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REVIEW ARTICLE

Incidence, Pathogenesis, and Management of Proton Pump Inhibitor-Induced Nephrotoxicity

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Abstract

Proton pump inhibitors are widely used in the treatment of various acid-related diseases and are among the most commonly used drugs. Studies estimate that 25–70% of proton pump inhibitors are prescribed for inappropriate treatments, doses, and indications, where the benefits of proton pump inhibitor use may be less than the risk of adverse drug reactions for many patients. Acute interstitial nephritis is an immune-mediated atypical kidney injury in the long-term use of proton pump inhibitors that causes problems for clinicians and patients. In this review, we summarize the current knowledge of proton pump inhibitors inducing acute interstitial nephritis, chronic kidney disease, and even end-stage renal disease in terms of incidence, pathogenesis, factors, clinical features, and diagnosis. We discuss how these factors change under conditions of acute interstitial nephritis, chronic kidney disease, and end-stage renal disease. The purpose of this review is to assess the current evidence to help clinicians and patients interpret the potential causal relationship between proton pump inhibitor intake and nephrotoxicity. This prompts clinicians to consider the appropriate dose and duration of proton pump inhibitor therapy to avoid inappropriate use.

Key Points

Proton pump inhibitors are typical drugs for digestive system diseases, and their nephrotoxicity should be given special attention by clinicians and patients.

This article discusses the incidence of proton pump inhibitors inducing acute interstitial nephritis, chronic kidney disease, and end-stage renal disease, mechanisms, clinical manifestation and treatment, and influencing factors.

We explain the potential causal relationship between proton pump inhibitor intake and nephrotoxicity for prevention or treatment to delay the progression of proton pump inhibitor nephrotoxicity.

1 Introduction

Proton pump inhibitors (PPIs), also known as H^+/K^+-ATPase inhibitors, specifically bind H^+/K^+-ATPase on the secretory surface of parietal cells and reduce the secretion of

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gastric acid. PPIs are widely used in the treatment of various acid-related diseases, such as peptic ulcers, gastroesophageal reflux disease, and upper gastrointestinal bleeding. PPIs are among the most commonly used drugs in the world. The clinically used PPIs are omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole. It was found that there were more than 43 million prescriptions for anti-ulcer treatments in 2005 in the USA, totaling more than 8 billion dollars spent on PPIs [1]. However, the number continues to grow. In 2013, it was estimated that at least 15 million Americans used prescription PPIs, with 164 million prescriptions and annual sales of more than 10 billion dollars [2]. In addition, a survey found that the global PPI market size was estimated to be more than 13 billion dollars in 2020. PPIs are widely used in clinical applications because they have greatly improved our approach to acid-related diseases, while their efficacy and safety are recognized.

However, the expanding PPI market has raised many concerns about the potential for inappropriate prescribing. Research estimates that between 25 and 70% of PPI prescriptions are for inappropriate therapies, doses, and indications, of which the benefits of PPI use may be less than the risk of adverse drug reactions (ADRs) for many patients [3]. This unreasonable recent phenomenon has not significantly improved [4–6]. A growing number of reports have linked the long-term use of PPIs to serious ADRs, including gastric carcinoid, hip fracture, hypomagnesemia, nutritional deficiencies, cardiovascular events, intestinal infections, and especially kidney injury [7–9]. Acute interstitial nephritis (AIN) is an immune-mediated kidney injury characterized by acute tubulointerstitial inflammation and accounts for approximately one-quarter of all cases of acute kidney injury (AKI) [10]. Among the various etiologies of AIN, specific drug reactions are the most important. Although many patients will recover renal function after drug discontinuation, some will develop chronic kidney disease (CKD) or even end-stage renal disease (ESRD) [11]. As the timely identification and discontinuation of drugs is the cornerstone of managing drug-related kidney injury, identification of causative drugs is crucial.

In 1992, Ruffenach et al.'s team reported the first case of AIN caused by omeprazole [12]. Since then, cases of other PPIs inducing AIN (PPIs-AIN) have been reported. In addition to inducing AIN, there is an association between PPIs and a high risk of developing CKD, or even progression to ESRD [8, 13]. The specific mechanism of PPI-induced nephrotoxicity is not well clarified. Furthermore, the symptoms of PPIs-AIN are atypical. Therefore, systematic recognition of PPI nephrotoxicity is the key to early clinical diagnosis.

In this review, we summarize the current knowledge of PPIs-AIN, CKD, and ESRD in terms of incidence, pathogenesis, factors, clinical features, and diagnosis. We discuss how these factors change under conditions of AIN, CKD, and ESRD. Furthermore, we focus on delineating the role of effective therapeutic drugs in this disease. In summary, we discuss the role of PPIs in AIN, CKD, and ESRD, providing strategies and ideas for understanding the pathogenesis of PPI nephrotoxicity. This review aims to improve clinicians' understanding of PPIs and promote their rational clinical application.

