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Chronic use of Proton Pump Inhibitor Leading to Iron Deficiency Anemia in a Middle Aged Women

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ABSTRACT

Iron deficiency anemia (IDA) is one of the most common hematological disorders. Proton pump inhibitors (PPIs) are widely used to treat various gastrointestinal diseases; however, their prolonged use has been increasingly associated with nutrient deficiencies, including iron deficiency. The underlying mechanism involves the alteration of the acidic gastric environment, resulting in impaired iron absorption. This case describes a case of a 43-year-old female who presented with fatigue and hair loss. She had a history of hypothyroidism, migraine, and gastroesophageal reflux disease (GERD), and had been taking omeprazole for the past eighteen years. Investigations revealed microcytic hypochromic anemia, characterized by low serum iron and ferritin levels. Other causes of iron deficiency anemia were ruled out through clinical assessment and laboratory workup. Oral iron therapy was poorly tolerated; however, intravenous iron led to symptomatic and hematologic improvement. This case highlights the underrecognized risk of iron deficiency associated with prolonged PPI use. In the absence of established guidelines, it further advocates for routine monitoring of iron status in long-term PPI users. Judicious prescribing and regular follow-up can help prevent avoidable nutritional deficiencies in patients requiring extended acid suppression therapy. The case is unique and rare in a country like Pakistan, as only a few similar cases have been reported in the literature. Moreover, PPI usage is often overlooked while investigating iron deficiency anemia.

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INTRODUCTION

Approximately one-third of the global population is affected by anemia, with iron deficiency responsible for about half of these cases.[1] Iron depletion may be attributed to various factors, including inadequate dietary intake, blood loss, impaired absorption, or increased body requirements. Patients with iron deficiency often present with nonspecific symptoms such as fatigue and exertional dyspnea. Management involves addressing the underlying cause and providing iron supplementation. Proton pump inhibitors (PPIs) are commonly prescribed for the treatment of conditions like gastroesophageal reflux disease (GERD), erosive esophagitis, duodenal ulcers, and hypersecretory disorders.[2] Over the past two decades, their use has significantly increased in clinical practice. PPIs work by inhibiting the H?/K? ATPase pump in gastric parietal cells, which results in suppression of both basal and stimulated gastric acid secretion. Non-heme iron requires an acidic environment for its absorption.[2,3] Prolonged PPI use reduces gastric acid secretion, impairing the absorption of essential vitamins and minerals, including iron.[4] Although PPIs are primarily intended for short-term use, they are frequently prescribed for long-term maintenance therapy, contributing to potential nutritional deficiencies.

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Case report

A 43-year-old female resident of Jhelum presented with fatigue and hair loss for the past couple of months. She reported persistent fatigability without evening exacerbation and no history of body aches and pains, fever, shortness of breath or weight loss.. She was a known case of hypothyroidism, gastroesophageal reflux disease (GERD), and migraine. Her current medications included tablet thyroxine 100 µg OD, tablet Inderal 20 mg BID for migraine prophylaxis, and omeprazole 40 mg OD. Her migraine attacks were well controlled and responded well to paracetamol. There was no history of nonsteroidal anti-inflammatory drug (NSAID) use. Notably, she did not have

any symptoms suggestive of uncontrolled hypothyroidism, such as constipation, sleepiness, cold intolerance, or weight gain. She had no history of passage of worms. Her diet included red meat, dairy products, and leafy vegetables. She never experienced per rectal bleeding or melena. Her menstrual cycles were regular, with no episodes of menorrhagia. Given her history of hypothyroidism, other autoimmune conditions that could cause fatigue—such as Addison's disease, celiac disease, and pernicious anemia—were considered. There were no features suggestive of cortisol deficiency, such as muscle cramps, vomiting, or hyperpigmentation of the skin or creases. She had no history of loose stools, abdominal pain or flatulence, suggestive of celiac disease. Additionally, there were no signs of autoimmune disorders, such as fever, rash, joint pain, photophobia, or mouth ulcers.

Her past medical history revealed that she had been suffering from GERD and gastritis for 18 years. Initially, she was prescribed omeprazole 20 mg OD, but her dose was increased to 40 mg OD over the past year due to worsening GERD symptoms. On examination, she appeared mildly pale and overweight but was not jaundiced. Her vital signs were: pulse rate 86 beats per minute, blood pressure 110/82 mmHg, and respiratory rate 14 breaths per minute. Her BMI was 29. Systemic examination was unremarkable.

Her laboratory investigations showed:
- CBC: Hb 10.6 g/dL, MCV 71 fL
- Serum iron: 33ug/dL (50-170)
- Serum ferritin: 22 ng/mL. (24-307)
- TIBC: 454ug/dL (250-450)
- Thyroid function tests (TFTs): Within normal limits
- Stool for occult blood: Negative
- H. pylori stool antigen (HpSA) test: Negative
- HbA1c: 5.4%
- Celiac disease autoaantibodies: Negative
- Ultrasound abdomen: Grade 1 fatty liver

She was advice to undergo an upper GI endoscopy, but she refused. She was initially prescribed oral iron supplements; however, she developed nausea and constipation. Subsequently, intravenous iron replacement in the form of iron sucrose was administered. Her symptoms improved, and at one month follow up her Hb increased to 12.2 g/dL. Her omeprazole dose was reduced to 20 mg OD, and she was advised on weight reduction and lifestyle modifications.

