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Review Article

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Long-Term Use of Proton Pump Inhibitors Increases the Risk of Renal Diseases

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Abstract: Proton pump inhibitors (PPIs) are drugs that successfully inhibit stomach acid secretion. They are used for the management of various acid-related conditions, including gastroesophageal reflux disease (GERD) and other gastric illnesses. It can reduce hydrochloric acid output via irreversible binding to the hydrogen potassium adenosine triphosphatase (H+/K+ ATPase) enzyme and inhibiting its action in the stomach. PPIs are among the most often prescribed drugs; however, 25% to 70% of these prescriptions have no legitimate indication. As a result, patients frequently take these treatments without benefit, exposing themselves to unwanted adverse events. PPIs can cause acute interstitial nephritis (AIN), which can be a serious side effect associated with acute kidney injury (AKI). It has been reported that the long-term use of PPIs has been associated with an elevated risk of chronic kidney disease (CKD). As a result, this review aims to investigate the adverse effects of long-term use of PPIs on renal function.

Keywords: Proton pump inhibitors; acute kidney injury; chronic kidney disease; acute interstitial nephritis; adverse effects.

1. INTRODUCTION

Precise regulation and production of gastric acid secretion are necessary to maximize its advantages and minimize its drawbacks. Acid renders the small intestine and stomach comparatively sterile and destroys bacteria, including *Helicobacter pylori (H pylori)*. It facilitates the absorption of calcium, vitamin B12, and nonheme iron in addition to aiding in the digestion of proteins. Ulcers, however, develop when mucosal defense mechanisms are overpowered by acid and pepsin levels [1]. Several medications were developed to target the parietal cell and stop acid production since it was discovered that the parietal cell secretes stomach acid. The primary functional targets of the parietal cell were the gastric hydrogen potassium adenosine triphosphatase (H+/K+ ATPase) enzyme, and the histamine type 2 (H2) receptor [2]. Acid-lowering medications that treat GERD include histamine type 2 receptor antagonists (H2RAs) like ranitidine and proton pump inhibitors (PPIs) like omeprazole. H2RAs cannot effectively control reflux symptoms, and their capacity to suppress postprandial stomach acid output is restricted. Unlike H2RAs, PPIs inhibit the last stage of acid secretion, resulting in strong and sustained acid suppression [3]. In this review, we will focus on PPIs.

1.1. Proton pump inhibitors.

Gastric acid secretion is inhibited by PPIs, also known as H+/K+ ATPase inhibitors [4]. These medications, which belong to a class of substituted benzimidazole sulfoxides drugs, considerably diminish the output of hydrochloric acid in the stomach's parietal cells [5]. PPIs are among the most frequently prescribed medications, they are frequently used to treat patients suffering from acid-related disorders such as peptic ulcer disease (PUD) and GERD. They are being prescribed excessively and used for unsuitable conditions, and their utilization is on the rise, especially for extended periods of treatment [6]. Between 25% and 70% of these prescriptions are thought to be inappropriately prescribed [7].

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In 1989, their use was initially approved [8]. Launched in 1989, omeprazole was the first medication in this class. Lansoprazole (1995), rabeprazole (1999), pantoprazole (2000), esomeprazole (2001), and dexlansoprazole (2009) were the subsequent drugs in this family. Due to the availability of omeprazole, esomeprazole, and lansoprazole for over-the-counter (OTC) purchase in the US, the accessibility for the public has increased, so there is now concern regarding the possible long-term negative effects of PPIs, as well as their increased and occasionally improper use [9]. Among the top twenty medications delivered globally, omeprazole is the most commonly used PPI [10].

1.1.1. Omeprazole:

1.1.1.1. Structure:

Omeprazole (OME) IUPAC name is, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulphinyl]-1H-benzimidazole [11,12]. OME is a weak, lipophilic base [13]. It is made up of two heterocyclic moieties such as a benzimidazole ring and a substituted pyridine ring which are linked via methylsulfinyl group [14]. It can exist in two distinct optically active forms, S-omeprazole (esomeprazole) and R-omeprazole since it has a tri-coordinated sulfur atom in a pyramidal structure [11]. It is available as a racemic mixture of its two optical isomers, although pharmacological research has shown that esomeprazole is more effective than R-omeprazole [15]. Since it has 2 pKa (negative logarithms of the acid ionization constant) values, 4.0 for pyridinium and 8.8 for benzimidazole, fifty percent of it protonated at lower physiological pH values [10].

