Original Article
DOI: https://doi.org/10.70749/ijbr.v3i7.1826

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Frequency of Iron Deficiency Anemia among Patient with Chronic Use of Proton Pump Inhibitor

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ARTICLE INFO

Keywords: Iron deficiency anemia, proton pump inhibitors, chronic PPI use, ferritin, TIBC, prevalence, Pakistan.

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Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 04-06-2025 Revised: 01-07-2025
Accepted: 05-07-2025 Published: 15-07-2025

ABSTRACT

Background: Proton pump inhibitors (PPIs) are widely used for managing acid-related disorders. However, prolonged use may impair iron absorption, potentially leading to iron deficiency anemia (IDA). This study aimed to determine the prevalence of IDA among chronic PPI users and assess its association with demographic and clinical factors. **Methods:** A cross-sectional study was conducted on 291 patients using PPIs for 6 months, at Department of Medicine at Jinnah Postgraduate Medical Centre (JPMC), Karachi, from December 2024 to May 2025. Data on age, gender, place of residence, diabetes, hypertension, family history of anemia, smoking status, and family monthly income were collected. Hemoglobin, ferritin, and total iron-binding capacity (TIBC) levels were measured to diagnose IDA. Associations between IDA and independent variables were analyzed using chi-square tests, with a significance level of $p \le 0.05$. **Results:** The prevalence of IDA was 21.3%. Trends indicated that IDA was slightly more common in males (53.2%) than females (46.8%) and was equally distributed among rural and urban participants (50.0% each). IDA occurred at similar rates in diabetic (50.0%) and non-diabetic participants. Non-hypertensive individuals (58.1%) had a higher prevalence of IDA compared to hypertensive individuals (41.9%). Participants without a family history of anemia (54.8%) had more IDA cases than those with a positive history (45.2%). Non-smokers accounted for the majority of IDA cases (56.5%), while ex-smokers and current smokers represented 25.8% and 17.7%, respectively. IDA was more common among participants earning ≤60,000 PKR (56.5%) compared to those with higher incomes (43.5%). **Conclusion:** This study found a 21.3% prevalence of iron deficiency anemia among patients on long-term PPI therapy. Although no significant associations were identified, trends suggest that gender, income, and lifestyle factors may influence IDA.

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent medications currently available to reduce gastric acid secretion and are widely prescribed in the treatment of peptic ulcer disease and gastroesophageal reflux disease (GERD)(1). Although the long-term use of PPIs is considered safe, there are several reported cases of iron deficiency anemia due to PPI use (2-4) and a community-based case control study reported that the risk of iron deficiency was increased among long-term PPI users(5).

Iron deficiency is a common nutritional deficiency and the leading cause of anemia around the world, The prevalence of iron deficiency anemia in developed countries like USA among adult females is up to 9% in those aged 5069 years and 6% in those older than 70 years. Iron deficiency can result in multiple symptoms including fatigue, impaired exertion, sleep disorders, and other complications(6, 7). Identifying modifiable factors that influence the risk for iron deficiency or impede its treatment, such as through impaired absorption, can significantly influence public health.

Acid inhibitors are among the most commonly used pharmaceuticals around the world: in 2012 alone, 14.9 million patients received 157 million prescriptions for proton pump inhibitors (PPIs)(8). Gastric acid facilitates nonheme iron absorption by releasing iron from food particles and converting it from its ferrous form to the more absorbable ferric form(9, 10). Thus, PPIs suppress gastric acid production, can lead to iron malabsorption. Acid suppression is of interest as a potential primary risk factor for iron deficiency, as a contributing risk factor and as an impediment to iron-replacement therapy. The few earlier studies of acid suppression and iron deficiency have been largely limited to small case series (the largest found was 109 patients) or niche populations (e.g. patients with hemochromatosis); in addition, they have yielded