2 Methods

The purpose of this review was to analyze the relationship between PPIs and nephrotoxicity. The PubMed databases were searched for this purpose using the following subject terms: proton pump inhibitors, nephrotoxicity, acute kidney injury, acute interstitial nephritis, chronic kidney disease, and end-stage renal disease. Article types included all original research, clinical trials, meta-analyses, randomized studies, case reports, and reviews from 1998 to 2022. We reviewed drug safety information published by the US Food and Drug Administration, the European Medicines Agency, and the National Medical Products Administration of China. We also refereed the annual data report of the United States Renal Data System and the Global Proton Pump Inhibitors Market Status and Future Trends Report 2021. Only publications related to PPIs and nephrotoxicity are included and discussed in this article. By reading each article, poorly relevant and unsuitable articles were excluded.

3 PPIs-AIN

3.1 Mechanism of PPI Inhibition of Gastric Acid

PPIs are mostly weakly acidic benzimidazoles that are rapidly transported to the gastric lining cells after absorption in the intestine. They are then converted to hyposulfite and sulfenamide, which covalently bind to H^+-K^+-ATPase to inactivate it and inhibit gastric acid secretion (Fig. 1) [14]. As PPIs bind irreversibly to H^+-K^+-ATPase, they have a strong effect in inhibiting gastric acid secretion. The clinical use of PPIs has been extended to all diseases in which gastric acid is a major contributor. In addition, PPI therapy solves previously unmet needs, such as the healing and prevention of peptic ulcers [15].

3.2 Mechanism of PPIs-AIN

The occurrence of AIN does not appear to be significantly positively correlated with the duration of patient exposure to PPIs, suggesting that more than one pathophysiological pathway may be involved in PPIs-AIN [16]. The first

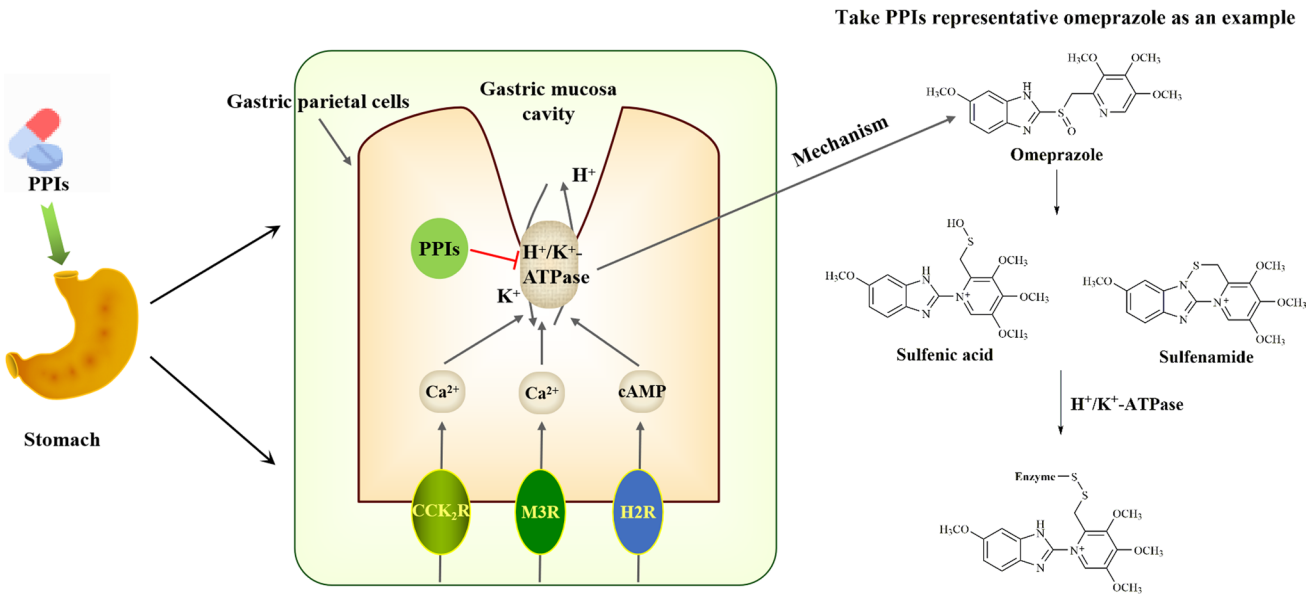

Fig. 1 Mechanism of proton pump inhibitors (PPIs) inhibition of gastric acid. *cAMP* cyclic adenosine monophosphate, *CCK2R* cholecystokinin 2 receptor, *H2R* histamine 2 receptor, *M3R* muscarinic acetylcholine 3 receptor

