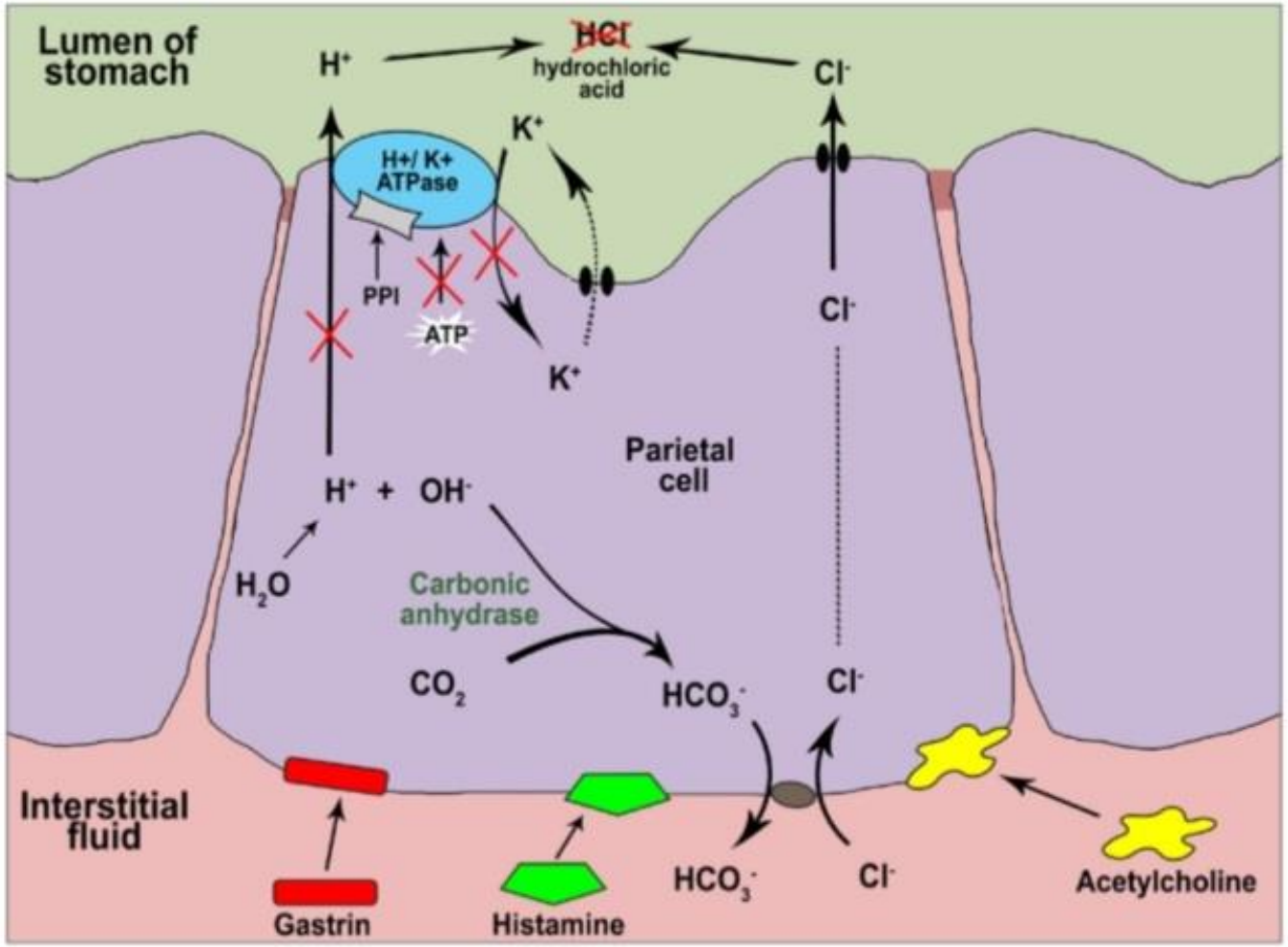
Proton Pump Inhibitors(PPIs) and The kidney

Ali sadoogh abbasian,MD,nephrologist

Arak university of medical science(AUMC)

- Enzyme H+/K+_ATPase(proton pump),found in the canaliculi of the parietal cells of the stomach,plays a key role in the secretion of hydrochloric acid in the gastric lumen.the enzyme is activated by three distinct stimuli:histamine,gastrin,acetylcholine.
- The production of acid occurs with the exchange of K+ for H+ in an ATP-consuming process.
- PPIs inhibit the action of enzyme H+/K+_ATPase and prevent the exchange of K+ for H+,inhibiting the last step in the production of hydrochloric acid.
- PPIs inhibit the enzyme by merging with its receptor and covalently binding to cysteine residues known as irreversible inhibitors.after the reaction,the proton pump cannot regenerate and acid production occurs only after the synthesis of new enzymes.irreversible inhibition ensures the medication is active for 24-48 hours.
- PPIs are inactive when administered,and under acidic PH will form sulfamide derivatives or sulfenic acid.
- PPIs receive gastro-resistant coating to prevent the activation and degradation of the drug before it arrives at the targeted site.with a plasma half-life 1-2 hours, they are quickly absorbed and activated after administration.

