Biochemical Changes Associated with Chronic Proton Pump Inhibitor Use in Adults

Gulfreen Waheed[1], Haroon Habib [2]

[1]Department of Obstetrics & Gynaecology, Avicenna Medical College & Avicenna Hospital, Lahore; [2]Department of Biochemistry, Avicenna Medical & Dental College, Lahore

Correspondence: Prof. Dr. Haroon Habib, Professor of Biochemistry, Avicenna Medical & Dental College Lahore-Pakistan
Email: dr.haroonhabib@gmail.com
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The Proton Pump Inhibitors (PPIs) amount to one of the most extensively prescribed drug family worldwide. The PPIs are widely indicated in the management of various acid relation gastrointestinal disorders. Diseases like gastroesophageal reflux disease, dyspepsia, Zollinger-Ellison syndrome and peptic ulcer disease readily respond to the PPIs.[1,2] This drug class achieves sustained, profound suppression of gastric acid secretion through irreversible inhibition of the hydrogen-potassium ATPase enzyme on the gastric parietal cell membrane. [2,3] Before the introduction of PPIs, in the late 1980s, histamine-2 receptor antagonists (H2RAs) were commonly used but H2RAs were ousted by the PPIs because of their short-term safety profile and superior efficacy.[4] Despite of the short-term safety profile, recent studies have raised severe concerns about the biochemical and metabolic ramifications of prolonged PPI usage, specially in the population who are already at risk such as elderly patients or patients who receive polypharmacy. [3,6] The developing unnecessary long-term use of PPIs is bestowed upon the availability of numerous PPI formulations that also includes over the counter options.[5]

Pharmacological Mechanisms

Gastric Acid Suppression: In gastric parietal cells the primary pharmacological effects of PPIs are brought to bear by the irreversible inhibition of the H^+/K^+ ATPase enzyme system that results in the efficacious blockage of final common pathway of gastric acid secretion.[2,5] The degree of acid suppression achieved with PPIs is substantially greater than that of other acid-suppressive therapies, which accounts for their superior clinical efficacy.[5] Nevertheless, this intense acid suppression results in unintended consequences because the gastric acid plays numerous vital roles in multiple physiological processes such as digestion, antimicrobial defence and nutrient absorption.[3,5]

Systemic Bioavailability: The H+/K+ ATPase enzyme is present in multiple tissues, raising the possibility of extra-gastrointestinal effects from chronic PPI therapy.[4] Studies have suggested that PPIs may influence gene expression related to collagen synthesis and extracellular matrix organisation, potentially contributing to microarchitectural compromise independent of mineral density changes.[4] Moreover, potential endocrine disruptions are observed among long term PPIs users with significant variations in testosterone and serum sex hormone-binding globulin levels.[4] Although incompletely understood, these systemic effects may contribute to multiple biochemical alterations associated with chronic PPI therapy.

Epidemiology of PPI Prescribing

The consumption of PPIs has risen substantially over the past couple of decades. Various studies have shown that this increase in utilization of PPIs owes its existence to inappropriate or prolonged usage beyond the period of clinical necessity.[1,4] Research examining prescribing patterns in various nations has demonstrated that large percentages of PPI prescriptions could be unnecessary, with estimates suggesting that up to 50% of patients may receive PPIs inappropriately due to unsuitable indications, excessive treatment duration or inappropriate dosage.[5,7] The common symptoms of gastritis and acidity are customarily treated empirically with PPIs in Indo-Pak Subcontinent, leading to prolonged and extensive exposure to PPIs.[1] "Inappropriate chronic use" is observed in many patients that continue PPI therapy without periodic reassessment of clinical need and beyond recommended treatment durations. [3]

Rationale for Long-Term Use

The chronic nature of acid related conditions that require mucosal protection and ongoing symptom control justifies the extended duration of PPI therapy.[1] Sustained acid suppression is legitimately indicated in

patients with diseases such as GERD, Barrett's oesophagus, or those necessitating chronic NSAID administration.[2,4] Moreover, the prevention of gastric mucosal damage is considered to be a cause for frequent prophylactic prescription of PPIs.[1] The chronic nature of these prescribing patterns has prompted increased scrutiny of the long-term safety profile of PPIs, particularly regarding nutrient absorption and metabolic disturbances.[1,5]

