combination with antibiotics.
Management of pathologic hyper secretory conditions (including Zollinger-Ellison syndrome).
FDA -Food and Drug Administration; NSAID –non steroidal anti-inflammatory drug.

Vitamin B12 is a crucial B vitamin. It is needed for nerve tissue health, brain function, and the production of red blood cells. Normal vitamin B12 level in blood is 200 – 900 Pg/ml. But 200 – 300Pg/ml is a border line which requires a medical treatment. Vitamin B12 deficiency is common, especially among the older population (4). The clinical manifestations and complications of vitamin B12 deficiency result from the effects of low vitamin B12 levels on the body systems, including: impaired cognition, depression, delusions, sensory loss, autonomic dysfunction, pancytopenia, macrocytosis, and cardiomyopathy (5).

Proton Pump Inhibitors are among the most commonly prescribed medications, and their use has increased in the recent years (6). Medications that reduce gastric acid may decrease vitamin B12 absorption since gastric acid plays a role in dissociation of vitamin B12 from food proteins, and the reduction of the production of intrinsic factor which impairs vitamin B12 absorption (7). Several studies reported an association between long-term PPI use and increased risk of developing vitamin B12 deficiency (8).

The average intake of vitamin B12 in the United States is 3.4 mcg per day, and the recommended dietary allowance is 2.4 mcg per day for adult men and non-pregnant women, and 2.6 mcg per day for pregnant women.30 Patients older than 50 years may not be able to adequately absorb dietary vitamin B12 and should consume food fortified with vitamin B12. 30 Vegans and strict vegetarians should be counselled to consume fortified cereals or supplements to prevent deficiency (9).

Risk factors [10, 11, 12]

Risk Factors for Vitamin B12 Deficiency
Decreased ileal absorption
Crohn disease
Ileal resection
Tapeworm infection
Decreased intrinsic factor
Atrophic gastritis
Pernicious anaemia
Post gastrectomy syndrome (includes Roux-en-Y gastric bypass)
Genetic
Trans cobalamin II deficiency
Inadequate intake
Alcohol abuse
Patients older than 75 years
Vegans or strict vegetarians (including exclusively breastfed infants of vegetarian/vegan mothers)
Prolonged medication use
Histamine H2 blocker use for more than 12 months
Metformin use for more than four months Proton pump inhibitor use for more than 12 months

If left untreated vitamin b12 deficiency leads to impaired cognition, depression, delusions, sensory loss, autonomic dysfunction, pancytopenia, macrocytosis, and cardiomyopathy (2). Therefore, the initial step that should be taken is to reduce the dose of proton pump inhibitors followed by intake of calcium carbonate and vitamin b12 supplements as per the patient's requirement (13).

MATERIALS AND METHODS

Study population

A retrospective case-control study was conducted within a sample of 240 people of the Indian

population aged 18 and older from the Tirupur government hospital.

Data collected include: We excluded from the study, patients taking drugs that lead to vitamin B12 deficiency like Metformin. It is known that long-term use of metformin reduces the absorption of vitamin B12. The name of the drug used, the dose, number of pills per day, duration of intake, continuous intake or not, and the medical conditions for which these drugs are being taken.

Case definition

Case patients were a sample from Tirupur government hospital who were at least 18 years of age and had an initial diagnosis of vitamin B12 deficiency between Jan 2018 and Jan 2019. Vitamin B12 deficiency was defined as an abnormally low value for serum vitamin B12 (less than 191 pg/ml). The index date was the first date of diagnosis for vitamin B12 deficiency.

Control definition

For every case patient, two control patient were randomly selected from the adult population. Controls were chosen from among people who were at least 18 years of age and lacked a diagnosis of vitamin B12 deficiency at the time of the case diagnosis. Controls were matched by sex and age.

Study procedure

Fasting blood samples were collected from the antecubital vein at 8 AM, and were centrifuged within the first hour to separate the serum. The measurements of serum vitamin B12 concentrations were measured by Electrochemiluminescence Immunoassay using Elecsys 2010 system. Hypovitaminosis B12 was defined as serum levels of < 191 pg/ml.