1.1.1.2. Pharmacokinetic properties of omeprazole:

1.1.1.2.1. Absorption and distribution:

Due to the susceptibility of OME to acid degradation, it must be prepared with an enteric protective coating to withstand the breakdown caused by stomach acid and enable absorption in the small intestine's more alkaline environment [16]. After passing from the stomach, PPIs are absorbed in the proximal small bowel [17]. After oral administration, it is absorbed quickly but unevenly, with a 30%–40% oral bioavailability and a 95% plasma protein binding. Its action starts within 60 minutes, with maximum activity at 120 minutes, and has significant effects that persist for three to five days [18].

1.1.1.2.2. Metabolism**:**

The cytochrome P450 system is an indispensable component in the metabolic process. The fundamental components of this process encompass the polymorphisms of CYP2C19 and CYP3A4. The enzyme CYP2C19 is responsible for the conversion of OME into hydroxyl and 5-O-demethyl metabolites, whilst CYP3A4 facilitates its transformation into sulfone [2]. The two main OME metabolites detected in plasma are sulfonated and 5-hydroxylated compounds, while the most common metabolite in urine is 5-hydroxylated omeprazole [19].

1.1.1.2.3. Excretion**:**

Approximately 80% of OME taken orally is eliminated as metabolites in the urine, with the remaining 20% coming primarily from biliary secretions excreted in the feces [18,19].

1.1.2. The biochemical reaction steps of stomach H+/K+ ATPase and physiology of gastric acid secretion:

The discharge of gastric acid is accompanied by notable morphological changes in the parietal cells. Intracellular compartments beneath the apical membrane contain tubulovesicles that are abundant in H+/K+ ATPase and form a reticulated meshwork when parietal cells are at rest. Tubulovesicles undergo translocation and apical membrane attachment upon stimulation, thereby instigating a substantial secretion of acid [20].

The H+/K+ ATPase facilitates the exchange of intracellular hydrogen ions for extracellular potassium ions by utilizing ATP [21]. The biochemical reaction steps of H+/K+ ATPase include phosphorylation and de-phosphorylation, which occur in conjunction with cyclic conformational changes denoted by E 1→ E 2→ E 1, in which the cation-binding sites of the enzyme are oriented either towards the extracellular surface at the E2 state or the cytoplasm at the E1 state [20].

The catalytic subunit of ATPase undergoes cyclic phosphorylation and dephosphorylation, which drives conformational changes that enable H+/K+ ATPase to catalyze transport. The hydronium ion is bound by H+/K+ ATPase. Upon phosphorylation, the conformation changes from E1P•H3O+ to E2P•H3O+ form. The E2P•K+ conformation is created by the release of H3O+ and the binding of K+ on the extracytoplasmic surface of the enzyme. After dephosphorylation, the E2P•K+ conformation changes into the E1K conformation. The E1K conformation releases K+ to the cytoplasmic side, enabling H3O+ to rebind and the enzyme cycle to be completed [21,22].

1.1.3. Pharmacodynamics of proton-pump inhibitors:

They act by preventing the production of gastric acid by irreversibly blocking the enzyme H+/K+ ATPase in the stomach parietal cells [9]. All PPIs have the crucial chemical property that their pyridine nitrogen pKa values are nearly 4.0. This suggests that

they are weakly basic substances that will be maximally protonated in the extremely acidic intracellular canaliculi of actively secreting parietal cells in the stomach and barely protonated at neutral pH of blood [23]. PPIs are weak bases that are sensitive to acid; therefore, to prevent them from being destroyed by gastric acid and to enable intestinal absorption, they need to have an enteric coating [24].

These prodrugs are absorbed from the small intestine and enter the systemic circulation following oral administration. Then, they diffuse to the extracellular canaliculus after entering the gastric parietal cell [25]. Upon reaching the parietal cell's acidic site of action, the PPIs will undergo acidic activation which is essential to inhibit the proton pump [24]. Activation of the PPIs occurs by the addition of two protons to the nitrogen atom on both sides of the sulfinyl group [16]. Subsequently, it rearranges to produce a sulfenic acid which exists in equilibrium with a sulfenamide. Then both chemical entities can form covalent bonds with thiol groups at cysteine residues on the luminal surface of the H+/K+ ATPase α-subunit. As a consequence of this covalent attachment, the enzyme becomes selectively and nearly irreversibly inactivated leading to sustained inhibition of stomach acid output [26]. The functionality of the H+/K+ ATPase enzyme is compromised by covalent bonding, necessitating the synthesis of new H+/K+ ATPase molecules by parietal cells to restore its activity [23].

