Original Article

Hypovitaminosis B_{12} is Associated with Long Term Consumption of Proton Pump Inhibitors

Vit. B_{12} after use of Proton Pump Inhibitors

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ABSTRACT

Objective: Determining vitamin B_{12} levels in subjects using Proton pump inhibitors (PPIs) for more than 3 years reporting at a tertiary care hospital of Sindh

Study Design: Case control study

Place and Duration: This study was conducted at the Department of Pathology and Biochemistry, Bilawal Medical College from January – December 2017.

Materials and Methods: A sample of 100 subjects was selected; 50 cases using PPIs > 3 years duration and 50 controls (no PPIs) by convenient sampling through inclusion and exclusion criteria. 5 ml blood was collected; 3 ml put into EDTA tubes for complete blood counts and 2 ml for sera. Vitamin B_{12} was measured by ELISA assay. Results were analyzed on SPSS (ver 21.0) by Student t-test and Chi-square test at 95% CI ($P \leq 0.05$).

Results: Vitamin B_{12} in control and cases was found as 315.15±41.33 vs. 276.91±90.1 pg/dl (P=0.0001). Frequency and % of normal, borderline deficiency, deficiency and severe deficiency of vitamin B_{12} were noted as 31 (62%) vs. 11 (22%), 9(18%) vs. 21 (42%), 7 (14%) vs. 11 (22%), and 3 (6%) vs. 7 (14%) (P=0.0001). Cumulative vitamin B_{12} deficiency in 38% of control and 78% of cases (P=0.0001).

Conclusion: In conclusion, the long term use of Proton pump inhibitor is associated with hypovitaminosis B_{12}.

Key Words: Proton pump inhibitors, Hypovitaminosis B_{12}, MCV, Sindh

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INTRODUCTION

Proton pump inhibitors (PPIs) are widely used for acidity problem. PPIs are used as first line therapy for acid peptic disease and are potent for day time dyspepsia.[1] It is claimed the PPIs inhibit approximately 80% to 95% acid production at optimal dose. PPIs are now the most frequently prescribed drugs the World over. Its major indications are in acid-peptic disorders, peptic ulcers, gastro-esophageal reflux disease (GERD) and Zollinger-Ellison syndrome (ZES).[1,2] One major drawback of acid suppression is inhibition of intrinsic factor secretion that is essential for the vitamin B_{12}. Vitamin B_{12} (cobalamin) is involved as co-enzyme in biochemical reactions catalyzed by methionine synthetase and methylmalonyl- CoA mutase.[3,4]

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Body produces 2 active co-enzymes; the "methyl-cobalamin" and "S- adenosyl cobalamin" from the vitamin B_{12} and function as 1-carbon donor for the nucleotide synthesis. Methionine synthetase and methylmalonyl- CoA mutase need methyl- cobalamin and S- adenosyl cobalamin respectively.[3,4] Vitamin B_{12} is necessary for the myelin sheath and nuclear maturation of rapidly proliferating cells such as those of bone marrow along with folic acid. Vitamin B_{12} deficiency leads to a number of disorders such as megaloblastic anemia, hemolysis, pancytopenia, myelopathy, neuropathy, and malabsorption syndrome.[5,6] Thus vitamin B_{12} deficiency has been thought resulting from long-term use of PPIs. Previous studies[5-8] suggest long term consumption of PPIs lead to vitamin B_{12} deficiency. Gastric acid suppression by PPIs inhibits vitamin B_{12} gut absorption through several mechanisms. One is the altered extraction of vitamin B_{12} bound to dietary proteins by changed intra gastric pH. Second is the gastric intrinsic factor deficiency through suppression of parietal cell and third is the intestinal bacterial growth which increases bacterial consumption of vitamin B_{12}.[5,6] Currently, the PPIs are widely used drugs in Pakistan[9] this needs evaluation of vitamin B_{12} in the long term consumers of proton pump inhibitors. As the vitamin B_{12} is essential for biochemical reactions, it is worth to analyze the blood levels of this vitamin among chronic long term users of PPIs in the society. The present study will provide

information on vitamin B_{12} deficiency (hypovitaminosis B_{12}) in the setting of long term PPIs consumption. The present study may help to make awareness on the use of PPIs in relation to vitamin B_{12} deficiency and associated deficiency disorders.