Exposure status

Exposure was arranged by the duration of intake. The duration of intake was defined as the interval between the first and last prescriptions (before the index date). Exposed patients were defined as those who took a 2-year supply of PPIs before the index date, and unexposed group was defined as people who were not given any current or prior supply of PPIs, or those who took a PPIs supply for duration of less than 2 years.

Statistical Analysis

The analysis of the data was done in a simple manner using percentage calculations and graphical representation of data in Ms Excel sheet.

RESULTS

After excluding the cases that have no matched control about 80 cases with 160 controls were selected.

Table 1. The association between case and control based on gender, age and PPI use

Gender	Case	Control
Male	28(34.29%)	55(34.29%)
Female	52(65.71%)	105(65.71%)
Age at index date		
≤ 30	11(14.3%)	20(12.9%)
30-39	25(31.4%)	53(32.9%)
40-49	21 (25.7%)	41 (25.7%)
50-59	16 (20%)	32 (20%)
≥60	7 (8.6%)	14 (8.6%)
PPI use		
≥2y	38 (47.1%)	32 (20%)
<2y	25 (31.43%)	64 (40%)
None	17 (21.4%)	64 (40%)

Table 2. The association between the duration of treatment and the group

	Case	Control
No treatment or duration of treatment < 2 years	52.5	80
Duration of treatment ≥2 years	47.5	20

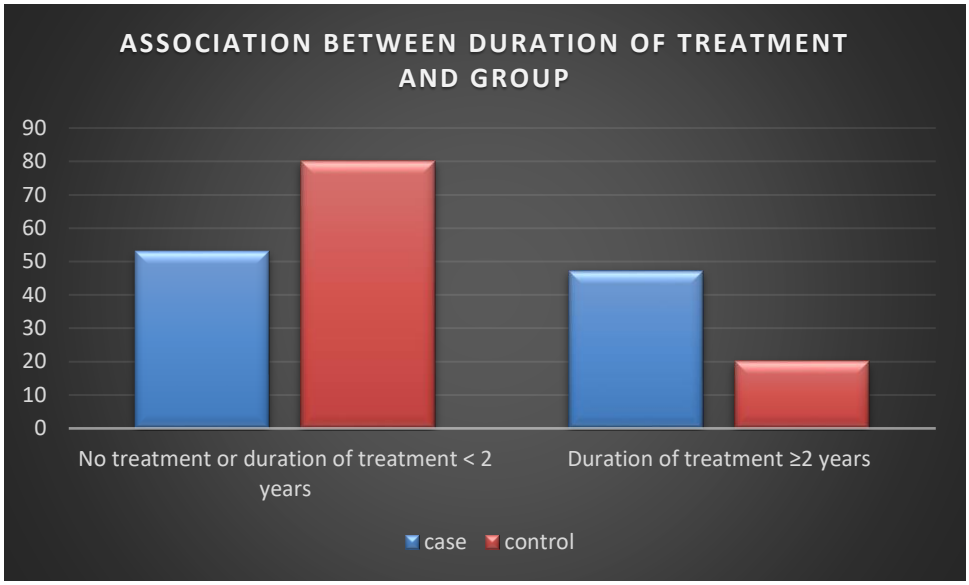

Figure 1: indicates that the number of long-term PPI users (equal or more than 2 years) has a higher proportion among the cases (vitamin B12 deficiency) than among the controls (no vitamin B12 deficiency).

Table 3. Association between duration of treatment less than or equal to 2 years and more than two years with the groups.