1.1.4. Prevalence of proton pump inhibitors

PPIs rank as the fourth most commonly dispensed drug in the United States, with up to 21 million Americans receiving prescriptions for them annually [27]**.** Off-label use of medications is common in intensive care settings, with PPIs being among the most frequently used off-label drugs, reaching prevalence rates as high as 55% in intensive care units**.** [28]**.** PPIs are usually used in ICUs for short-term as stress ulcer prophylaxis (SUP) [29]**,** for those at high risk of gastrointestinal Bleeding [30]**.** According to data gathered in 2013 and 2014, approximately 2.5% of individuals who were acutely admitted to an intensive care unit (ICU) experienced upper gastrointestinal bleeding. To avoid this bleeding, 70% of these persons were provided stress ulcer prophylaxis. [31]. The estimated prevalence of PPI use is 7-8% among adult individuals residing in the community in the United Kingdom and Denmark, However, in Canada, rates as high as 40-50% have been documented among older individuals, and similarly in Australia among those in residential care. Notably, in England alone, over 50 million prescriptions for PPIs were dispensed in 2015 [32]**.**

1.1.5. Uses of proton-pump inhibitors:

The primary indication for PPI use is to manage stomach acid-related disorders, such as duodenal and stomach ulcers, reflux esophagitis, and Zollinger-Ellison syndrome [27]. Moreover, they are commonly used to avoid gastrointestinal bleeding in patients undergoing dual antiplatelet medication consisting of clopidogrel and aspirin following myocardial infarction (MI) and percutaneous coronary intervention (PCI). Additionally, PPIs are considered to be an important adjunctive component of a conventional antibiotic regimen that includes amoxicillin and clarithromycin to eradicate *H.Pylori* because of their strong acid-suppressive properties, which enhance the anti-*H. Pylori* properties of the combined antibacterial [5].

They are frequently provided as co-prescription for patients who take nonsteroidal anti-inflammatory drugs (NSAIDs), ulcer avoidance in patients with a history of PUD, and critically ill patients in the intensive care unit (ICU) [28,29]. It is estimated that 15 million persons in the US use prescription PPIs (with a 7.8% estimated prevalence in the US adult population) [30]. PPIs are also sometimes prescribed inappropriately; according to cross-sectional studies, only around 30% of patients received PPI prescriptions with suitable indications and in line with guidelines [28].

1.1.6. Clinical PPI recommendations and GERD recommendations and their doses:

The recommendations of PPI in the treatment of GERD and the recommended doses have been shown in Table (1).

1.1.7. Drug interactions of proton pump inhibitors:

1.1.7.1. Modification of gastric PH

Because of their ability to reduce gastric acidity, PPIs can alter the release from products with pH-dependent dissolving characteristics or change the solubility of other drugs. A co-administered single dosage of OME 60 mg dramatically decreased the bioavailability of oral ketoconazole. It is believed that this effect results from ketoconazole's incredibly low solubility at pH values greater than 3 [31].

1.1.7.2. Interaction with efflux transporter

Since digoxin is a substrate of P-glycoprotein with limited metabolic biotransformation, omeprazole has been demonstrated to improve the bioavailability of digoxin. The potential mechanism underlying the drug-drug interaction between digoxin and omeprazole may involve the blockade of

digoxin efflux into the intestinal lumen induced by omeprazole, which is mediated by P-glycoprotein [5].

1.1.7.3. Modification of drug metabolism in the liver

They can contribute to Drug-Drug interactions by modifying how simultaneously given medicines are metabolized by either stimulating or inhibiting the activity of particular enzymes. Pharmacokinetic interactions denote the impacts on cytochrome P450 (CYP450) and the possibility of drug interactions that may arise from the concurrent use of two or more medications. The most researched combination is clopidogrel and PPIs, which have been linked with an elevated risk of adverse cardiovascular consequences [28]. Clopidogrel is classified as a prodrug, necessitating it is transformation into an active metabolite via the liver CYP450 enzyme system. The polymorphisms CYP2C19 and CYP3A4 seem to have the main metabolic roles. PPIs work by competitively inhibiting CYP2C19, to prevent the prodrug clopidogrel from transforming into an active metabolite. So the antiplatelet action of clopidogrel is potentially diminished due to the inefficient conversion of the prodrug to its active metabolite [32].

1.1.7.4. Alteration of drug eli**mination**

Administration of PPI can alter the elimination of some drugs such as delaying the elimination of methotrexate[5].