case report of PPIs-AIN was a 74-year-old woman taking omeprazole for recurrent oesophageal ulcers for 6 months, accompanied by general malaise and a five-fold to six-fold increase in blood urea nitrogen (BUN) and serum creatinine (SCr), from AIN [12]. Since then, other PPIs-AIN have been reported to confirm this association [17–19]. In 2015, the results from a cohort study of more than 290,000 individuals showed that people treated with PPIs had an increased risk of AIN with an incidence of approximately 0.32 per 1000 person-years in people over 66 years of age [10]. This would seem to be a class effect, as all PPIs were found to cause AIN. The pathogenic mechanism of PPIs-AIN has not been fully elucidated, and most researchers believe that it is a specific immune-mediated response [18–21]. PPIs can induce an immune response in different ways leading to AIN. One mechanism suggests that PPIs and/or their metabolites may be deposited in the renal tubular interstitium and bind to normal components of the tubular basement membrane, acting as semi-antigens or directly stimulating T cells to mediate AIN [18, 21, 22]. Another view is that PPIs can cause antibody production and deposition in the renal interstitium as circulating immune complexes, causing the immune complex AIN (Fig. 2).

In addition to being a mechanism for antigen deposition in the tubular basement membrane to induce AIN, the direct toxicity of PPIs and/or their metabolites lead to the problem of interstitial inflammatory response. It may be that the renal interstitium is more susceptible to damage in the elderly because their peritubular blood flow is compromised, allowing a longer time for an interaction between the PPIs and the interstitium [16]. Other viewpoints suggest that macrophages activated by PPIs in the renal interstitium can release proteolytic enzymes, reactive oxygen species, reactive nitrogen species, and inducible nitric oxide synthase through a non-antigen-specific immune response, which exacerbates the progression of AIN [23].

3.3 Clinical Pathological Features and Diagnosis

The onset of AIN is usually insidious, and patients present with acute renal failure that improves after discontinuation of PPIs. The period from initiation of treatment with PPIs to clinical diagnosis of AIN is large. In reported cases, there was diagnosis of AIN after 2.7 months of treatment with an average of 20–40 mg of omeprazole per day [24]. The first patient diagnosed with PPIs-AIN was found to have a Wright's stain of urine sediment showing 6% eosinophils and a five-fold to six-fold increase in SCr, BUN, and 24-h urine protein. This was accompanied by increased general malaise, fatigue, and anorexia [12]. A report of 15 cases of AIN associated with PPIs was identified by the Greater Auckland Renal Service between 2002 and 2005 [16]. The Simpson research team summarized the clinical diagnostic highlights of PPIs-AIN and found that patients had a mean age of 78 years, a baseline SCr level of 83 $\mu mol \cdot L^{-1}$, a peak level of 392 $\mu mol \cdot L^{-1}$, and a recovery level of 139 $\mu mol \cdot L^{-1}$. Some patients present with an acute systemic allergic reaction with both an elevated erythrocyte sedimentation rate and C-reactive protein levels. However, many patients are non-symptomatic with renal failure initially. These