	Case	Control
Duration of treatment< 2 years	59.5	50
No treatment	40.5	50

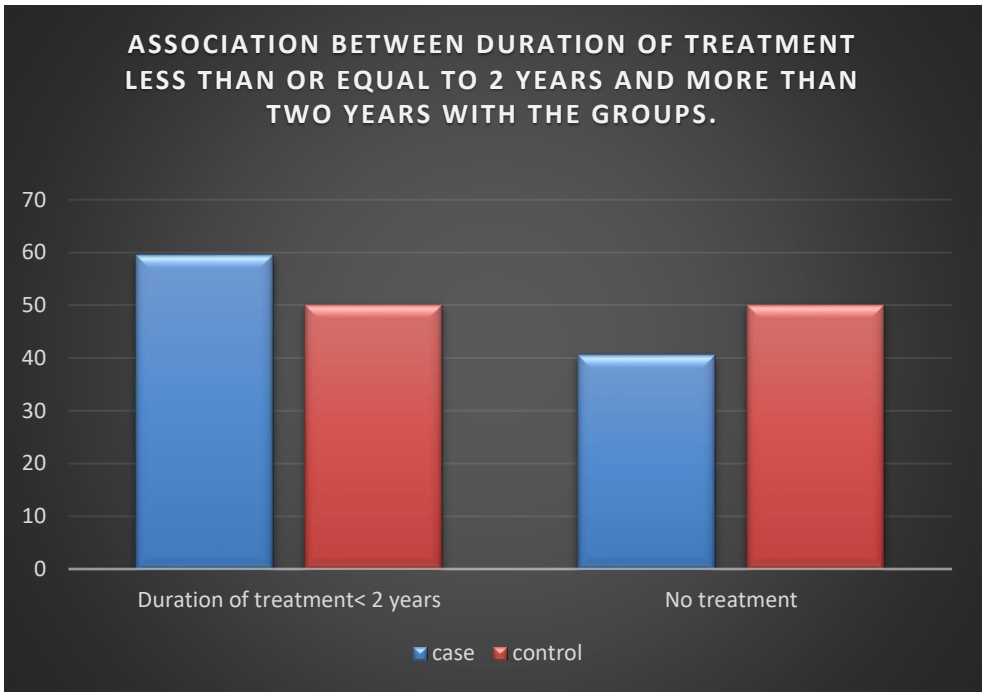

FIGURE 2

Table 4. Association between duration of treatment more than 2 years and no treatment with the group

	Case	Control
Duration of treatment ≥ 2 years	69.1	33.3
No treatment	30.9	66.7

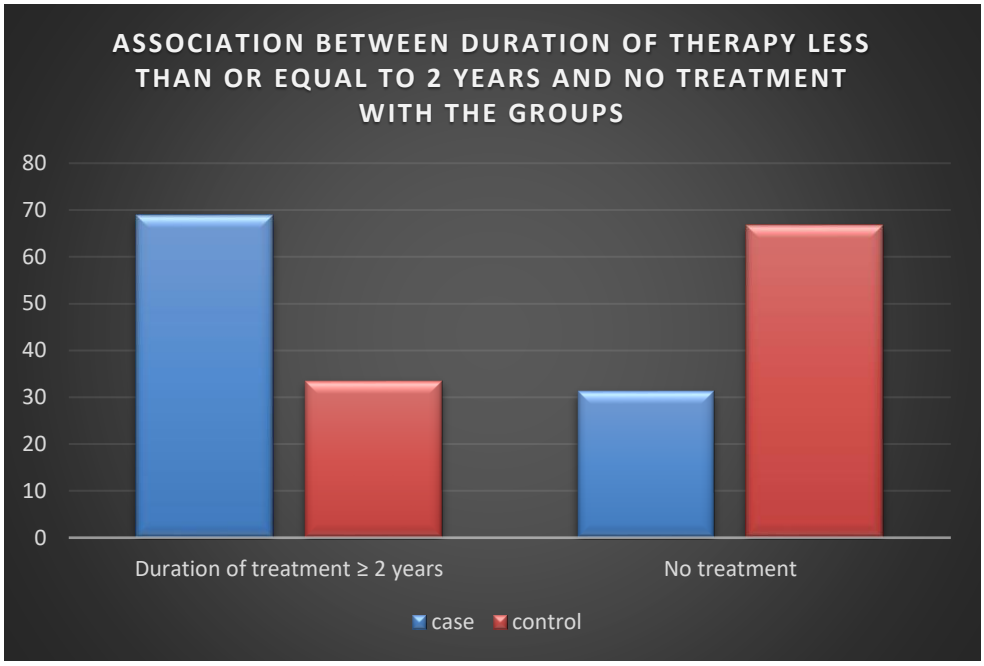

FIGURE 3

Figure 2 and 3 shows that there is no difference between taking the medications for a duration of less than 2 years and not taking any medications, while there is a difference between taking the medications for two or more years and not taking any medications. Thus, we can put the two groups "No treatment" and "duration of treatment < 2 years" in the same category, and that the difference exists only for the long-term treatment (≥ 2 years).