inconsistent results[11, 12].
Study by Hafeez et al[13] reported the frequency of iron deficiency anemia in patient with chronic use of proton pump inhibitor was 25.33%. Another study reported the frequency of anemia in patient using proton pump inhibitor was 51%[14]. Study by Qorraj-Bytyqi et al[15] reported iron deficiency among proton pump users was 3.8%.
The aim of our study is to determine the frequency of iron deficiency anemia in patient with chronic use of proton pump inhibitor. Currently very few studies available on this topic, most of the articles are case reports. Available literature shows the association between iron deficiency anemia and proton pump inhibitor use. However, in our routine practice there is no screening protocol for iron deficiency anemia among proton pump inhibitor users. Findings of our study will help the physician to modify the screening protocol and also develop some preventive strategies in order to reduce the risk of iron deficiency anemia among proton pump inhibitor users.

MATERIAL AND METHODS

This cross-sectional study was conducted in the Department of Medicine at Jinnah Postgraduate Medical Centre (JPMC), Karachi, over six months following approval from the College of Physicians and Surgeons Pakistan (CPSP) and the institutional ethical review committee. A total of 291 patients were enrolled, with the sample size determined using the WHO formula based on a reported frequency of iron deficiency anemia (IDA) among chronic proton pump inhibitor (PPI) users of 25.33%, a 5% margin of error, and a 95% confidence level. Patients were selected using non-probability consecutive sampling from the outpatient department. Patients aged 18–65 years, of either gender, with a history of chronic PPI use for at least six months, were included in the study. Exclusion criteria encompassed patients with renal failure, chronic liver disease, prior history of IDA, vitamin B12 or other mineral deficiencies, and pregnant women.
Following informed consent, demographic and clinical details, including age, gender, place of residence, family monthly income, body mass index (BMI), diabetes, hypertension, smoking history, duration of PPI use, and family history of anemia, were recorded on a predesigned proforma. BMI was calculated using the formula weight (kg)/height (m^2), with weight measured using a digital weighing machine in light clothing and height measured using a wall-mounted scale without shoes. Smoking was categorized into current smokers, defined as individuals who had smoked at least 100 cigarettes in their lifetime and had smoked in the past month, and ex-smokers, defined as those who had smoked at least 100 cigarettes in their lifetime but had not smoked in the past month. Blood samples (5 mL) were collected by a trained phlebotomist under aseptic conditions for the diagnosis of IDA. Iron deficiency anemia was defined as ferritin levels below 30 µg/L and/or transferrin saturation (TIBC) below 16%, with hemoglobin concentrations less than 12 g/dL in men and less than 13 g/dL in women.
Data were analyzed using SPSS version 26. Quantitative variables, such as age, BMI, family monthly income, and duration of PPI use, were summarized as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data, with normality assessed using the Shapiro-Wilk test. Qualitative variables, including gender, place of residence, diabetes, hypertension, smoking, family history of anemia, and IDA, were reported as frequencies and percentages. Stratification was performed for age, gender, place of residence, duration of PPI use, diabetes, hypertension, smoking, and family history of anemia to control for confounders. Post-stratification, the chi-square test or Fisher's exact test was applied, with a p-value ≤0.05 considered statistically significant.

