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RESEARCH ARTICLE

PREVALENCE OF SERUM VITAMIN B12 DEFICIENCY AND CORRELATION BETWEEN SERUM VITAMIN B12 DEFICIENCY WITH DOSAGE POTENCY AND DURATION OF PPI USE AMONG ELDERLY USING LONG TERM PPI

Dr. Mudasir Ahmad Sofi MD^{1,*}, Dr. Masood Tanvir², Dr. Rakib Ahmad Wani³ and Dr. Sobia Nisar⁴

¹MD General Medicine GMC Srinagar

²Prof General Medicine GMC Srinag

³MD, Radio diagnosis & Imaging, GMC Srinagar

⁴Assistant professor GMC Srinagar

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*Corresponding author:

Dr. Yael D. Arnon

ABSTRACT

Introduction: Vitamin B-12, also called Cobalamin Water soluble vitamin. It is the largest and structurally complex vitamin. Sources of Vitamin B12 are Produced by microorganisms (bacteria/fungi) inhabit in gut, Plants do not produce or contain VitaminB12. Liver, Kidney, Muscle, Egg, Milk, Cheese and other dairy products, Seafood and Foods fortified with B12 are also sources of the vitamin B12. Individuals who lack intrinsic factor have a decreased ability to absorb B12. Gastric acid releases the vitamin from food particles. Therefore antacid and acid-blocking medications may inhibit absorption of B12. In addition some elderly people produce less stomach acid thereby increasing their probability of B12 deficiencies. **Methodology:** In this observational study, 102 study patients were included on the basis of inclusion and exclusion criteria. The data was collected by administering a clinical questionnaire, relevant medical, drug history and dietary history. All baseline investigations, serum vitamin B12 level was investigated to document the deficiency. Data was analyzed through Epiinfo using student's t-test, Chi square test. $p < 0.05$ was considered statistically significant. **Result:** It was observed that only (6.9%) of patients are deficient and (11.8%) are on borderline while as (81.4%) of study patients are not having any abnormality with regard to vitamin B12 deficiency. Among 102 patients ; 80 patients were prescribed PPI for peptic ulcer disease and rest 22 patients were having co morbid disease where PPIs were prescribed prophylactically. Around (6%) of patients are having deficiency in vitamin B12 who receive 40 mg dosage of PPI while as around (94%) of patients are not having any deficiency. However, around 12 percent of patients are having vitamin B12 deficiency who received 80 mg dosage of PPI and (88.2%) does not report any deficiency on this dosage. **Discussion:** The present study deficiency in Vitamin B12 alternatively named as cobalamin is a disorder that is most commonly seen in individuals who are beyond 59 years of age with a supporting prevalence of (10-40%). Vitamin B12 deficiency is generally thought to be synonymous with pernicious anemia (intrinsic factor deficiency); however, studies suggest that pernicious anemia is rare among types of vitamin B12 deficiency in the older population. Research conducted by Scarlet, suggested that most older adults with vitamin B12 deficiency have a normal Schilling test, but do not adequately absorb food-bound cobalamin.

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INTRODUCTION

Vitamin B-12, also called Cobalamin Water soluble vitamin. It is the largest and structurally complex vitamin. It exists in four chemical forms 1. Cyanocobalamin (digested form),

2. Hydroxycobalamin, 3. Methylcobalamin and 4. Adenosylcobalamin. Cynocobalamin and hydroxycobalamin are used to prevent or treat vitamin deficiency. Once absorbed they are converted into Methylcobalamin and Adenosylcobalamin which are the forms having physiological activities.

Cobalamins are characterized by a porphyrin-like corrin nucleus that contains a single cobalt atom bound to a benzimidazolyl nucleotide and a variable residue R group. It plays a key role in the normal functioning of the brain and nervous system and for the hematopoiesis. It is a coenzyme for enzymes that transfer methyl groups and produce red blood cells. Vitamin B-12 is composed of a complex tetrapyrrole ring structure (corrin ring) with a cobalt ion in the center. Sources of Vitamin B12 are produced by microorganisms (bacteria/fungi) that inhabit the gut. Plants do not produce or contain Vitamin B12. Liver, Kidney, Muscle, Egg, Milk, Cheese and other dairy products, Seafood and Foods fortified with B12 are also sources of the vitamin B12. Normal body stores of vitamin B12 are about 3-4 mg, primarily in the liver. This would be sufficient for 3 years if dietary intake ceased or if the ability to absorb the vitamin was lost. Plants are not sources of Vitamin B12. Recommended intake (RDA) is 3 µg/day and 6 µg/day in pregnancy & Lactation. Vitamin B12 normally plays a significant role in the one-carbon transfer reactions which in turn are required for DNA synthesis, fatty acid synthesis, energy production and one-carbon transfer reactions are required in the biosynthesis of amino acids, serine, methionine and glycine.