Table1. The recommendations of PPI in the treatment of GERD and the recommended doses

PPIs	Dose of PPIs in GERD [39]	Recommendations [40–42]
Dexlansoprazole	30 to 60 mg administered orally once daily	It has been recommended PPIs be trialed for GERD if antacids, diet, and lifestyle modifications fail to resolve symptoms For patients with classic GERD symptoms of heartburn and regurgitation who have no alarm symptoms, we recommend an 8-week trial of PPIs once daily 30–60 min before a meal usually in the morning before breakfast rather than at bedtime for GERD symptoms control. We advocate the discontinuance of PPIs in patients with classic GERD symptoms who respond to an 8-week empiric trial of PPIs. If symptoms persist beyond 8 weeks, it is advised to first evaluate adherence to the prescribed regimen and dosing. Following this assessment, the necessity for ongoing treatment should be reevaluated. For extraesophageal and typical GERD symptoms. We suggest considering a trial of twice-daily PPI therapy for 8–12 weeks. For (Los Angeles C or D) esophagitis: indefinite maintenance treatment with a PPI or surgery is recommended Patients who necessitate maintenance therapy with PPIs should receive them at the lowest effective dose. For refractory GERD we recommend the optimization of PPI therapy as the first step in the management of refractory GERD.
Esomeprazole	40 mg administered orally once daily	
Lansoprazole	30 mg administered orally once daily	
Omeprazole	20 mg administered orally once daily	
Pantoprazole	40 mg administered orally once daily	
Rabeprazole	20 mg administered orally once daily	
Immediate-release omeprazole	20 mg administered orally once daily	

1.1.8. Proton pump inhibitors' adverse effects:

Over the past few decades, there has been a notable rise in the utilization of PPIs [28]. PPIs are commonly utilized for extended periods and for indications that have not been evaluated or authorized by the Food and Drug Administration (FDA). They are commonly overprescribed, infrequently deprescribed, frequently initiated improperly during hospitalization, and used for prolonged duration even in the absence of a medical indication [30]. It's estimated that between 25% and 70% of PPI prescriptions are for improper indications [33]. PPIs are often well tolerated, with side effects occurring less frequently than 5% [34]. The most frequent side effects were nausea, diarrhea, headaches, and abdominal pain [35]. The most recent adverse effects associated with prolonged PPI use have been investigated as shown in Figure (1).

1.1.8.1. Nutritional deficiencies

1.1.8.1.1. Magnesium

Prolonged PPI treatment use has been linked to many cases of severe hypomagnesemia throughout the last ten years [36]. In 2006, hypomagnesemia was first reported as a side effect of PPI therapy [37]. It has particular clinical importance because it can lead to coexisting metabolic disorders (primarily hypocalcemia and hypokalemia), hypoparathyroidism, osteomalacia (probably from vitamin D deficiency), osteoporosis, and neuromuscular disturbances (such as tetany, seizures) as well as cardiac complications (mainly arrhythmias) [34,38]. The FDA issued a warning in 2011 that prolonged usage of PPIs could result in low

serum magnesium levels, based on case reports [39]. Additionally, the FDA noted that unless the PPI is discontinued, magnesium supplements might not be enough to treat low serum magnesium levels [40].

1.1.8.1.2. Iron

The acid present in the stomach plays an important role in facilitating the absorption of non-heme iron. It accomplishes this by liberating iron from the particles of the ingested meal and converting it from its ferric state to the more easily absorbable ferrous form [41]. Furthermore, it has been observed that gastric acid has a role in promoting the chelation process between ferrous salts and ascorbate in the stomach. These resulting chelates remain soluble in the duodenum, which has a more alkaline environment. As a result, the absorption of iron is enhanced. Prolonged use of PPIs may significantly increase the risk of developing iron deficiency anemia, however, there is very little evidence to support this [36].