Vitamin and Mineral Absorption

Vitamin B12 Deficiency: The role of gastric acid in the process of vitamin B12 absorption is pivotal, as in facilitation of binding to intrinsic factor and release of vitamin from the dietary proteins. A progressive depletion of vitamin B12 is observed in hypochlorhydria induced by chronic PPI usage.[1,5] Studies have shown a significant reduced serum vitamin B12 levels in the PPI users as compared to the non-users i.e. mean levels of 312±128 pg/mL versus 418±152 pg/mL reported in one tertiary-care study.[1] Vitamin B12 deficiency, defined as levels below the normal level of 200-900 pg/mL, was present in more than 24% of patients using PPI as opposed to about 9.2% of non-users.[1] A quasi-experimental study found that after a year of PPI therapy, vitamin B12 levels decreased by a mean of 88.04 pg/mL.[5] The odds of vitamin B12 deficiency were higher in patients on PPIs compared to those not on PPIs, as demonstrated in a meta-analysis of 25 studies.[5] A 12-18 % fall in serum vitamin B12 was observed in a systemic review over 12 months of PPI use in older adults.[3]

Magnesium and Hypomagnesemia: Adequate gastric acidity is a requirement for the absorption of magnesium so if the chronic acid suppression occurs, the bio availability of magnesium is reduced considerably.[1,5] Studies have consistently demonstrated lower serum magnesium levels among PPI users, with mean levels of 1.86±0.24 mg/dL in users versus 2.02±0.21 mg/dL in non-users in one study ($p<0.001$).[1] Hypomagnesemia, defined as magnesium below the normal value of 1.7-2.2 mg/dL, was observed in more than 28% of patients using PPI as compared to about 10.0% of non-users.[1]

Calcium Malabsorption: Impaired absorption of insoluble calcium salts is observed in achlorhydric patients because of the fact that the calcium absorption is facilitated by gastric acidity through pH-dependent ionisation of calcium salts.[2,4] Studies have demonstrated significant decreases in serum calcium levels among PPI users, showing a mean difference of 0.450 mg/dL after a year in one study.[5] However, the evidence remains conflicting, with some research finding no significant differences in calcium levels between PPI users and controls.[2]

Renal Function Alterations

Acute Kidney Injury Patterns: The association between acute kidney injury and PPI use has been recognised increasingly, although its mechanism is not yet completely understood.[6] The incidence of acute interstitial nephritis is enhanced by the chronic use of PPI. Case reports and observational studies have documented this complication, while the precise incidence of PPI-associated acute kidney injury is not well established. This emphasizes the need for clinical vigilance in patients presenting with unexplained renal dysfunction during PPI therapy.[6]

Chronic Kidney Disease Progression: An increased risk of chronic kidney disease progression is associated with long-term use of PPI, beyond acute kidney injury.[3,6] Association between renal disease and prolonged PPI exposure is identified by a systemic review focusing on older adults, although further investigations are required to strengthen the clinical significance of this association.[3] The proposed mechanisms that bring about chronic kidney disease are electrolyte disturbances, chronic tubulointerstitial inflammation and potentially direct tubular toxicity.[6] The association between PPI use and renal impairment exists, whereas the causal relationship and clinical implications remain areas of ongoing investigation.[3,6]

Skeletal Health Implications

Bone Mineral Density (BMD) Changes: The systematic review evaluating BMD changes in PPI users found that 71% of studies reported significant BMD depletions among the users of PPI, distinctly at the femoral neck and at the hip.[4] The mean BMD reduction ranged from 0.009-0.022 g/cm² over 1-10 years.[4] The systematic review by Sundar et al. noted that while the overall decrease in BMD is small, its clinical significance is concerning for older adults, postmenopausal women, and chronic PPI users.[4]