Vitamin B12 Absorption Requires Two Binding Proteins: Gastric acid and pepsin release the vitamin from protein binding in food and make it available to bind to cobalophilin, a binding protein secreted in the saliva. Vitamin B12 is absorbed bound to intrinsic factor, a small glycoprotein secreted by the parietal cells of the gastric mucosa. In the duodenum, cobalophilin is hydrolyzed, releasing the vitamin for binding to intrinsic factor. In the duodenum, proteases digest B12 binding proteins and release B12, which then binds to IF, to form a complex (IF/B12). B12 must be attached to IF for it to be absorbed, as receptors in the terminal ileum of the small bowel only recognize the B12-IF complex; in addition, intrinsic factor protects the vitamin from catabolism by intestinal bacteria. Once the IF/B12 complex is recognized by specialized ileal receptors, it is transported into the portal circulation. Following absorption, the vitamin is transported to the liver in the blood bound to transcobalamin-II (TC-II/B12). The transcobalamin-II is degraded and free B12 is finally released into the cytoplasm, where it may be transformed into the proper coenzyme. Absorption of food Vitamin B12 thus requires an intact and functioning Stomach, Exocrine Pancreas, Intrinsic Factor and Small Bowel. Problems with any one of these organs makes a vitamin B12 deficiency possible. Individuals who lack intrinsic factor have a decreased ability to absorb B12. Gastric acid releases the vitamin from food particles. Therefore, antacid and acid-blocking medications may inhibit absorption of B12. In addition, some elderly people produce less stomach acid, thereby increasing their probability of B12 deficiencies.

MATERIALS AND METHODS

This was an observational study. Aim of the study was to study the prevalence of serum vitamin B12 deficiency in elderly using long-term PPI and to study correlation between serum Vitamin B12 deficiency with dosage potency and duration of PPI use. Long-term PPI users (more than one year), elderly >60 years were included in the study and patients on multivitamins, patients with post-gastrectomy status and patient known case of megaloblastic anemia, Renal failure patients, patients on metformin (diabetes mellitus),

hypothyroidism and strict vegetarian were excluded from the study. Total 102 subjects were included in the study on the basis of inclusion and exclusion criteria. All study subjects were investigated by administering a clinical questionnaire, relevant medical, drug history and dietary history. All baseline investigations, serum vitamin B12 level was investigated to document the deficiency. Data was analyzed through Epi-Info using student's t-test, Chi-square test. $p < 0.05$ was considered statistically significant.

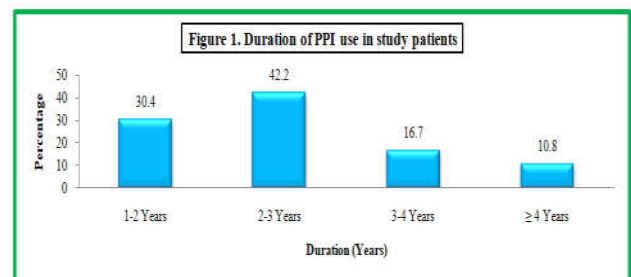
RESULTS

It was observed that a mean age of patients was (73.4 ± 12.53) years. Around 29% of patients were falling in the age group of (60-69) years followed by 52.9% in the age interval of (70-79) years. The least number of patients constituting about 17.6% were either 80 years of age or more. Total of 65 females constituting (63.7%) of patients took part in the given study while as there were only 37 males comprising (36.3%) of all the patients. Hence the ratio of females to males was 1.8:1.

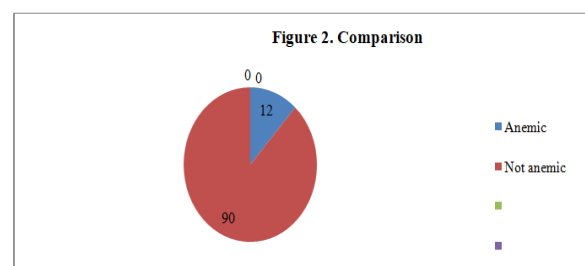
Table 1. Distribution of study patients as per dosage of PPI

Dosage of PPI	Number	Percentage
40 mg	85	83.3
80 mg	17	16.7

Table 1, displays the number and percentage corresponding to different dosage of PPI, we observe that most of the patients, i.e., 85 (83.3%) patients take 40mg while as 16.7% of patients receive 80 mg drug dosage of PPI. It was observed that mean duration of PPI use by patients is (2.6 ± 1.78) in which most of the patients (42.2%) are on (2-3) years of duration followed by (30.4%) of patients on (1-2) years of duration and (16.7%) of patients on (3-4) years of duration of PPI use. Only around (11%) of patients are either on 4 years of duration of PPI use or more as depicted in Figure 1.