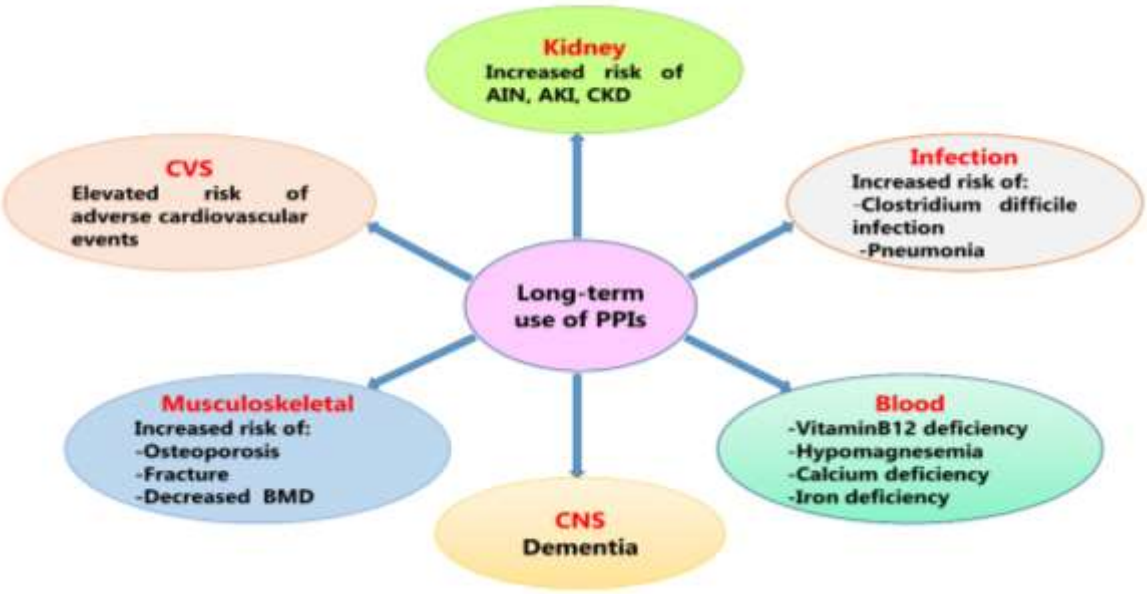

Figure 1. Adverse effects associated with long-term PPI use

1.1.8.1.3. Calcium

The majority of calcium from the diet is absorbed by the small intestine. Gastric acid is necessary for the dissolution of calcium salts in the diet, such as calcium carbonate, and facilitates the release of ionized calcium from them. In contrast, recent prospective studies have provided results indicating that there are no significant alterations in bone mineral density or fracture risk among individuals who use PPI within a relatively brief to moderate period. It is suggested that the proposed mechanisms that may explain the association between a long period of PPIs therapy and decreased bone mineral density include hypochlorhydria which impairs the absorption of calcium. Additionally, gastrin-induced parathyroid hyperplasia, and inhibition of bone resorption by blocking local H+/K+ ATPase contribute to this association [14,42-44].

1.1.8.1.4. Vitamin B12

Cobalamin, a water-soluble vitamin, has been extensively linked to dietary protein. In a typical acidic state of the stomach, the release of hydrochloric acid and pepsin facilitates the liberation of cobalamin, allowing it to associate with salivary R proteins and then transfer cobalamin to intrinsic factor (IF). The cobalamin-intrinsic factor complex subsequently increases cobalamin absorption in the distal portion of the small intestine known as the terminal ileum. It is postulated that hypochlorhydria generated by PPIs can interfere with the abovementioned absorption mechanism, leading to anemia development [45].

1.1.8.2. Infections

1.1.8.2.1. Clostridium difficile Infection

The potential of PPIs to increase the susceptibility to infection is due to their ability to

reduce stomach acidity, which could support bacterial colonization in the gastrointestinal system, [46]. A meta-analysis of 39 studies revealed that PPI users had a 74% higher probability of acquiring *Clostridium difficile* infection and a 2.5-fold increased risk of recurrent *Clostridium difficile* infection when compared to nonusers. In response to these findings, the FDA published a safety guidance in 2015, cautioning about the association between PPIs and *Clostridium difficile* infection [40].

1.1.8.2.2. Pneumonia

Decreasing the stomach PH by PPIs may promote the proliferation of aerobic bacteria in the stomach, resulting in microaspiration and lung colonization, potentially leading to pneumonia [47]. Moreover, PPIs may impair neutrophil function, raising the risk of bacterial pneumonia [9].

1.1.8.3. Cardiovascular risk

To reduce the risk of gastrointestinal bleeding, PPIs are widely used in conjunction with antiplatelet therapy. Clopidogrel, a routinely prescribed antiplatelet medicine, is transformed to the active form by liver enzymes that also metabolize PPIs, implying that competitive metabolism by PPIs may result in diminished activation of clopidogrel, reduced antiplatelet effects, and elevated risk of cardiovascular events. Indeed, pharmacologic investigations have demonstrated that the coadministration of clopidogrel with PPIs results in decreased platelet inhibition, which prompted the FDA to publish a caution against the combination of clopidogrel with PPIs in 2009 [48]. Additionally, there is a great concern that the proton pump inhibitors cause hypomagnesemia which may be linked to an increased risk of serious ventricular arrhythmia and recurrent coronary heart disease because hypomagnesemia extends QT interval [44].

1.1.8.4. Dementia

Based on the effect of PPIs on amyloid metabolism in animal models. It is proposed that PPIs use, particularly in elderly patients, is associated with an elevated risk of dementia. Indeed, PPIs promote amyloid-β and regulate its degradation by lysosomes in microglia. This causes a higher level of amyloid-β in mice brains, which is similar to the extracellular deposition of amyloid-β peptides found in the development of Alzheimer's disease. Furthermore, it was observed that patients on PPIs had a significantly greater incidence of dementia and Alzheimer's disease compared to patients not taking PPI drugs [49]. Furthermore, PPIs may impair vitamin B12 absorption, which has been linked to cognitive deterioration [50].