MATERIALS AND METHODS

The present case control study was planned and conducted at the Department of Pathology and Biochemistry, Bilawal Medical College from January–December 2017. Sample size was calculated by 'sampling for proportions'. A sample of 50 PPIs users were labeled as cases (n=50). Age and gender matched control (n=50) were also studied. A case was defined as using PPIs for >3 years duration and a control as never used PPIs. Cases were selected by convenient sampling by inclusion and exclusion criteria. Inclusion criteria were; age 25- 50 years, both gender, PPIs of >3 years duration, PPIs dose of ≤ 40 mg daily. Strict vegetarians, chronic diarrhea, malabsorption syndrome, pancreatic disease, autoimmune disease process, history of abdominal tuberculosis, thyroid disorders, diabetic patients and chronic liver disease, were excluded. Subjects taking calcium supplements, vitamin pills and meat and liver during last 3 months were excluded. Subjects attending the outpatient department of the hospital, using the PPIs for long durations were communicated. Drug history was inquired. Volunteers were fully intimated the purpose of study. And willing participants were asked to sign consent form. Benefits and harms of study protocol were explained by researcher. Volunteers were informed that the study will cause no harm and no expense of laboratory investigations. A proforma of study protocol was used for proper history, physical findings, clinical problem, and blood findings. Confidentiality of data was ensured. Volunteers were informed that the data will never be publicized. Medical officers were asked to help selecting the cases to fulfill the inclusion and exclusion criteria. Volunteers equaling the selection criteria were asked for blood sampling. Volunteers were taken to examination couch; a tourniquet was put above the cubital fossa. Body part was sterilized with alcohol swab. A sterilized Disposable syringe (BD, USA) was used for venesection. 5 ml blood was collected in Disposable syringe (BD, USA). 3 ml of blood sample was put into EDTA tubes, and processed for complete blood counts in a hematology analyzer. 2 ml blood was used to extract sera by centrifugation for measuring vitamin B_{12} by ELISA assay. Vitamin B_{12} levels were defined as; >240pg/ml as normal, 170-240 pg/ml as borderline deficiency, <170 pg/ml as deficiency and <100 pg/ml as severe vitamin B_{12} deficiency.[4] Data was typed on excel sheet and copied to SPSS (version 21.0) for statistical analysis. Student t-test analyzed the numerical variables and output presented as mean and standard deviation (SD). Chi-square test analyzed the categorical data and output tabulated as frequency and %. Data was analyzed at 95% CI ($P \leq 0.05$).

RESULTS

Age (mean± SD) of control and cases was 47.5±11.9 and 48.3±9.57 years respectively (P=0.81). Male and female in control and cases were noted as 27 (54%) vs. 26 (52%) and 23 (46%) vs. 24 (48%) respectively (P=0.076). Hematocrit, hemoglobin, RBC counts and Platelets shows statistical difference between control and cases (P>0.05) (Table-1).

Table No. 1: Demography, Vitamin B_{12} and Hematological findings of study subjects (n=100)

	Control	Cases (PPI)	P-value
Age (years)	47.5±11.9	48.3±9.57	0.81
Male	27 (54%)	26 (52%)	0.076
Female	23 (46%)	24 (48%)	
Hematocrit (Hct.) (%)	43.5±1.29	37.4±5.07	0.014
Hemoglobin (g/dl)	12.3 ±2.01	11.6±2.5	0.001
White Blood cells (/µL)	9870.6±13.5	9671.6 ±12.1	0.91
RBC counts ($x10^9$/µL)	4.15±0.91	3.91±1.35	0.071
MCV (fl)	76.5±3.31	91.4±9.35	0.0001
Platelet ($x10^6$/ µL)	365±1.31	423.4±0.95	0.054
Vitamin B_{12} (pg/dl)	315.15±41.33	276.91±90.1	0.0001