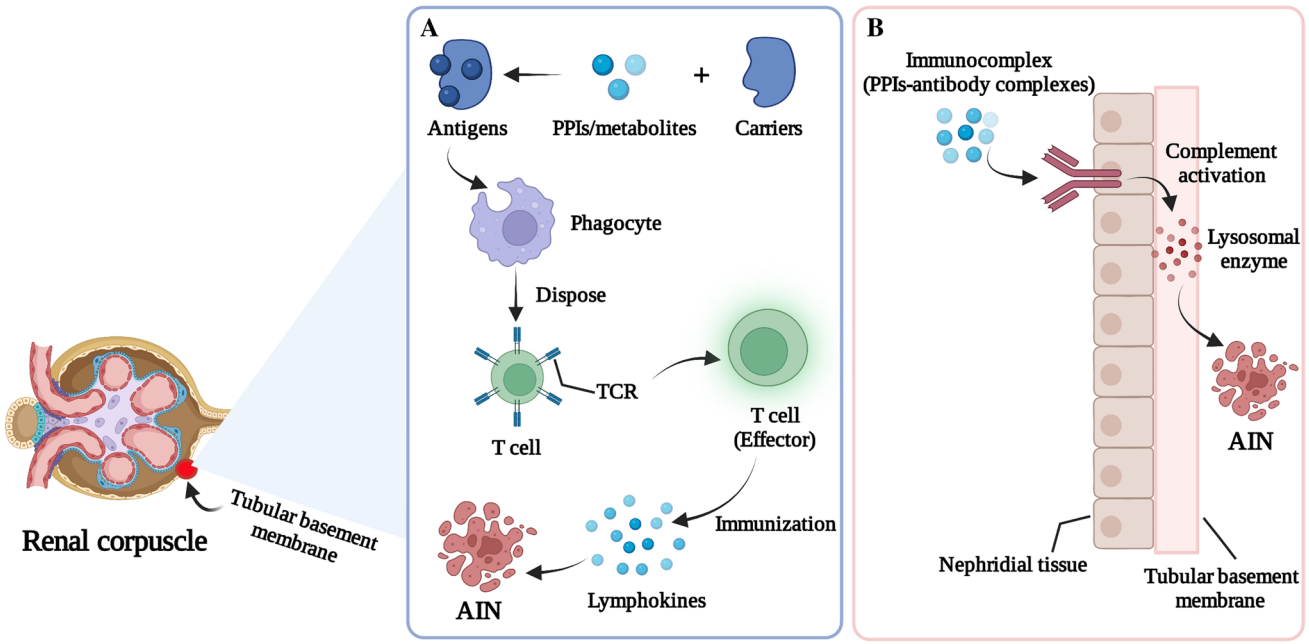

Fig. 2 Mechanism of proton pump inhibitors inducing acute interstitial nephritis (PPIs-AIN). **A** PPIs and/or their metabolites bind to carriers as semi-antigens and induce cellular immune responses, leading to AIN. **B** PPIs and/or their metabolites may be deposited in the renal tubular interstitium and bind to the tubular basement membrane, acting as semi-antigens or directly stimulating T cells to mediate AIN. *TCR* T-cell receptor

observations also have limitations, such as the number of cases, populations, and regions.

3.4 Clinical Manifestations

The diagnosis of drug-induced AIN becomes apparent when a triad of hypersensitivity reactions such as rash, fever, and eosinophilia occur within a few days after the initiation of typical drugs such as methicillin and penicillin derivatives [25, 26]. However, these findings occur in 10% of patients, and the onset of AIN may be delayed for weeks or months after the start of PPI administration [27]. As such, patients with PPIs-AIN are older, less symptomatic, have longer drug exposure, and have longer delays in receiving renal biopsies and steroids. When evaluating renal function in patients in the setting of PPI administration, clinicians must be aware that AIN may occur long after drug exposure. If there is no other obvious trigger or a gradual unexplained increase in SCr over weeks or months, then clinicians should consider the possibility of PPIs-AIN and examine the symptomatic onset of AIN upon reintroduction if a PPI is on the medication list [21, 28].

In addition to the above-mentioned patients who experienced triple allergic reactions, symptoms of PPIs-AIN are non-specific, such as nausea, vomiting, backache, fever, and weight loss. These presentations highlight the complexity of the diagnosis of PPIs-AIN. In particular, drugs associated with AIN are common in coprescription, such as penicillin, cephalosporins, and nonsteroidal anti-inflammatory drugs [19, 29]. However, urine tests such as urine volume, uroscopy, urine chemistry, urinalysis for eosinophiluria, leukocyte tubular pattern, and urine sediment are often used in the hope that AIN can be differentiated from other causes of kidney injury [25]. Ultimately, a kidney biopsy is required to make an accurate diagnosis and guide treatment for patients with PPIs-AIN. A renal biopsy showed typical PPIs-AIN manifestations with mixed interstitial lymphoid and plasma cell infiltration with tubular injury, and eosinophils were present in 83% of the biopsy specimens [19, 20, 29]. In addition to clinical symptoms and a kidney biopsy, laboratory tests are essential in PPIs-AIN. As the available case reports are based on regional surveys and individual cases, here we only suggest tests and their limitations in the diagnosis of PPIs-AIN for clinicians to accurately diagnose.

3.5 Drug Therapy and Prognosis

The immune mechanism of PPIs-AIN supports the use of steroids as an effective treatment option, which can dissolve T-cell infiltration and improve renal function [30]. The primary treatment for PPIs-AIN is discontinuation, which can be a challenging task for patients receiving multiple medications. Torpey et al. [31] retrospectively analyzed eight patients with biopsy-proven PPIs-AIN at Norfolk and Norwich University Hospital between 1995 and 1999. Among these eight patients, seven of them were given