RESULTS

The study included 291 participants with a mean age of 42.4 years (SD = 14.4), ranging from 18 to 65 years. Participants had a mean duration of PPI use of 66.2 months (SD = 32.3), with a range from 12 to 120 months. Family monthly income averaged 58,380 PKR (SD = 23,682), with a median of 59,405 PKR and a range from 15,648 to 99,304 PKR. Laboratory results showed a mean ferritin level of 80.7 ng/mL (SD = 42.5), total iron-binding capacity (TIBC) of 328.4 µg/dL (SD = 69.9), and hemoglobin of 11.5 g/dL (SD = 2.4). Hemoglobin levels ranged from 7.6 to 15.5 g/dL, and ferritin levels varied from 5.3 to 149.9 ng/mL.
The prevalence of iron deficiency anemia (IDA) was 21.3% (62 of 291 participants). Among anemic patients, 53.2% were male, and 46.8% were female. IDA was equally distributed between rural and urban residents, each accounting for 50% of cases. Diabetes was not associated with IDA, as half of the anemic patients had diabetes, and the other half did not. Hypertension was present in 41.9% of anemic patients, while 58.1% were non-hypertensive. Family history of anemia did not show a clear link either, with 45.2% of anemic patients having a family history and 54.8% not.
Regarding smoking, 43.5% of anemic patients were smokers, including 17.7% current smokers and 25.8% ex-smokers. Non-smokers made up 56.5% of the anemic group. Income also showed a trend: 56.5% of anemic patients earned ≤60,000 PKR, while 43.5% earned more than this amount.
No statistically significant associations were found between IDA and gender ($p = 0.588$), place of residence ($p = 0.976$), diabetes ($p = 0.831$), hypertension ($p = 0.113$), family history of anemia ($p = 0.443$), smoking ($p = 0.915$), or income ($p = 0.351$). However, some trends emerged. Males had a slightly higher prevalence of IDA than females, and IDA was more common in participants earning ≤60,000 PKR. Although these trends were not significant, they suggest that lifestyle, income, and gender may play a role in IDA and merit further study.

Table 1
Distribution of Characteristics of the Study Population.

Variables		Frequency (percentage) N=291	Mean ± SD
Gender	Male	146 (50.17)	
	Female	145 (49.83)	
Place of Residence	Rural	146 (50.17)	
	Urban	145 (49.83)	
Diabetes	Yes	149 (51.20)	
	No	142 (48.80)	

Hypertension	Yes No	148 (50.86) 143 (49.14)
Family history of Anemia	Yes No	144 (49.48) 147 (50.52)
Smoking status	Current smoker Ex-smoker Non-smoker	59 (20.27) 66 (22.68) 166 (57.04)
Iron Deficiency Anemia	Yes No	62 (21.31) 229 (78.69)
Family Monthly Income	≤ 60000 > 60000	149 (51.20) 142 (48.80)
Duration of PPI Use (Months)		66.16 ± 32.31
Ferritin Level (ng/mL)		80.70 ± 42.46
TIBC (μg/dL)		328.35 ± 69.88

Table 2

Distribution of characteristics among those with IDA and those without IDA.

Variables	Iron Deficiency Anemia No	Iron Deficiency Anemia Yes	P value
Gender Male Female	 113 (49.34) 116 (50.66)	 33 (53.23) 29 (46.77)	0.58
Place of Residence Rural Urban	 115 (50.22) 114 (49.78)	 31 (50.0) 31 (50.0)	0.97
Diabetes Yes No	 118 (51.53) 111(48.47)	 31 (50.0) 31 (50.0)	0.83
Hypertension Yes No	 122 (53.28) 107 (46.72)	 26 (41.94) 36 (58.06)	0.11
Family History of Anemia Yes No	 116 (50.66) 113 (49.34)	 28 (45.16) 34 (54.84)	0.44
Smoking Current Ex-smoker Non-smoker	 48 (20.96) 50 (21.83) 131 (57.21)	 11 (17.74) 16 (25.81) 35 (56.45)	0.74
Family Monthly Income ≤ 60000 > 60000	 114 (49.78) 115 (50.22)	 35 (56.45) 27 (43.55)	0.35
Age (years) mean±Standard error	43.12 ± 0.95	39.73 ± 1.75	0.09
Duration of PPI use (months)	65.52 ± 2.05	68.54 ± 4.63	0.51
Ferritin Level (ng/mL)	82.81 ± 2.72	72.92 ± 5.86	0.10
TIBC (μg/dL)	328.87 ± 4.49	326.45 ± 9.74	0.80
Hemoglobin (g/dL)	11.44 ± 0.16	11.60 ± 0.29	0.67

DISCUSSION

The prevalence of iron deficiency anemia (IDA) in this study was 21.3%, with 62 out of 291 patients diagnosed with IDA based on laboratory findings (e.g., hemoglobin, ferritin, and TIBC levels). Proton pump inhibitors suppress gastric acid secretion, which is essential for dissolving and absorbing dietary non-heme iron. Reduced gastric acidity disrupts this process, leading to iron deficiency over time, especially with prolonged use.[16-17]

While no statistically significant associations were found, notable trends emerged. Men had a slightly higher prevalence of IDA (53.2%) than women (46.8%), a pattern that contrasts with the general population, where women are typically more affected due to menstrual blood loss.[18-19] This could suggest that PPIs equally impair iron absorption in both genders, reducing the typical disparity seen in anemia rates.