Table No.2: Vitamin B_{12} levels in different categories (n=100)

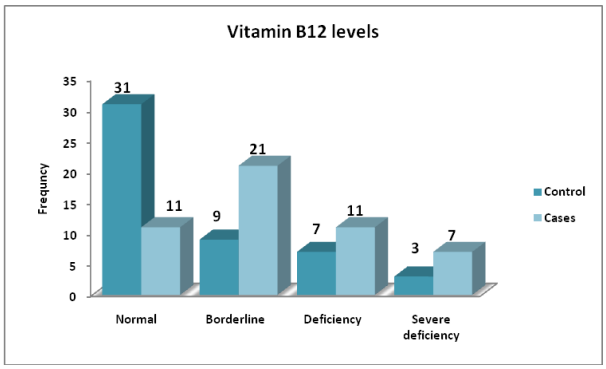
Vitamin B_{12} categories	Control	Cases	P-value
Normal (>240 pg/ml)	425.1±35.1	323.5±27.3	0.0001
Borderline deficiency (170-240 pg/dl)	193.8±15.6	189.6±10.4	
Deficiency (<170 pg/dl)	160.9±5.2	131.9±35.2	
Severe deficiency (<100 pg/dl)	91.8±5.7	51.7±13.5	

Mean corpuscular volume (MCV) and vitamin B12 in control and cases shows statistical significant difference. MCV (mean± SD) in control and cases was noted as 76.5±3.31 vs. 91.4±9.35 fl (P=0.0001).

Vitamin B_{12} (mean± SD) in control and cases were noted as 315.15±41.33 vs. 276.91±90.1 pg/dl (P=0.0001). Vitamin B_{12} (mean± SD) as normal, borderline deficiency, deficiency and severe deficiency shows statistical difference between control and cases (Table- 2).Frequency and % of normal, borderline deficiency, deficiency and severe deficiency of vitamin B_{12} were noted as 31 (62%) vs. 11 (22%), 9(18%) vs. 21 (42%), 7 (14%) vs. 11 (22%), and 3 (6%) vs. 7 (14%) (P=0.0001). Cumulative vitamin B_{12} deficiency was noted in 38% of control and 78% of cases (P=0.0001).

Table No.3: Frequency of Vitamin B_{12} in study subjects (n=100)

Vitamin B_{12}	Control	Cases	P-value
Normal levels (>240 pg/ml)	31 (62%)	11 (22%)	0.0001
Borderline deficiency (170-240 pg/dl)	9 (18%)	21 (42%)	
Deficiency (<170 pg/dl)	7 (14%)	11 (22%)	
Severe deficiency (<100 pg/dl)	3 (6%)	7 (14%)	
Total	50	50	