1.1.8.5. Bone mineral density

The precise mechanism by which PPI use causes a decrease in bone mineral density and a subsequent increase in fracture risk is currently unknown. There are various suggested mechanisms by which PPIs reduce BMD and increase the risk of fracture [56]. One of the possible biological mechanisms is the malabsorption of calcium attributed to hypochlorhydria, which then causes a negative calcium balance and subsequent hyperparathyroidism [67]. Increased secretion of parathyroid hormone (PTH) induces calcium resorption from bones by activating osteoclasts leading to an increase in bone resorption [14]. Moreover, hypochlorhydria causes hypergastrinemia, which can result in secondary hyperparathyroidism and a consequent decrease in bone mineral density [68]. Additionally, PPIs lead to decreased absorption of vitamins B6, B9, and B12, as well as hyperhomocysteinemia, which has been associated with a detrimental impact on collagenous matrix synthesis by inhibiting the lysyl oxidase enzyme. Also, PPIs inhibit osteoblast activity by affecting the activity of alkaline phosphatase enzyme [69].

1.1.8.6. Other adverse effects

The use of PPI may increase the risk of coronavirus disease 2019 (COVID-19). Patients who use these medications have a higher chance of testing positive for COVID-19 than those not taking PPIs. This relation could be explained by residual confounding [51].

1.1.8.7. Proton pump inhibitor adverse effects on the kidney:

1.1.8.7.1. Kidney diseases*:*

The nephron, which is a long and morphologically segmented tubule, is the basic functional unit of the kidney. A typical human kidney comprises around one million nephrons that consist of the glomerulus, Bowman's capsule, and a tubular system (the proximal tubule, the loop of Henle, and the distal tubule) [52]. Nephrons collaborate to sustain the major renal functions which include waste elimination from the blood, maintenance of the body's overall fluid balance, controlling of blood pH, and hormonal functions that stimulate red blood cell formation, bone health, and blood pressure regulation. Any of these functions may be impacted by the loss of a sufficient number of cells along any segment of the nephron [53].

Kidney disease can be defined as either a reduced ability to filter metabolic products (such as creatinine) or a loss of protein in the urine (proteinuria) [54]. The total amount of blood that is filtered via glomeruli is referred to as the glomerular

filtration rate (GFR) [55]. It has been established that even little abnormalities in measures of kidney structure and function have been linked to an increased risk of developing disorders in different organ systems as well as mortality, all of which occur significantly more frequently than renal failure. Duration of greater than 3 months is defined as chronic, while a duration of 3 months or fewer is termed acute [56].

Acute kidney injury (AKI), alternatively referred to as acute renal failure, is characterized by an abrupt decline in renal function or GFR, leading to azotemia and/or insufficient urine production. It is predominantly attributed to renal ischemia, nephrotoxic drugs, sepsis [57], and a reduction in effective intravascular volume. Additionally, a variety of ROS sources have been implicated in the development of AKI [58]. In which alterations in renal functions occur within one week [56].

Acute interstitial nephritis (AIN) is an instance of tubulointerstitial kidney injury mediated by the immune system. It may arise from medications, autoimmune disease, infections, and hematologic abnormalities, or as a reactive process [59]. This disorder is frequently associated with an abrupt decline in renal function and is distinguished by the presence of inflammatory infiltrates and interstitial edema [59]. In certain studies, AIN accounted for 1-3% of all renal biopsies [60]. AIN comprised 10-25% of the lesions when the study was restricted to patients with acute renal failure. According to these studies, AIN is a prevalent cause of acute renal dysfunction [61].

AIN has been estimated to contribute to approximately 8% of AKI cases [62], with drugs being responsible for 70-90% of these instances [60]. The pharmacological drug classes most commonly associated with AIN include antibiotics, PPIs, and non-steroid anti-inflammatory drugs [61,62]. PPIs are identified as the second most prevalent etiological factor contributing to drug-induced AIN (DI-AIN), accounting for 14%-64% of reported cases [45]. Currently, the exact mechanism by which PPIs induce AIN is unknown. It is possible that PPIs or their metabolites deposit inside the tubulointerstitium of the kidney where they act as a hapten or directly trigger T cells to mediate AIN [63].

Chronic kidney disease (CKD) is a condition characterized by a progressive decline in renal function over time, necessitating the use of renal replacement therapies such as hemodialysis and peritoneal dialysis in cases where it advances to end-stage renal disease (ESRD) [58].