DISCUSSION

Anemia is diagnosed when hemoglobin levels fall below 13 g/dL in males and below 12 g/dL in females. Iron deficiency anemia (IDA) is the most prevalent form of anemia globally and is characterized by a reduction in hemoglobin synthesis due to inadequate iron availability. It commonly arises from chronic blood loss, insufficient dietary intake, impaired iron absorption, or increased physiological demands, such as during pregnancy or growth spurts. Clinically, IDA manifests as fatigue, pallor, exertional dyspnea, and decreased physical performance. Diagnostic evaluation typically reveals microcytic hypochromic anemia with low serum ferritin, reduced serum iron levels, and elevated total iron-binding capacity.

Dietary iron has two forms; heme iron and nonheme iron with 32% and 68% contribution. Heme iron exists in a ferrous state ($Fe^{2?}$), which is readily absorbed after being released from globin by pancreatic enzymes.[3] Non-heme iron is present in the ferric state ($Fe^{3?}$). It is commonly found in cereals, vegetables, and beans and its absorption depends on an acidic gastric environment. Gastric acid enhances its solubility and facilitates its reduction to the ferrous state for absorption.[3] Various medical and surgical conditions, as well as factors affecting gastric acidity, can impair this process and lead to iron deficiency.

Worldwide, more than 25% of the population is affected by acid-related conditions, including dyspepsia and gastroesophageal reflux disease (GERD). Proton pump inhibitors (PPIs) are presently considered the first-line therapy for acid-related conditions like gastroesophageal reflux disease (GERD).[5,6] They rank among the top ten most commonly prescribed medications globally. PPIs reduce gastric acidity by inhibiting the production of hydrogen ions ($H^?$) by blocking the hydrogen/potassium ATPase pump in the parietal cells of gastric mucosa. This limits the conversion of $Fe^{3?}$ to $Fe^{2?}$, resulting in impaired intestinal iron absorption.[7] While PPIs provide prompt and effective symptom relief, their prolonged use has raised concerns due to potentially rare but serious adverse effects. These include an increased risk of osteoporotic fractures, interstitial nephritis, chronic kidney disease, infections, rebound acid hypersecretion, and deficiencies in essential nutrients such as iron, vitamin B12, and magnesium.

In one study, a systematic review and meta-analysis assessed the link between proton pump inhibitor (PPI) use and iron deficiency anemia (IDA). Findings from nine studies showed a significant association, with PPI users having more than twice the risk of developing IDA (RR 2.56; 95% CI, 1.43–4.61; $p < 0.00001$).[8] The study recommends cautious long-term PPI prescribing and regular monitoring of patients' iron levels to mitigate the risk of IDA.

A large case-control study utilizing the UK Clinical Practice Research Datalink (CPRD) database examined the association between PPI use and the risk of iron deficiency (ID). The study assessed the first occurrence of ID in PPI full users (PFUs) and PPI limited users (PLUs) compared to non-users (PNUs). The adjusted odds ratio for ID was 3.60 (95% CI [3.32–3.91]) in PFUs and 1.51 (95% CI [1.44–1.58]) in PLUs compared to PNUs.[9] Additionally, a positive dose-response and time-response relationship was observed.

An observational study conducted in Lodhran, Pakistan, investigated the association between proton pump inhibitor use and iron deficiency anemia. Serum ferritin and iron concentrations were assessed both at the initiation of PPI

therapy and after 8 months of continued use. The mean serum ferritin level significantly declined from 68.72 ± 30.41 ng/ml at the start of treatment to 27.45 ± 16.26 ng/ml after 8 months ($p < 0.001$). Similarly, the mean serum iron level decreased from 18.28 ± 6.54 µmol/l to 15.86 ± 5.72 µmol/l over the same period, also showing a significant difference ($p = 0.001$).[10]

Patients with conditions such as Barrett's esophagus, severe esophagitis, a history of bleeding gastrointestinal ulcers, or those on long-term non-steroidal anti-inflammatory drugs (NSAIDs) often require prolonged PPI therapy. Therefore, these individuals should be closely monitored for potential adverse effects related to extended PPI use.[11]

Currently, no guidelines or recommendations exist for monitoring body iron stores in patients on long-term PPI therapy. The American Gastroenterological Association advises using non-pharmacological approaches and histamine-2 receptor blockers to alleviate the gastrointestinal symptoms of gastroesophageal reflux disease, reserving proton pump inhibitor (PPI) therapy for cases with a clear clinical indication.

The patient had been using proton pump inhibitors (PPIs) continuously for 18 years, with high-dose intake over the past year. She had no history of overt blood loss, including menorrhagia or per rectal bleeding. Stool occult blood and *Helicobacter pylori* stool antigen (HpSA) tests were negative. Serological tests for celiac disease were also negative. Although upper gastrointestinal endoscopy was recommended, the patient declined the procedure. No evidence of other endocrinological or autoimmune disorders was found. Given the absence of other identifiable causes, her iron deficiency was attributed to long-term PPI use. She was treated with intravenous iron sucrose, resulting in noticeable clinical improvement within a few days. She was advised to undergo regular monitoring with complete blood count (CBC) and iron studies every three months.

CONCLUSIONS

IDA or iron depletion due to prolonged exposure to PPI is more common than previously recognized. As the number of long-term PPI users continues to rise and the duration of PPI use extends, new PPIs with stronger acid suppression are also being developed and introduced. Consequently, the prevalence of iron deficiency anemia among long-term PPI users is expected to increase globally. Therefore, it is crucial to limit prolonged PPI use when possible and to consider it as a potential contributor in the differential diagnosis of iron deficiency anemia among long-term users.

Authors Contribution:
Qurat ul Ain: Conceptualization, Literature research
Eeraj Saeed: Manuscript writing
Nadia Noreen: Literature Research
Nagina Asgher: Manuscript writing
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