oral corticosteroid therapy, in addition to discontinuation of PPIs. Treatment was performed with 0.5 $mg \cdot kg^{-1}$ body weight prednisolone until SCr was stabilized, followed by a gradual reduction to zero after 2–3 months. When patients with AIN present with symptoms such as recurrent vomiting, back pain, oliguria, SCr, and BUN, more than four-fold elevated (e.g., SCr ≥ 4.9 $mg \cdot dL^{-1}$ and BUN ≥ 76 $mg \cdot dL^{-1}$), depending on the individual patient, PPI discontinuation, hemodialysis treatment, intravenous methylprednisolone 10 $mg \cdot kg^{-1}$ for 3 days, followed by oral prednisolone 1 $mg \cdot kg^{-1}$ gradually reduced to 0.5 $mg \cdot kg^{-1}$ for 8–12 weeks are recommended [19, 32]. In addition to kidney recovery treatment, a positive urine bacterial culture should be given corresponding antibiotic treatment. Furthermore, it was found that there was no difference in remission between elderly and younger people treated with steroids [26].

3.6 Influencing Factors

We have suggested that the use of PPIs can be associated with an increased risk of AIN or AKI. In particular, an interrelationship between the use of PPIs and the pathogenesis of AIN has been proposed in several large observational studies. Recently, PPI use was an independent risk factor for the development of immune checkpoint inhibitor-induced AIN in a multicenter retrospective cohort study. This implies that the use of other drugs while taking PPIs increases the risk of AIN in patients [33, 34]. A nested case–control study found that the combination of nonsteroidal anti-inflammatory drugs with PPIs significantly increased the risk of AIN. In addition, concomitant use of cephalosporins or fluoroquinolones was associated with an increased risk of AKI in patients taking PPIs [35]. Disease status can also influence the risk of PPIs-AIN. A national cohort study supports a two-fold increased risk of AKI in patients with acquired immunodeficiency syndrome receiving PPIs compared with healthy individuals [36]. The use of PPIs in patients with rheumatoid arthritis is also associated with an increased risk of AKI [37]. Furthermore, PPI use in renal transplant recipients is associated with a 1.56-fold increased risk of hypomagnesemia [9]. In conclusion, these findings may help in clinical decision making when considering the risks and benefits of PPIs for the treatment of related diseases.

4 PPIs-CKD

CKD is a condition caused by a progressive decline in renal function, which is defined by a sustained estimated glomerular filtration rate (eGFR) < 60 $mL \cdot min^{-1}$ per 1.73 m^2 (> 3 months) or the development of ESRD [38]. As already discussed, early identification and PPI withdrawal and possibly early steroid treatment may lead to a better prognosis for PPIs-AIN. Although renal function indicators, such as SCr, BUN, and eGFR, improved after PPI discontinuation or steroid treatment, renal function did not return to baseline levels before PPIs-AIN [16, 29, 31]. This implies CKD is a potential complication and risk factor for PPIs-AIN. In severe conditions (based on eGFR levels), ESRD requires long-term renal replacement therapy (Fig. 3). In a prospective community-based cohort study of over 10,000 adults, the association between the use of PPIs and the incidence of CKD was quantified. Lazarus et al. [8] found that, after adjusting for several potential confounding variables (including demographics, socioeconomic status, clinical measures, and prevalent comorbidities), baseline use of PPIs was independently associated with a 20–50% increased risk of developing CKD (hazard ratio, 1.50; 95% confidence interval [CI] 1.14–1.96).

4.1 Mechanism

Regarding the progression of AKI to CKD, several mechanisms have been proposed. It is generally believed that interstitial fibrosis does not return to a quiescent state and persists after the AKI trigger is treated, involving a process known as maladaptive repair that develops into chronic interstitial scarring and tubular atrophy, which contributes to the development of CKD (Fig. 3) [39, 40]. An exception to the mechanism of fibrosis, Rudler et al. [41] proposed that the spontaneous breakdown product of PPIs, 2-mercaptobenzimidazoles may be one of the mechanisms leading to the progression of CKD. 2-Mercaptobenzimidazoles are antioxidant endocrine disruptors with impaired renal clearance, tubular atrophy, and renal mineralization effects, which accumulate over time and thus cause nephrotoxicity [42]. Further studies found that administration of PPIs bound and inhibited dimethylarginine catabolic enzymes, increased plasma dimethylarginine levels, and decreased nitric oxide levels and endothelium-dependent vasodilation in mouse models and isolated human tissues. This observation provides a plausible biological mechanism to explain the observed association of PPI treatment with increased major adverse cardiovascular events in patients with acute coronary syndrome [8, 43]. Last, but not least, long-term PPI use causes a decrease in gastric acid, and alterations in the gut microbiota and translocation of endotoxins into the circulation may be associated with uremic toxicity, inflammation, and progression of CKD [44]. For example, the ADR of PPI *Clostridium difficile*-induced intestinal infections.