CKD causes a decline in functioning nephrons as well as the compensation of nephron triggers. Molecular and cellular events promote compensatory growth of residual tissue, however, in certain instances, this compensatory process becomes pathological, leading to the development of renal lesions and End-stage renal disease [64]. In the clinic, the most usually estimated parameter are estimated GFR <60 ml/min, or the presence of kidney damage markers, or both, for at least 3 months [65]. It has been reported that 11–13% of the global population suffers from CKD [66]. It is often associated with diabetes and hypertension [67] and is responsible for a range of complications including cardiovascular diseases (CVDs), anemia, kidney disease deterioration, acute kidney injury, mineral and bone problems, and cognitive impairment [66]. CKD is anticipated to be the fifth greatest cause of mortality globally by 2040 [68].

The primary distinction between AKI and CKD in each of these criteria is the duration and rate of time at which renal function declined, with CKD characterized by functional and structural disturbances that persist longer than 3 months [53,69,70]. Renal morphology and function often improve as a consequence of AKI repair mechanisms, whereas CKD repair mechanisms lead to aberrant cell proliferation, cell hypertrophy, and increased extracellular matrix (ECM) accumulation [71]. Excessive deposition and accumulation of ECM results in renal fibrosis [72].

Kidney fibrosis is the most prevalent clinical characteristic and the ultimate manifestation of CKD, exhibiting morphological attributes such as glomerulosclerosis, tubule atrophy, interstitial chronic inflammation [73], and fibrogenesis, in addition to vascular rarefaction. Fibrosis occurs as a consequence of impaired wound healing, resulting in excessive deposition and accumulation of ECM [74].

Fibrotic alterations may develop in the glomerulus, which is known as glomerulosclerosis, or in the tubules, which is known as tubulointerstitial fibrosis. Notably, glomerulosclerosis and tubulointerstitial manifest similar biological alterations that include the depletion of epithelial cells and their associated vascular capillary bed, as well as the upregulation of activated myofibroblasts, extracellular matrix, and inflammatory cells [75]. This serious outcome is typically the result of both underlying complicated cellular processes such as epithelial-to-mesenchymal transition, fibroblast activation, monocyte-macrophage infiltration, and cellular apoptosis, as well as the activation of signaling molecules such as transforming growth factor beta (TGFβ) and angiotensin II [76].

The activation of myofibroblast and the subsequent ECM buildup are instances of significance in kidney fibrosis[72]. The principal molecules and cells associated with the progression of renal fibrosis and their activity in the biological process of renal fibrotic development, including the Ang II, TGFβ, connective tissue growth factor (CTGF), plasminogen activator inhibitor-1 (PAI1), nuclear factor-κB (NF-κB), fibroblasts, and proteins[76].

1.1.8.7.2. Proton pump inhibitor (PPI) induced kidney diseases:

Omeprazole-induced AIN was initially reported in 1992 [77], and other cases of AIN due to omeprazole have been documented since then. Pantoprazole-induced AIN was first published in 2004 [78], and rabeprazole-induced AIN was first reported in 2005 by Geevasinga [59]. It is postulated that PPIs-induced AIN may result from an allergic response to the medicine or one of its metabolites. These substances might potentially accumulate in the renal tubulointerstitium and function as haptens, or directly stimulate T-cells, leading to the development of AIN [77]. AIN is difficult to identify since the symptoms are nonspecific, such as oliguria, lethargy, anorexia, nausea, and vomiting [78,79]. PPIs are now known to be one of the main global causes of drug-induced AIN [27]. The most prevalent adverse renal consequence is AIN [80].

The interval between initiating PPI medications and the onset of clinical AIN is quite varied. In published cases, the symptoms often appear anywhere from 1 week to 9 months after the first exposure to PPIs, with the mean delay to clinical manifestation in instances that have been documented is 9.9 weeks [81]. It has been documented that 30-70% of the patients who suffer from drug-induced AIN have insufficient recovery of the renal function allowing the inflammatory tubulointerstitial process to advance to chronic irreversible interstitial fibrosis over time, which might develop CKD and eventually ESRD [82,83].

One potential contributing factor to the onset of chronic interstitial nephritis in patients with PPIs-induced AIN is the possibility of a delayed or inaccurate diagnosis resulting from the presence of atypical clinical symptoms associated with allergic reactions generated by PPIs usage. Due to the protracted duration required for establishing a diagnosis of AIN after the onset of symptoms, certain individuals unavoidably develop chronic renal interstitial fibrosis before the initiation of treatment. [77].