Graph No.1: Bar graph showing vitamin B_{12} in control and cases

DISCUSSION

A search of literature review, this is the first study reporting hypovitaminosis B_{12} in PPIs users of long (> 3 years) duration. We found cumulative vitamin B_{12} deficiency was noted in 38% of control and 78% of cases (P=0.0001). The hypovitaminosis B_{12} of present study is in agreement with previous studies.[5-8] Qorraj-Bytyqi et al[10] reported a study from Kosovo including 200 cases (PPIs) and 50 controls. Serum Fe++, ferritin, homocysteine and vitamin B_{12} were measured at baseline and after 1 year. They[10] reported hypovitaminosis B_{12} in 2.9% and hypoferrimeia in 3.8% of cases at 1 year of PPIs use. They[10] reported hypovitaminosis B_{12} in 2.9% and hypoferrimeia in 3.8% of cases at 1 year of PPIs use. The frequency of deficiency of vitamin B_{12} and serum Fe++ is very low but supports our present study`s findings. However, the reason of low frequency of vitamin B_{12} and serum Fe++ is clear that above study evaluated the parameters for12 month's duration while the present study determined the effects of PPIs use in chronic users of >3 years duration. Most probably this difference is because of short duration of above study. Mindiola et al[2] conducted study of vitamin B12 levels in chronic users of PPIs of long duration and found statistically significant differences. They found low vitamin B_{12} levels in those who consumed PPIs for more than 3 years. Our findings are supported by the above study. Another previous study[11] reported low vitamin B_{12} levels in those using PPIs for longer durations. In present study, the frequency and % of normal, borderline deficiency, deficiency and severe deficiency of vitamin B_{12} in control and cases were noted as 31 (62%) vs. 11 (22%), 9(18%) vs. 21 (42%), 7 (14%) vs. 11 (22%), and 3 (6%) vs. 7 (14%) (P=0.00016). These findings are supported by previous studies.[2,10-12] A Latin American study[12] reported 40% deficit of vitamin B_{12} in general population and 20% showed borderline deficit. Heidelbaugh et al[13] in their review article analyzed the effects of PPIs use and risk of minerals and vitamins deficiencies and clinical evidence in patients with GERD, dyspepsia, erosive esophagiitis and acid peptic disease. It was concluded that the people are using PPIs as on-demand and step-down therapy that created financial deficits to the public in addition to the medical problems. They[13] reported increased risk of minerals (Fe++, Ca++, Mg++and vitamins deficiencies (vitamin C, B_{12}, etc) that may be relatively low in the general population but enough in the elderly and malnourished patients.[13] A recent study from Lebanon population conducted by Makhoul et al[14] (2018) reported retrospective case-control study of 210 sample of age 18- to older from the Lebanese population. They found that the PPIs use >2 years in Lebanese was associated with hypovitaminosis B_{12}. They further added the female gender and young people showed strong association with PPIs use and hypovitaminosis B_{12}. The findings of above studies are in keeping with present studies. We are also supported by a nested case control study[15] from Kaiser Permanente Northern California (KPNC) that analyzed vitamin B_{12} in 25956 cases and 184199 controls and comparison showed statistical significant low vitamin B_{12} levels in long term PPIs cases.[15] The findings are in full agreement with the present study. A case report by Ruscin et al[16] reported severe vitamin B_{12} deficiency in a 78-year-old woman with symptomatic GERD who ingested the PPIs for 4.5 years. Vitamin B_{12} was found normal at baseline and severe deficiency was noted after 4.5 years PPIs consumption. A cross sectional study by Den Elzen et al[17] analyzed vitamin B_{12} in old aged individuals (age ≥65 years) using PPIs. They found no association vitamin B_{12} deficit with the long term PPIs use. The findings of above study are in contrast to present and other previous studies.[10-12] Reason could be of different geographical areas, dietary habits, qualitative differences of diet in different communities and research bias because of small sample size and statistical errors. Previous studies[18-20] from Pakistan have reported high prevalence of vitamin B_{12} in young age while in western countries vitamin B_{12}

deficiency is common in elderly[21], these discrepancies have created difficulties of estimating the true frequency of vitamin B_{12} in developing countries. The present study has many imperfections; 1st – effect of residual confounding factor of prevalent vitamin B_{12} cannot be fully eliminated, hence results may vary, 2nd – small sample size is not representative of total study population of area, and findings cannot be generalized. The strengths of present study are; case- control study, prospective study design, age and gender matched controls. Selection of cases by inclusion and exclusion criteria adds to the strength to the findings of present study. With evidence based findings and review of published literature, it is worth to say the hypovitaminosis B_{12} may be one of the grave health problem that needs to overcome through proper screening.

CONCLUSION

The present concludes the long term use of proton pump inhibitors is associated with hypovitaminosis B_{12}. It is suggested to conduct more studies at national level with large sample size to reach to the bitter fact of causality of hypovitaminosis B_{12} and Proton pump inhibitors as these are widely used in Pakistan.

Author's Contribution:

Concept & Design of Study:	Muhammad Akbar
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Revisiting Critically:	Muhammad Akbar, Abdul Karim Soomro
Final Approval of version:	Muhammad Akbar

Conflict of Interest: The study has no conflict of interest to declare by any author.

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