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PROTON PUMP INHIBITOR USE AND VITAMIN B12 DEFICIENCY IN A LEBANESE POPULATION

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ABSTRACT

Vitamin B12 is a crucial B vitamin. It is needed for nerve tissue health, brain function, and the production of red blood cells. Vitamin B12 deficiency is common, especially among the older population (1). 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. (2). Proton Pump Inhibitors are among the most commonly prescribed medications, and their use has increased in the recent years (4). 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. (5). Several studies reported an association between long-term PPI use and increased risk of developing vitamin B12 deficiency (6). In our study, we performed the case-control method to evaluate the relationship between the use of PPIs and the risk of vitamin B12 deficiency, based on a sample from the Lebanese population.

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INTRODUCTION

PPIs, which prevent the production of gastric acid, may cause a malabsorption of vitamin B12 and increase the risk of vitamin B12 deficiency. Thus, identifying modifiable predisposing factors for vitamin B12 deficiency in the Lebanese population is crucial for public health. Since, to our knowledge, we lack studies in Lebanon that highlight the link between the use of proton-pump inhibitors and vitamin B12 deficiency, we aim, by this study, based on a sample from the Lebanese populationto evaluate this correspondence.

MATERIALS AND METHODS

Study population

We conducted a retrospective case-control study within a sample of 210 people from a Lebanese population aged 18 and older.

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Data collected include: 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. 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 reduce the absorption of vitamin B12 (14).

Case definition

Case patients were a sample from a Lebanese population who were at least 18 years of age and had an initial diagnosis of vitamin B12 deficiency between May 2016 and May 2017. The index date was the first date of diagnosis for vitamin B12 deficiency. Vitamin B12 deficiency was defined as an abnormally low value for serum vitamin B12 (less than 191 pg/ml).

Control definition

For each case patient, up to 2 matched control patients were randomly selected from the adult Lebanese 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.

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

With a 95% confidence interval and a 5% margin of error, the data was analyzed using SPSS (Statistical Package for Social Science) software version 20. Descriptive statistics were calculated using percentages for qualitative variables and mean ± standard deviation for quantitative variables to analyze baseline characteristics and clinical parameters of study participants. The association between the variables was analyzed using Chi-Square test, Student's test and One Way Anova test for parametric tests as well as non-parametric tests were used when one of the two groups had a number N <30 (Fisher exact test, Mann Whitney test, Kruskall Wallis test).

RESULTS

After excluding case patients who lacked matched controls, probable cases and controls with medical conditions known to directly cause vitamin B12 deficiency, we ended up getting 70 cases and 140 controls in the final study. Among cases patients, 33 (47.1%) were taking PPIs for a duration of 2 or more years, 22 (31.43%) were taking PPIs for a duration of less than 2 years and 15 (21.4%) were not taking PPIs. Among controls patients, 28 (20%) were taking PPIs for a duration of 2 or more years, 56 (40%) were taking PPIs for a duration of less than 2 years and 56 (40%) were not taking PPIs.

Table 1.

Gender	Cases	Controls
Male	24 (34.29%)	48 (34.29%)
Female	46 (65.71%)	92 (65.71%)
Age at index date		
≤30	10 (14.3%)	18 (12.9%)
30-39	22 (31.4%)	46 (32.9%)
40-49	18 (25.7%)	36 (25.7%)
50-59	14 (20%)	28 (20%)
≥60	6 (8.6%)	12 (8.6%)
Ppi use		
≥2y	33 (47.1%)	28 (20%)
<2y	22 (31.43%)	56 (40%)
None	15 (21.4%)	56 (40%)

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

	Cases	Controls	P value
No treatment or duration of treatment < 2 years	52.9	80	0.0001*
Duration of treatment ≥2 years	47.1	20	

- Qualitative variables are expressed as a percentage
- Indicates a significant difference between the two groups with a value of P <0.05.

Table 2 shows a significant P value of 0.0001, indicating 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.

	Cases	Controls	P value
Duration of treatment< 2 years	59.5	50	0.318
No treatment	40.5	50	

Qualitative variables are expressed as a percentage
* Indicates a significant difference between the two groups with a value of P <0.05.

Table 4.

	Cases	Controls	P value
Duration of treatment ≥ 2 years	68.8	33.3	0.0001*
No treatment	31.2	66.7	

Qualitative variables are expressed as a percentage
* Indicates a significant difference between the two groups with a value of P <0.05.

Tables 3 and 4show an insignificant P value (0.318) between the two groups « duration of treatment < 2 years » and « no treatment » and a significant P value (0.0001) between the two groups « duration of treatment ≥ 2 years" and "no treatment", meaning 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)	Cases	Controls	P value
< 2 years	80	33.3	0.001*
≥ 2 years	20	0	
No treatment	0	66.7	
No treatment or duration < 2 years	80	100	0.049*
Duration ≥ 2 years	20	0	

Qualitative variables are expressed as a percentage
* Indicates a significant difference between the two groups with a value of P <0.05.

We found that the P value is the most significant for the age group of ≤ 30 years, 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 (only men)	Cases	Controls	P value
< 2 years	16.7	16.7	0.013*
≥ 2 years	58.3	25	
No treatment	25	58.3	
No treatment or duration < 2 years	41.7	75	0.0098
Duration ≥ 2 years	58.3	25	

Qualitative variables are expressed as a percentage
* Indicates a significant difference between the two groups with a value of P <0.05.

We found that the P value is significant in each gender group, meaning that for each gender group the association between long-term PPI use and vitamin B12 deficiency is significant. We also note that the P value is more significant in the "only women" group, thus the association is stronger among women.

Duration of treatment (only women)	Cases	Controls	P value
< 2 years	39.1	52.2	0.009*
≥ 2 years	41.3	17.4	
No treatment	19.6	30.4	
No treatment or duration < 2 years	58.7	82.6	0.004*
Duration ≥ 2 years	41.3	17.4	

Qualitative variables are expressed as a percentage

* Indicates a significant difference between the two groups with a value of P <0.05.

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). The use of PPIs in the Lebanese population is abused and uncontrolled without clear indications for the treatment and correct duration of therapy. A cross-sectional study based on a sample of 323 Lebanese adult patients about assessing the appropriate use of PPIs among the Lebanese population found that in the Lebanese community physicians who are prescribing PPIs are not reevaluating 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 (George, 2016). The primary target Proton pump inhibitors are the H-K-ATPase. These classes of drugs inhibit the gastric H-K-ATPase 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 in the Lebanese community (PPIs) and a serious medical condition, the vitamin B12 deficiency.

In our study, we performed the retrospective case-control method within a sample of 210 people from the Lebanese population aged 18 and older. We ended up finding that the long-term use of Proton Pump Inhibitors (more than 2 years) in the Lebanese community 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 outpatients Lebanese 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 esophageal 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 developed 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 vitamin B12 deficiency is even more common and starts in younger ages (Shin, 2008). Thus, identifying modifiable risk factors for vitamin B12 deficiency in the Lebanese population is important for public health.

Conclusion

This study found a correlation between long-termuses of proton pump inhibitors, more than 2 years, and vitamin B12 deficiency in a Lebanese 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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