In study WHO criteria was used to label the patients as anemic or otherwise which defines hemoglobin of $< 13 \text{ g/dl}$ and $< 12 \text{ g/dl}$ as anemia for males and females respectively, the findings are depicted in figure 2. Total 12 patients had anemia among them 7 patients had macrocytic hypochromic anemia, 3 patients had microcytic hypochromic anemia and 2 patients had normocytic normochromic anemia.



Among 102 patients; 80 patients were prescribed PPI for peptic ulcer disease and rest 22 patients were having co morbid disease where PPIs were prescribed prophylactically. Figure 3 showing underlying diseases of patients who were put on PPIs.

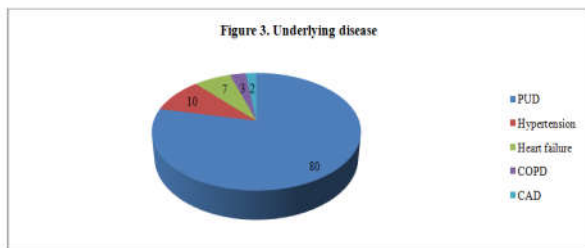


Table 3 presents the percentage of patients having vitamin B12 deficiency among study patients. It was observed that only (6.9%) of patients are deficient and (11.8%) are on borderline while as (81.4%) of study patients are not having any abnormality with regard to vitamin B12 deficiency. Table 4 presents the prevalence of serum B12 deficiency in study patients whereby we observe that the prevalence of vitamin B12 deficiency is only (6.9%). Table 5 analyzes the correlation of vitamin B12 deficiency with duration of PPI use in study patients, we observe that around (4%) of patients are having vitamin B12 deficiency who are on less than 3 years use of PPI while as almost (96%) are not having any abnormality in vitamin B12 levels. It was observed that around (14%) of patients are having vitamin B12 deficiency who are on three years duration of PPI use or more however, (86%) of patients are having unaltered vitamin B12 deficiency. It was observed that only around (6%) of patients are having deficiency in vitamin B12 who receive 40 mg dosage of PPI while as around (94%) of patients are not having any deficiency. However, around 12 percent of patients are having vitamin B12 deficiency who received 80 mg dosage of PPI and (88.2%) does not report any deficiency on this dosage as depicted in figure 4.

Table 2. Number and percentage of Anemia in study patients with underline diseases

Disease	No of anemic patients	Percentage
PUD	7	58.3%
Hypertension	2	16.7%
Heart failure	2	16.7%
CAD	1	8.3%

Table 3. Vitamin B12 levels in study patients

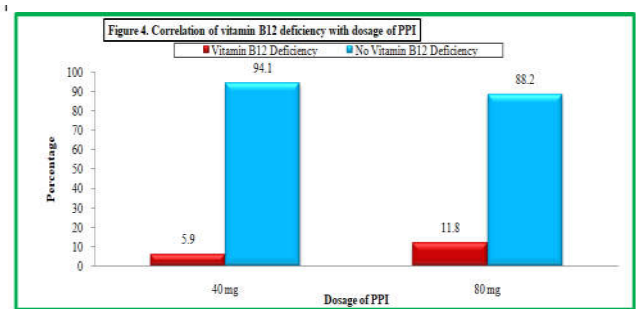
Vitamin B12 levels	Number	Percentage
Deficient (< 200)	7	6.9
Borderline (200-300)	12	11.8
Normal (> 300)	83	81.4

Table 4. Prevalence of serum vitamin B12 deficiency in study patients

Vitamin B12 Deficiency	Number	Percentage
Present	7	6.9
Absent	95	93.1

Table 5. Correlation of vitamin B12 deficiency with duration of PPI use in study patients

Duration (Years)	Vitamin B12 Deficiency				P-value
	Present		Absent		
	No.	%age	No.	%age	
< 3 Years	3	4.1	71	95.9	0.167
≥ 3 Years	4	14.3	24	85.7	
Total	7	6.9	95	93.1	