Figure 1. Mode of action of proton pump inhibitors in parietal cells.



- Side effects are rare.
- The most common include headache,nausea,constipation,flatulence,diarrhea,skin rash and dizziness.

- There is growing evidence of other adverse outcoms such as cardiovascular disease,gastric cancer,clostridioides difficile infections,osteoprotic bone fractures,pneumonia,dementia,hypomagnesemia and renal diseases including AIN,AKI,CKD,ESRD.
- PPIs use is associated with an increased burden of all-cause mortality and increased burden of death due to cardiovascular disease,CKD,and upper gastrointestinal cancer.
- AIN,is a immune mediated reaction involves the interstitium and the renal tubules.it may be induced by autoimmune disease,blood disorders,infection and medications.at first,tubule epithelial cells are injured,and subsequently a lymphocytic inflammatory infiltrate containing predominantly T-cells is observed.renal scarring may initiate as a consequence of the spread of the infiltrate,followed by decrease in renal function.
- Current PPI users have fivefold higher odds of developing ATIN.

- Although nonspecific symptoms such as malaise,fatigue,weakness,arthralgia,myalgia,fever,and skin rash may occur and confused AIN with other diseases,eosinophilia is a frequent finding.

- The time until the onset of PPI-induced AIN ranges between hours and months.there is no evident relationship between dosage,latency,time to recovery,age or sex,indicating that this is a condition of immune origin.

- Differently from AIN induced by other drugs,patients rarely present with the characteristic triad seen in hypersensitivity reaction(fever,skin rash and eosinophilia).urinary findings include strile leukocyturia,hematuria and urinary eosinophils.

- Treatment to reverse acute disease includes the discontinuation of PPIs,administration of corticosteroids,and possibly the prescription of RRT.despite these interventions,over half of the patients cannot fully recover their renal function after AIN.the fast decrease of renal function derived from tubulointerstitial lesions may promote the onset of AKI.

- When biopsy is contraindicated,patients have the option of undergoing Gallium-67 scintigraphy,a test with great use in the differentiation of AIN from ATN.
- Approximately 30% patients who recover from AKI remain at increased risk of having CKD.

- Drug-induced AIN is considered primarily a T cell-deriven process that is often limited to the kidneys.high drug consentrations within kidneys,local drug metabolism before excretion, or damage caused to tubular epithelial cells are important factors.drugs can bind to the TBM and act as haptens or prohaptens,mimic an antigen that is normally present within the TBM or interstitium,or deposit in the tubulointerstitium and behave like a planted antigen.

- Dendritic cells interspersed between tubular cells recognize these drug-related antigens,migrate to local lymph nodes,and initiate adaptive immune responses.immune-mediated kidney injury is orchestrated by various CD4+ T-cell subsets and varies depending on the inciting agent,suggesting that AIN may be the final common pathway of distinct mechanisms of injury.

- CD4+ T-cells that produced TH1 and TH2 cytokines(INF-γ,IL.4,IL.13) were isolated from both kidney tissue and peripheral blood.TH1 cells can also lead to activation of proinflammatory M1-type macrophages;an elevated urinary M1/M2 macrophage ratio was noted in AIN patients.

- Patients with PPI-induced AIN were observed to have TH17 cells as a major part of the cellular infiltrate.

- Mast cells were also noted in biopsy specimens of patients with drug-induced AIN.additionally,IL.9,a cytokine responsible for mast cell accumulation,was also elevated in AIN patients versus non-AIN controls.

- Prior use of AIN-inducing drugs such as PPIs are associated with a higher risk for AIN in ICPI-treated patients,making reactivation of drug-specific T-cells due to loss of immune tolerance possible.