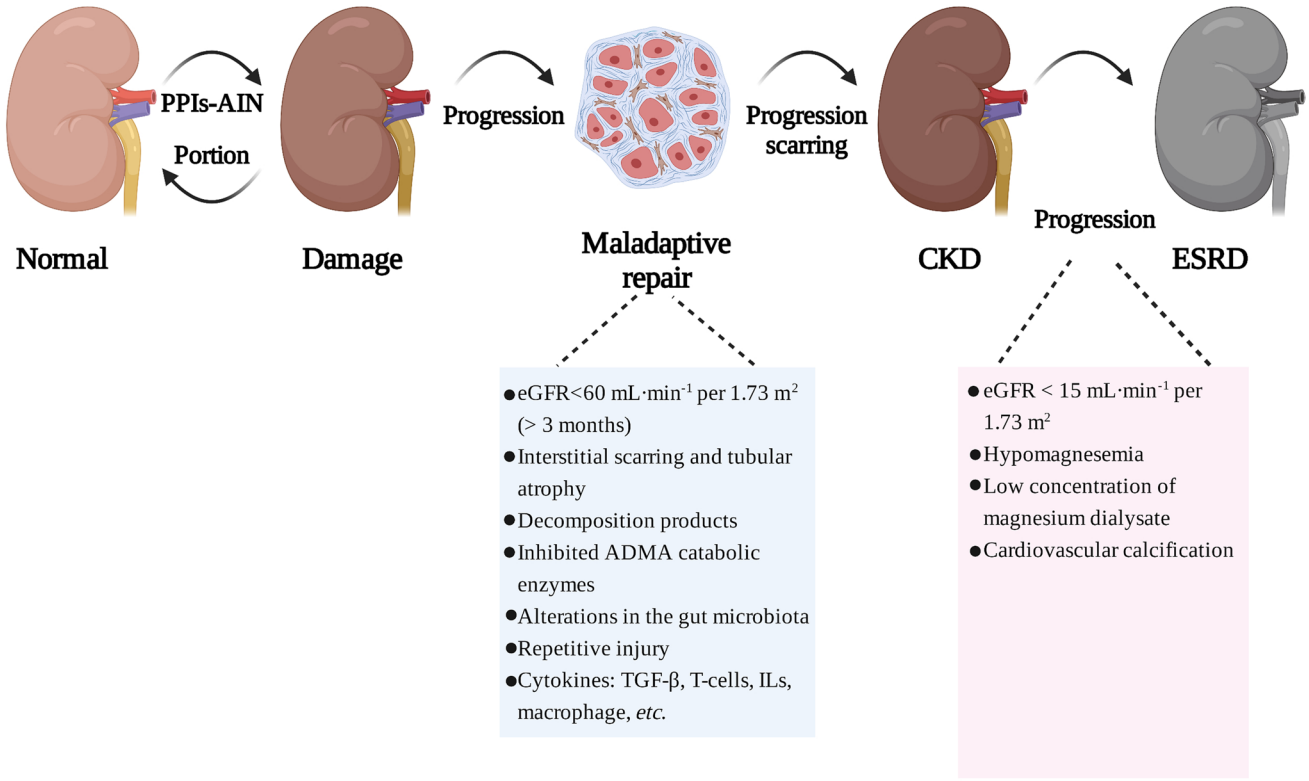

Fig. 3 Factors and mechanisms underlying the progression of proton pump inhibitors (PPIs) in nephrotoxicity. Interstitial fibrosis does not return to a quiescent state and persists after acute kidney injury-triggered therapy, although it partially returns to normal. This involves a process called maladaptive repair that develops into chronic interstitial scarring and tubular atrophy, influenced by a variety of factors that contribute to the development of chronic kidney disease (CKD). Severe cases can develop into end-stage renal disease (ESRD). *ADMA* dimethylarginine, *AIN* acute interstitial nephritis, *eGFR* estimated glomerular filtration rate, *ILs* interleukins, *TGF-β* transforming growth

4.2 Clinical Manifestations

Because of the widespread use of PPIs, the causal relationship between PPI and CKD may have considerable public health implications [45, 46]. A US Department of Veterans Affairs national database (n = 20,270) also found an association between PPIs and CKD and ESRD, which correlated with an increasing duration of PPI exposure [13]. An analysis of 15 cases diagnosed with PPIs-AIN at Renal Services in Auckland found the recovery of AIN after PPI discontinuation, but it was usually incomplete [16]. An increase in baseline SCr levels from 0.94 mg·dL^{-1} to 1.57 mg·dL^{-1} was observed 3–18 months after PPI discontinuation. The eGFR range was 29–86 mL·min^{-1} per 1.73 m^2. Similarly, four patients with PPIs-AIN were described by Sampathkumar et al. Two of them had only partial recovery of renal function after 6 months to 1 year of treatment, with an SCr of 1.6 mg·dL^{-1} [19]. PPI induced long-term AIN develops into CKD, which manifests as inflammatory interstitial infiltration and edema developing into chronic interstitial scarring and renal tubular atrophy.