The mechanisms underlying the links between PPIs usage and AKI could be interstitial nephritis [4]. The majority of AKI episodes have been identified as AIN. AKI has been correlated with the development of CKD and progression to ESRD [82]. The utilization of PPIs may present a plausible risk factor for the development of CKD, potentially through recurring AKI. The precise mechanism underlying this correlation remains unclear; however, the potential factors that may contribute to this association encompass the development of acute interstitial nephritis, which is an immune-mediated response that can precipitate a reduction in glomerular filtration rate and adverse renal consequences [84]. Other proposed hypotheses include suppression of the lysosomal proton pump, thereby impairing endothelial lysosomal acidification and enzyme function, a decrease in nitric oxide formation, and an increase in superoxide anion production. These can result in decreased endothelial proliferation and angiogenesis as well as accelerated endothelial aging [84,85], or hypomagnesemia which may cause endothelial dysfunction [82,86] by inducing pro-inflammatory and pro-atherogenic events [85]. as shown in figure (2).

2. CONCLUSIONS

PPIs are a group of drugs that have extensive global utilization. They are commonly employed in the management of several acid-related disorders. Among the different types of acid-suppressing drugs, PPIs were found to be the preferred and principal option of treatment. These agents were deemed to be safe when given rationally and utilized according to the physician's instructions. The use of this class of antisecretory drugs for a short time has been authorized by the FDA and subsequently prevented their usage for extended periods. Usually, short-term PPIs treatment at the recommended doses does not pose any adverse effects or potential hazards. Evidence currently available indicates that the use of PPIs is linked to an increased risk of both acute and chronic kidney disease, hypomagnesemia, *C difficile* infection, and osteoporotic fractures. So it is necessary to monitor serum creatinine and magnesium levels in patients using PPIs, especially those using high doses.

Furthermore, it is imperative to give careful consideration to extended courses of PPI prescriptions, particularly in geriatric individuals with substantial comorbidities and concurrent administration of multidrug treatments. Finally, PPI drugs should be used with caution, and with a clear clinical indication. The benefits yielded by PPIs must be monitored, and drug therapy must be terminated immediately as it is no longer required.

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List of Abbreviations: PPIs; Proton pump inhibitors, **CKD**; Chronic kidney disease, **OME**; Omeprazole, **H+/K+ ATPase**; Hydrogen potassium adenosine triphosphatase, **GFR**; Glomerular filtration rate, **AKI**; Acute kidney injury, **ECM**; Extracellular matrix, **AIN**; Acute interstitial nephritis.

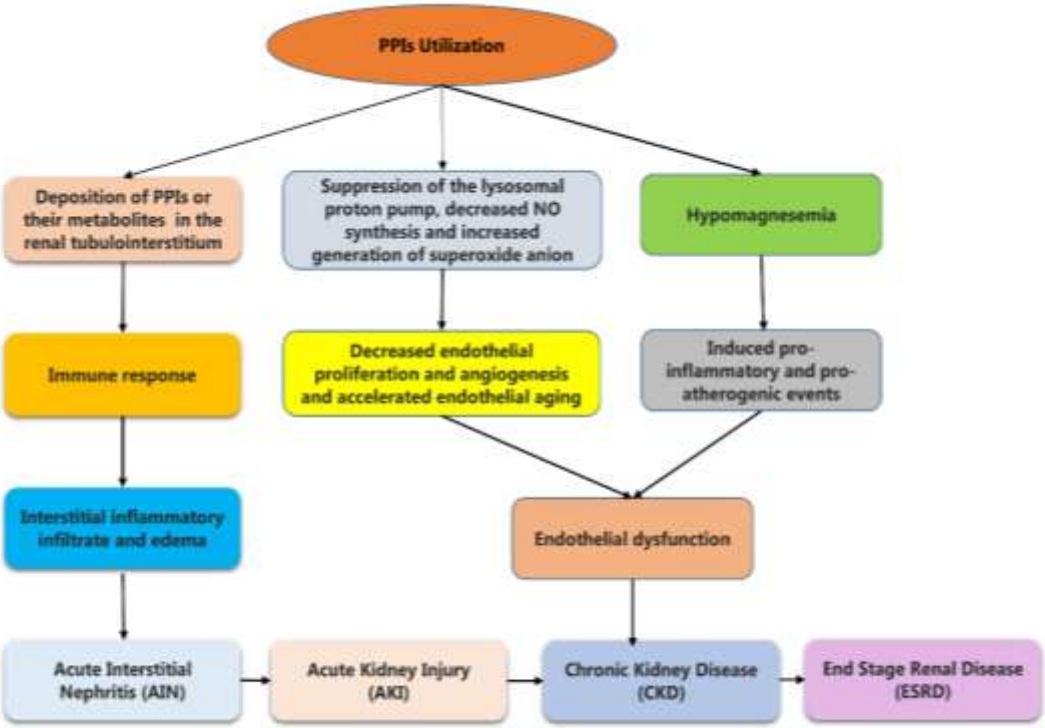

Figure 2. Hypothesis elucidating the probable association between PPIs and kidney disease

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