Fracture Risk Assessment: The relationship between PPI use and fracture risk has been extensively investigated, with several meta-analyses demonstrating an increased risk.[2,4,5] PPI use could moderately increase the risk of hip fracture as shown in a meta-analysis of

18 studies.[2] However, some studies have found no significant increase in fracture risk despite reduced BMD, suggesting that PPIs may not affect bone quality beyond mineral density.[4] The mechanism of increased fracture risk is likely multifactorial, involving impaired absorption of calcium and leading to resorption, increased bone turnover and secondary hyperparathyroidism, and direct effects on osteoblast and osteoclast function.[4,5] Both hypocalcaemia and altered bone metabolism can be caused by decrease parathyroid hormone secretion due to low magnesium levels.[5] The systematic review recommends that clinicians utilize the minimum effective dosage and treatment period, while ensuring routine BMD surveillance for patients at elevated risk who are receiving PPI therapy.[4]

Metabolic and Cardiovascular Effects

Gut Microbiome Alterations: Potentially contributing to nutrient malabsorption and metabolic disturbances, the chronic PPI use has been associated with alterations in the intestinal microbiome.[1] The first-line barrier against bacteria introduced with food is lowered by PPIs because the use of PPIs lead to reduction in gastric acidity. This potentially increases the susceptibility to enteric infections.[2,5] Associations have been documented in various studies between PPI use and increased risk of Campylobacter enteric infections, Clostridium difficile infection and non-typhoid Salmonella.[2,5] Moreover, changes in intestinal pH can affect the solubility and absorption of various nutrients and may influence the composition and function of the gut microbiota, with potential implications for systemic metabolism.[1,4] Long-term suppression of gastric acid can alter intestinal microbiota and also affect nutrient metabolism, potentially exacerbating deficiencies.[1] However, the clinical significance of these microbiome changes and their contribution to the observed biochemical alterations require further investigation.

Cognitive Decline Associations: Emerging evidence has raised concerns about potential associations between long-term PPI use and cognitive decline, particularly in older adults.[3,5] The systematic review identified that vitamin B12 deficiency, which is associated with PPI use, is a confirmed contributor to cognitive dysfunction.[3]

It is emphasized in the systemic review that the cumulative consequences of micronutrient depletion in older adults are often insidious but it is surely progressive, so the key to preserving the functions are early identification and intervention.[3]

Clinical Monitoring Recommendations

Periodic Biochemical Surveillance: A periodic monitoring of serum Vitamin B12 and magnesium is indicated in the patients consuming long-term PPI therapy, specially those who possess additional metabolic and nutritional risk factors, due to the evidence linking various biochemical alterations with chronic PPI use.[1,3,5] It has been repeatedly shown in various systemic reviews that the risk factors of chronic PPI use can be mitigated by appropriate prescribing practices, routine nutritional monitoring and targeted supplementation.[3,5] Although routine screening for all PPI users is not recommended by the American Gastroenterology Association but it is acknowledged that the high risk patients can benefit from monitoring.[2] Individualised risk assessment, appropriate laboratory surveillance, and targeted supplementation should be considered by the clinicians where necessary.[5] It has been suggested by the evidence that the early detection of biochemical alterations is vital, especially in patients who remain asymptomatic even in the presence of biochemical deficiencies.[1]

Deprescribing Protocols: In order to reduce the burden of chronic PPI therapy, some key strategies have been identified such as deprescribing, or systematic reduction or discontinuation of potentially inappropriate medication.[3,4,5] The ongoing need for PPI therapy should be evaluated by the clinicians and step-down or on-demand regimens should be considered, especially in patients with asymptomatic or mild GERD.[4] The evidence suggests that alternative acid-suppressive agents, such as H2 receptor antagonists, may have a lesser impact on BMD and nutrient status than PPIs when indicated for long-term use.[4,5] It is concluded by the systematic reviews that the preventable complications related to prolong PPI use maybe reduced by optimal treatment duration, medical re-evaluation, and evidence-based prescribing.[1,4].

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