4.3 Influencing Factors

In addition to incomplete recovery of renal function after PPIs-AIN treatment, CKD progression is influenced by many factors. First, we examined the dose, duration of treatment, and timing of steroid intervention. High-dose PPI use increases the risk of CKD [47]. Twice-daily doses of PPIs were associated with a higher risk of CKD than once-daily doses of PPIs [8]. Longer PPI exposure times such as 15, 30, and 130 days corresponded to significant differences between complete, partial, and no recovery of kidney function, respectively. There was a longer delay in steroid treatment initiation, with significant differences between 8, 11, and 35 days [20]. In particular, PPI exposure times > 3 months [47]. In addition, there was a significant correlation between scheduled omeprazole use and the stage of CKD progression in adult and elderly individuals [48]. However, episodes of AKI (mainly mediated by PPIs-AIN) culminated in CKD in less than half of cases. Unknown confounding factors may explain the increase in patients with CKD who took PPIs.

The Atherosclerosis Risk in Communities (ARIC) cohort study by Lazarus et al. [8] found an elevated hazard ratio for the risk of CKD from 1.45 (95% CI 1.11–1.90) to 1.50 (95% CI 1.14–1.96) in participants using PPIs compared with unadjusted analyses, after correcting for potential confounders. In a similar ARIC cohort study, Haring et al. found that the consumption of red and processed meats was associated with an increased risk of CKD (hazard ratio, 1.23; 95% CI 1.06–1.42) [49]. The consumption of red meat is associated with the indications for PPIs, including gastroesophageal reflux disease, duodenal ulcer, and *Helicobacter pylori* [50, 51]. Therefore, it is reasonable to assume that patients with a high consumption of red meat are more likely to use PPIs and should be concerned about dietary structure in PPIs-CKD. Furthermore, PPI induced hypomagnesemia may be a mediator of CKD progression by the mechanism that PPIs interfere with the active transport of magnesium and aggravate vascular calcification in patients with CKD [52–54]. Serum zinc concentrations appear to increase the risk of infection in patients with PPIs-CKD, but the role of zinc in the progression of CKD requires further investigation [55]. In the Taiwanese population in China, the use of PPIs was associated with a 1.52-fold increased risk of CKD in diabetic patients when the annual dose exceeded 180 defined daily doses [56].

In summary, numerous population-based cohort observational studies have found a correlation between PPI use and CKD progression, with possible mechanisms being the development of interstitial fibrosis, PPI breakdown products, and dimethylarginine catabolic enzymes. Considering the impact of multiple factors on PPIs-CKD, monitoring of patient disease history and the composition of prescribed medications should be enhanced, as should routine monitoring of eGFR after PPI discontinuation to ensure appropriate CKD care and alert people to the potential renal risk in patients with CKD. It may be time to consider limiting the use of PPIs in patients with CKD in the absence of an approved indication for their use, potentially reducing the burden on patients with CKD.

5 PPIs-ESRD

ESRD refers to the end stage (stage 5) of CKD and is diagnosed when eGFR is < 15 mL·min^{-1} per 1.73 m^2 [57]. As patients with ESRD have a low eGFR, they have to rely on regular hemodialysis to keep them alive, and the cost of dialysis is huge for the patients and their families as well as the government. In the US Renal Data System, annual data for 2021 reported that, in 2019, the incidence of ESRD was 373 per million people, 85% of patients with ESRD started central hemodialysis, 130,400 people were newly diagnosed with ESRD, and the mortality rate was 156.6 per 1000 person-years [58].

5.1 Mechanism

As mentioned above, patients with CKD have a degree of probability of developing ESRD. These findings raise significant concerns for people who are regularly and consistently treated with PPIs for extended periods. A controlled study from Taiwan's Health Insurance Research Database found that the use of PPIs was associated with a significantly higher risk of ESRD in 3,808 patients with kidney disease at 4 years of follow-up (adjusted odds ratio, 1.88; 95% CI 1.71–2.06) [59]. Another retrospective study found that eGFR levels did not significantly increase in patients with CKD, even when PPIs were discontinued for 1 year and remained at CKD stage levels, suggesting that PPI-CKD-ESRD progression is not reversed by discontinuing PPIs and that other treatments are needed [60]. In addition to the mechanisms of PPIs-CKD mentioned in Sect. 3, some PPIs-ESRD mechanisms have been proposed, although the mechanisms are less studied.