Place of residence showed no clear influence on IDA prevalence, with anemic cases evenly split between rural and urban areas. This reflects similar findings from study that suggest geographic factors, such as access to healthcare or diet, may play a limited role in the development of IDA among PPI users.[20]

The lack of association between diabetes and IDA aligns with another research study that found no direct link between diabetes and iron metabolism.[21] Although microvascular damage in poorly controlled diabetes can contribute to anemia, it may be less relevant in the presence of PPI-induced iron absorption issues. Similarly, hypertension showed no clear association with IDA, as a higher proportion of non-hypertensive individuals (58.1%) had anemia. This trend suggests that PPI use may outweigh other factors influencing iron deficiency.

Interestingly, family history of anemia was not strongly associated with IDA. A larger proportion of anemic patients (54.8%) reported no family history, emphasizing the role of environmental and lifestyle factors over genetic predisposition. Previous studies from Pakistan highlight the impact of poor nutrition and dietary deficiencies, particularly in resource-limited settings.[22-23]

Smoking status revealed minimal influence on IDA. Ex-smokers had a slightly higher prevalence (25.8%) compared to current smokers (17.7%), while non-smokers accounted for most cases (56.5%). Smoking's impact on hemoglobin levels, often elevated due to carbon monoxide exposure, may mask anemia, leading to its underestimation in smokers.[24]

Income levels showed a noticeable trend, with IDA being more common among participants earning ≤60,000 PKR (56.5%) compared to those with higher incomes (43.5%). This aligns with local studies linking lower socioeconomic status to inadequate access to iron-rich foods and healthcare services.[25-26]

The lack of statistical significance across variables may reflect the relatively small sample size or the multifactorial nature of IDA. However, these findings highlight the need for careful monitoring of iron status in patients on long-term PPI therapy. Unnecessary PPI prescriptions remain a concern, with studies reporting that up to 35% of prescriptions lack proper indications.[27] Clinicians should routinely reassess PPI therapy, particularly in at-risk populations, to prevent IDA and related complications.

CONCLUSION

This study found a 21.3% prevalence of iron deficiency anemia among patients on long-term PPI therapy. Although no significant associations were identified, trends suggest that gender, income, and lifestyle factors may influence IDA. Monitoring iron levels in chronic PPI users remains essential, particularly for individuals from lower socioeconomic backgrounds. Further research with larger sample sizes is necessary to confirm these observations and better understand the underlying contributors to IDA.

Limitations

This study has several limitations that should be acknowledged. Its cross-sectional design makes it impossible to establish a cause-and-effect relationship between proton pump inhibitor (PPI) use and iron deficiency anemia (IDA). Longitudinal research is needed to explore how PPI use contributes to the development of IDA over time. The sample size, while adequate for estimating prevalence, may have been too small to detect statistically significant associations between IDA and other variables. A larger sample would allow for more robust analysis and validation of observed trends. We did not account for dietary iron intake, gastrointestinal bleeding, or other conditions like malabsorption syndromes, which could influence iron levels. These factors may have affected the variability in ferritin, hemoglobin, and TIBC levels. Additionally, we relied solely on ferritin and TIBC to diagnose IDA, without considering inflammatory markers. Chronic inflammation, which can elevate ferritin levels, may have led to underestimation of anemia prevalence.

Since this study was conducted at a single center, the findings may not fully represent broader populations. Regional differences in diet, healthcare access, and socioeconomic conditions could influence anemia prevalence in other settings. Future studies should include larger, multi-center cohorts and a longitudinal design to address these limitations and provide a clearer understanding of the relationship between chronic PPI use and IDA.

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