Table 5. The association between the duration of treatment in each age group

Duration of treatment (age group ≤ 30 years)	**Case**	**Control**
< 2 years	76	31.3
≥ 2 years	24	0
No treatment	0	69.7
No treatment or duration <2 years	76	100
Duration ≥ 2 years	24	0

Table 5 shows that the age group of ≤ 30 years has high value, meaning that the association between long-term PPI use and vitamin B12 deficiency is the strongest among this age group, thus among the younger people.

Table 6. The association between the duration of treatment in each gender group

Duration of treatment	**Case (Male only)**	**Control**
< 2 years	18.5	18.5
≥ 2 years	60	21.5
No treatment	21.5	60
No treatment or duration <2 years	40	78.5
Duration ≥ 2 years	60	21.5

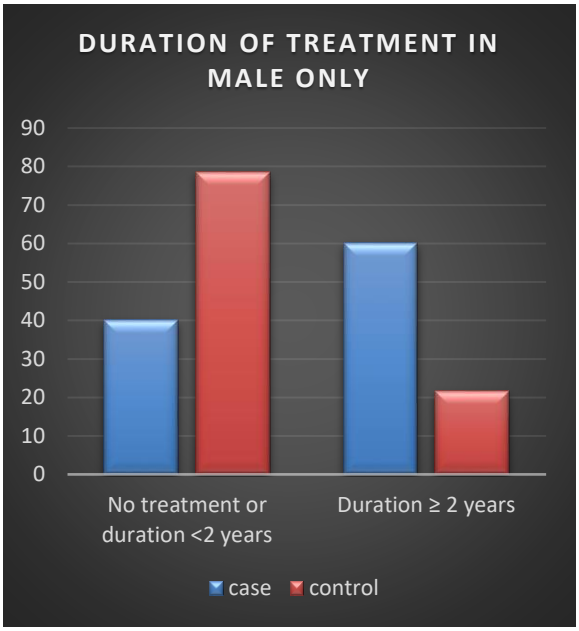

FIGURE 4

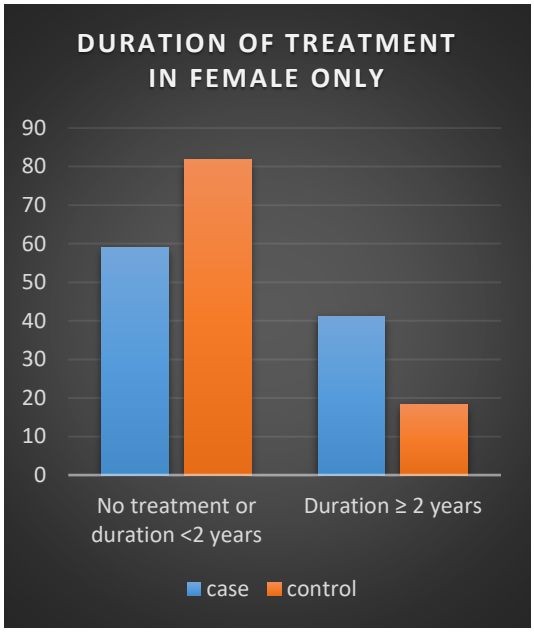

FIGURE 5

From the figure 4 and 5 we found in each gender group, the association between long-term PPI use and vitamin B12 deficiency is significant. We also note that the "only women" group is high in value, thus the association is stronger among women.

Table 7 Duration of treatment in female only

Duration of treatment	Case (Female only)	Control
< 2 years	38.3	50.4
≥ 2 years	41.1	18.2
No treatment	20.6	31.4
No treatment or duration <2 years	58.9	81.8
Duration ≥ 2 years	41.1	18.2

We conclude that there is a significant association between long-term PPI use and vitamin B12 deficiency, which is stronger among young age groups and among women.