5.2 Influencing Factors

Hypomagnesemia may be an important factor associated with the development of CKD. A recent study found that hypomagnesemia may be associated with higher overall mortality in patients with ESRD requiring dialysis [61–63]. In view of this, the focus of this section is on the role and mechanisms of hypomagnesemia in PPIs-ESRD. Hypomagnesemia is one of the ADRs of long-term use of PPIs, especially in patients with ESRD with low magnesium dialysate (0.4–0.5 mEq·L^{-1} [Mg]), with an incidence of approximately 33%. The mechanism affects intestinal magnesium absorption by interfering with the active transport of transient receptor potential melastatin 6/7 channels, with major clinical consequences, including electrolyte and potassium level imbalances, and neuromuscular and cardiovascular diseases [64, 65]. Supporting this finding is the predictable demonstration of reduced urinary magnesium excretion in PPI users, indicating chronic subclinical depletion in this population [66]. In addition, in 2011, the US Food and Drug Administration confirmed the association between long-term use of PPIs and hypomagnesemia in a Drug Safety Communication. Hypomagnesemia is an important risk factor for mortality in patients with ESRD. The study found that after adjusting for various demographic factors and laboratory data, the COX regression model showed that type 2 diabetic patients with hypomagnesemia had a higher risk of ESRD than the high-magnesium group (hazard ratio, 2.12; 95% CI 1.28–3.51; $p = 0.004$) [61, 67]. Research shows that hypomagnesemia reduces blood phosphorus and delays

the production of hydroxyapatite crystals through a passive pathway, and also participates in the osteogenic transformation of vascular smooth muscle cells through an active pathway, promoting the development of cardiovascular calcification in patients with CKD-ESRD [68]. Because of the ADR of PPI induced hypomagnesemia, adjustment of PPI dosing could be recommended for patients with ESRD who are undergoing hemodialysis.

Early intervention has an important role in ESRD. In the absence of intervention for AIN/AKI, long-term use of PPIs was significantly associated with the risk of CKD and the risk of developing ESRD. Even in the absence of AIN/AKI, wariness about the use of PPIs and careful attention to the renal function of PPI users may be a reasonable approach [69]. Patients with kidney disease requiring long-term PPIs should be considered for on-demand or intermittent treatment.

6 Conclusions and Future Perspectives

This review focuses on the mechanism, pathological features, diagnosis, clinical manifestations, pharmacological treatment, and influencing factors of PPIs-AIN; lists and discusses the currently available research results; and outlines the association of PPIs-AIN through cohort studies, observational studies, or retrospective analysis, which deserve further research and attention. Furthermore, this article discusses the incidence of progression of PPIs-AIN to CKD and ESRD, mechanisms of deterioration, clinical treatment, and influencing factors and then emphasizes the persistence of PPIs on nephrotoxicity, which requires special attention and reference by clinicians and patients in the long-term use of PPIs to enhance renal function monitoring and avoid the deterioration of kidney disease.

Although the medical value of PPIs is undeniable, their efficacy and good safety profile have seen a rapid increase in their use since their introduction to the market, which has led to one of the reasons for their overuse and misuse. Even though the US Food and Drug Administration has approved PPIs as safe for short-term treatment only, they are often used for even minor indigestion, leading to long-term use. The best current strategy to mitigate the potential risk of long-term PPIs is to avoid prescribing them when they are not indicated and to reduce them to a minimal dose when they are indicated [44]. For patients prescribed medications with known nephrotoxicity, CKD guidelines recommend monitoring eGFR at least once a year. As mentioned in this review of the role of PPIs in AIN, CKD progression, and exacerbation of ESRD, it is emphasized that awareness of the risk of PPI nephrotoxicity should not lead to patient anxiety but should prompt clinicians to consider the appropriate dose and duration of PPI therapy, including long-term monitoring strategies for patients based on their comorbidities and risk factors. Additionally, patients with valid indications for PPI therapy should not be denied PPI therapy because of a concern for nephrotoxicity [70].

In conclusion, the diagnosis of nephrotoxicity induced by PPIs currently relies exclusively on strong clinical suspicion followed by a renal biopsy. The purpose of this review is to assess the current evidence to help clinicians and patient providers critically evaluate the plethora of publications and to guide them in interpreting the potential causal relationship between PPI intake and nephrotoxicity. Elucidating the mechanism behind this association is essential for implementing prevention or treatment to delay the progression of PPI nephrotoxicity. This mechanism has not yet been fully elucidated and remains to be discovered by research.

Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Code availability Not applicable.

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