DISCUSSION

The present study deficiency in Vitamin B12 alternatively named as cobalamin is a disorder that is most commonly seen in individuals who are beyond 59 years of age with a supporting prevalence of (10-40%). There is no doubt that animal foods are primarily the main source of vitamin B12 for humans in the diet, where B12 is bound to protein. During digestion process, vitamin B12 must be released from a protein bound state, a process requiring the presence of gastric acid and gastric peptic activity. Vitamin B12 deficiency is generally thought to be synonymous with pernicious anemia (intrinsic factor deficiency); however, studies suggest that pernicious anemia is rare among types of vitamin B12 deficiency in the older population. Research conducted by Scarlet, suggested that most older adults with vitamin B12 deficiency have a normal Schillings test, but do not adequately absorb food-bound cobalamin. In the recent years health care providers attention has been on possible relationship of PPIs prolonged use and vitamin B12 deficiency; however there is still significant amount of uncertainty about providing monitoring recommendations. The present study aimed to study the prevalence of serum vitamin B12 deficiency in elderly people using long term PPI and to discover any possible correlation between serum Vitamin B12 deficiency with dosage potency and duration of PPI use. A total of 102 patients were included in the study that meets the inclusion criteria. It was observed that the mean age of study patients were (73.4±12.53) years, however, the mean age of such patients reported by Valuck et.al is (82.19±6.82) years. Around (29%) of patients were falling in the age group of (60-69) years followed by (52.9%) in the age interval of (70-79) years. The least number of patients constituting about (17.6%) were either 80 years of age or more. It was observed that a total of 65 females constituting (63.7%) of patients took part in the given study while as there were only 37 males comprising (36.3%) of all the patients. Hence the ratio of females to males was 1.8:1. Similar gender distribution was also reported by Valuck *et al*, Dharamrajan et.al and Hasime *et al*. In the present study we analyzed the percentage of patients taking different dosage of PPI use, we observed that most of the patients, i.e 85 (83.3%) patients are taking 40mg while as (16.7%) of patients receive 80 mg dosage. We analyzed the possible dose dependency of PPI on vitamin B12 deficiency whereby we observed an insignificant difference between different dosages of 40 mg and 80 mg on vitamin B12 deficiency, similar findings were observed by Hasimeet *al*. However, Marcuard *et al*. studied 10 healthy middle aged men and found a dosage dependent decrease in protein-bound vitamin B12 absorption with omeprazole 20 or 40 mg daily for two weeks. Saltzman *et al*. reported that patients with hypochlorhydria due to omeprazole 40 mg daily demonstrated reduction in protein-bound B12 as compared to normal elderly patients.

In the present study we found that only around (6%) of patients are having deficiency in vitamin B12 who receive 40 mg dosage of PPI while as around (94%) of patients are not having any deficiency. However, around 12 percent of patients are having vitamin B12 deficiency who received 80 mg dosage of PPI and (88.2%) does not report any deficiency on this dosage. Valucke *et al.* reported normal non protein-bound vitamin B12 absorption among patients who are treated with omeprazole. In the present study we observed that out of 100 patients only (6.9%) of patients were having deficiency in vitamin B12 levels and (93.1%) were having normal vitamin B12 levels. We found that there is no statistical significant difference in vitamin B12 levels in patients who take PPIs for less than 3 years and for patients who take PPIs for three or more years.

Although vitamin B12 malabsorption with H2-antagonists and PPIs has been considered a potential problem for several years, there is limited evidence to suggest that extended use of these agents can lead to vitamin B12 deficiency. In the studies conducted by Walanet *et al.* and Shenk, they found no significant differences on mean serum vitamin B12 concentrations on prolonged use of PPI. However, in a study by Termanini *et al.* involving Zollinger-Ellison syndrome, serum vitamin B12 levels were drastically reduced by (30%) of patients over 5 years in patients taking long term omeprazole therapy. Valucke *et al.* in their study revealed that on assuming the baseline risk of vitamin B12 deficiency in elderly people of (5%), the minimum no. of patients required to harm is approximately 7 i.e for every seven patients taking PPI for at least one year, one patient would be expected to develop vitamin B12 deficiency due to the presence of this additional risk factor.

CONCLUSION

The following conclusions were drawn from the study i.e., statistical significant difference on deficiency of vitamin B12 due to prolonged use of PPIs. We also found that deficiency of vitamin B12 is independent of dosage of PPIs. These findings are very supportive to some earlier studies; however there are some limited studies that have shown a fall on vitamin B12 levels due to long therapy of PPIs. For optimal patient benefits we recommend a periodical evaluation of vitamin B12 status.

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