DISCUSSION

Several studies reported an association between long-term PPI use and increased risk of developing vitamin B12 deficiency (Freedberg, 2017). A study based on a sample of 323 adult patients about assessing the appropriate use of PPIs among the Indian population found that in the Indian community physicians who are prescribing PPIs are not re-evaluating the symptoms, duration and indication of the treatment during a follow-up; therefore, patients continue to take their medications in an unsuitable way and for a very long period of time. The primary target Proton pump inhibitors are the H-KATPase. These classes of drugs inhibit the gastric H-KATPase which is a major step (final step) of the secretion of acid by the parietal cells. The gastric acid is an important factor that plays a role in the dissociation of vitamin B12 from food protein, the first step in absorption, which takes place in the stomach. Serum B12 levels are in part dependent on the presence of intrinsic factor secreted by parietal cells along with acid and the subsequent binding of intrinsic factor to free cobalamin in the small intestine. PPI use decreases the secretion of acid from parietal cells and of intrinsic factor as well. Thus, medications that suppress gastric acid secretion may lead to vitamin B12 deficiency (Wolfe, 2000; Shin, 2008; and Ahmed, 2016). For that reason, we conducted our study in order to evaluate the correlation between the long-term use of one of the mostly overused medication (PPIs) and a serious medical condition, the vitamin B12 deficiency. In our study, we performed the retrospective case-control method within a sample of 240 people aged 18 and older. We ended up finding that the long-term use of Proton Pump Inhibitors (more than 2 years) is in fact associated

with vitamin B12 deficiency. As we matched our groups by age and gender, we noticed that the significance of the association was stronger in women and young people. This study has several imperfections. First, we cannot fully eliminate the effect of residual confounding on the results we had. Second, "ascertainment bias" could be an issue if patients who are taking PPI therapy are more prone to be tested for vitamin B12 deficiency. The strengths of the study include a large sample size; data collected from adults which approximated the underlying general population, and matched case and controls by age and gender which decrease the risk of bias. Many studies were done to evaluate the association between long- term PPI use and vitamin B12 deficiency. A nested case-control study within the Kaiser Permanente Northern California (KPNC) integrated healthcare system compared 25956 cases with 184199 controls and found that long term use of gastric acid inhibitors was significantly associated with vitamin B12 deficiency (Boussery, 2015 and Lam, 2013). A case report about a 78-year-old woman with symptomatic gastro oesophageal reflux disease (GERD) who took acid suppressing medications for a duration of 4 years and a half, found that the woman had a normal serum vitamin B12 concentration prior to the therapy and that the serum vitamin B12 concentration decreases to be in the low normal range after the long-term therapy. This study suggests that the use of acid suppressing medications may impair the absorption of vitamin B12 and could lead to the development of vitamin B12 deficiency with extended use (Ruscin, 2002). In contrast, a cross-sectional study based on elderly individuals (aged 65 and above) who were proton pump inhibitors users and a reference group of non-users, found that there is no association between long-term proton pump inhibitor use and vitamin B12 deficiency (DEN ELZEN, 2008). Studies have shown that in the developing countries such as the United States, vitamin B12 deficiency is common among the elderly and has a prevalence of approximately 6% among this subgroup (people aged 60 and more), while in the developing countries such as India, vitamin B12 deficiency is even more common and starts in younger ages (2008). Thus, identifying modifiable risk factors for vitamin B12 deficiency in the Indian population is important for public health.

PREVENTION

Because of potential interactions from prolonged medication use, physicians should consider screening patients for vitamin B12 deficiency if they have been taking proton pump inhibitors or H2 blockers for more than 12 months, or metformin for more than four months. The average intake of vitamin B12 in the United States is 3.4 mcg per day, and the recommended dietary allowance is 2.4 mcg per day for adult men and non-pregnant women, and 2.6 mcg per day for pregnant women.30 Patients older than 50 years may not be able to adequately absorb dietary vitamin B12 and should consume food fortified with vitamin B12.30 Vegans and strict vegetarians should be counselled to consume fortified cereals or supplements to prevent deficiency. The American Society for Metabolic and Bariatric Surgery recommends that patients who have had bariatric surgery take 1 mg of oral vitamin B12 per day indefinitely.

CONCLUSION

This study found a correlation between long-term uses of proton pump inhibitors, more than 2 years, and vitamin B12 deficiency in an Indian population. Screening for vitamin B12 deficiency for all acid suppressing medications users and suppression for persons with clear indications for treatment is not recommendable, but clinicians should be careful when prescribing these medications and use the lowest possible effective dose to avoid the overuse, by prescribing PPIs only when there is a valid indication for it, and for the appropriate period of time.

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