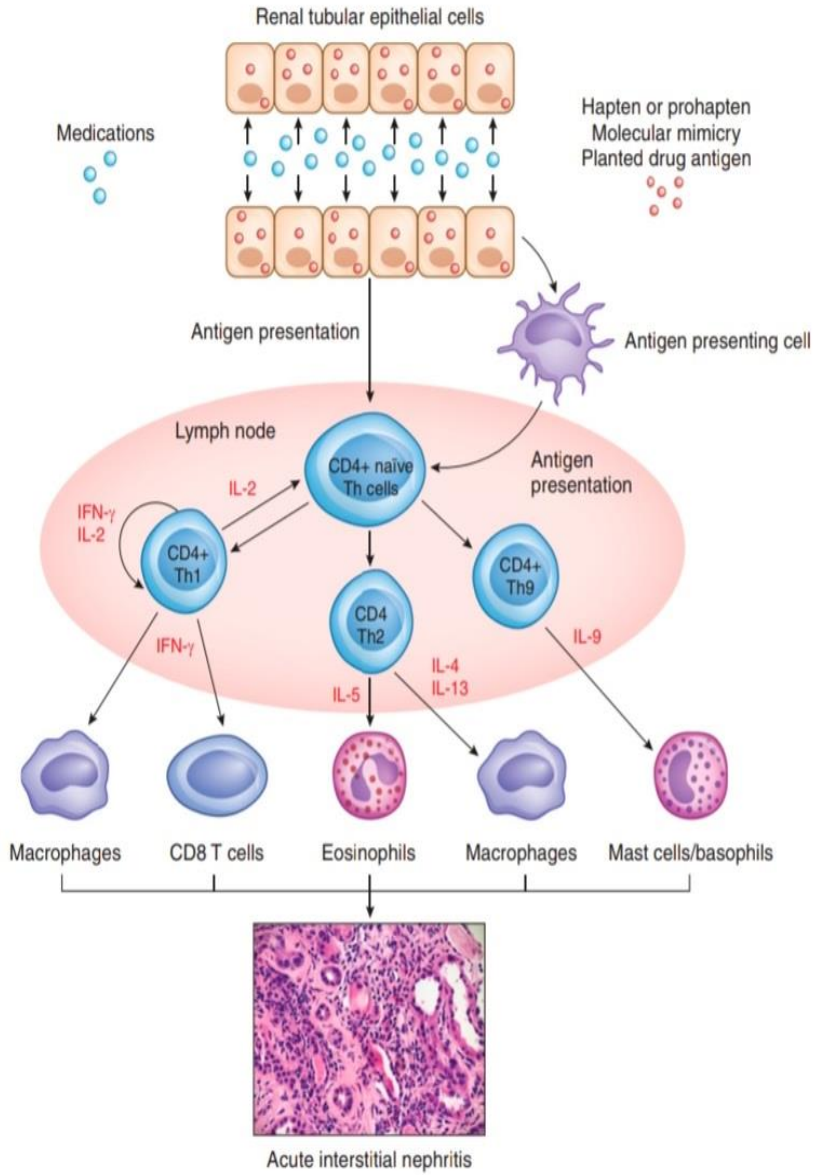


Figure 2. | **Pathogenesis of drug-induced acute interstitial nephritis.** Medications or their metabolites can incite an immune response through various processes. They can bind to TBM and act as haptens or prohaptens, Drugs can mimic an antigen that is normally present on TBM or interstitium, thereby inducing an immune response directed at this antigen. Drugs can also bind TBM or deposit within the interstitium, acting as a planted antigen. Dendritic and tubular cells present antigen to $CD4^+$ naïve Th cells, stimulating the formation of various subsets of Th cells. These cells then produce various cytokines such as ILs and IFNs, which attract a number of cells (macrophages, eosinophils, CD8 T cells, and mast cells/basophils) to the tubulointerstitium. These cells can participate in the development of acute interstitial nephritis. TBM, tubular basement membrane; Th, T-helper. This figure was generously provided by Dr. Dennis Moledina, with permission.

Box 1. Adverse Events Associated With PPI Use

Adverse nonkidney events

- Atrophic gastritis
- Vitamin B_{12} malabsorption
- Cardiovascular disease
- *Clostridioides difficile* infection
- Community-acquired pneumonia
- Dementia
- Gastric cancer
- Osteoporotic fractures

Adverse kidney outcomes

- Hypomagnesemia
- Acute kidney injury
- Acute interstitial nephritis
- Incident chronic kidney disease
- Kidney failure

Causes of death associated with PPI use

- All-cause mortality
- Death due to cardiovascular disease
- Death due to chronic kidney disease
- Death due upper gastrointestinal cancer

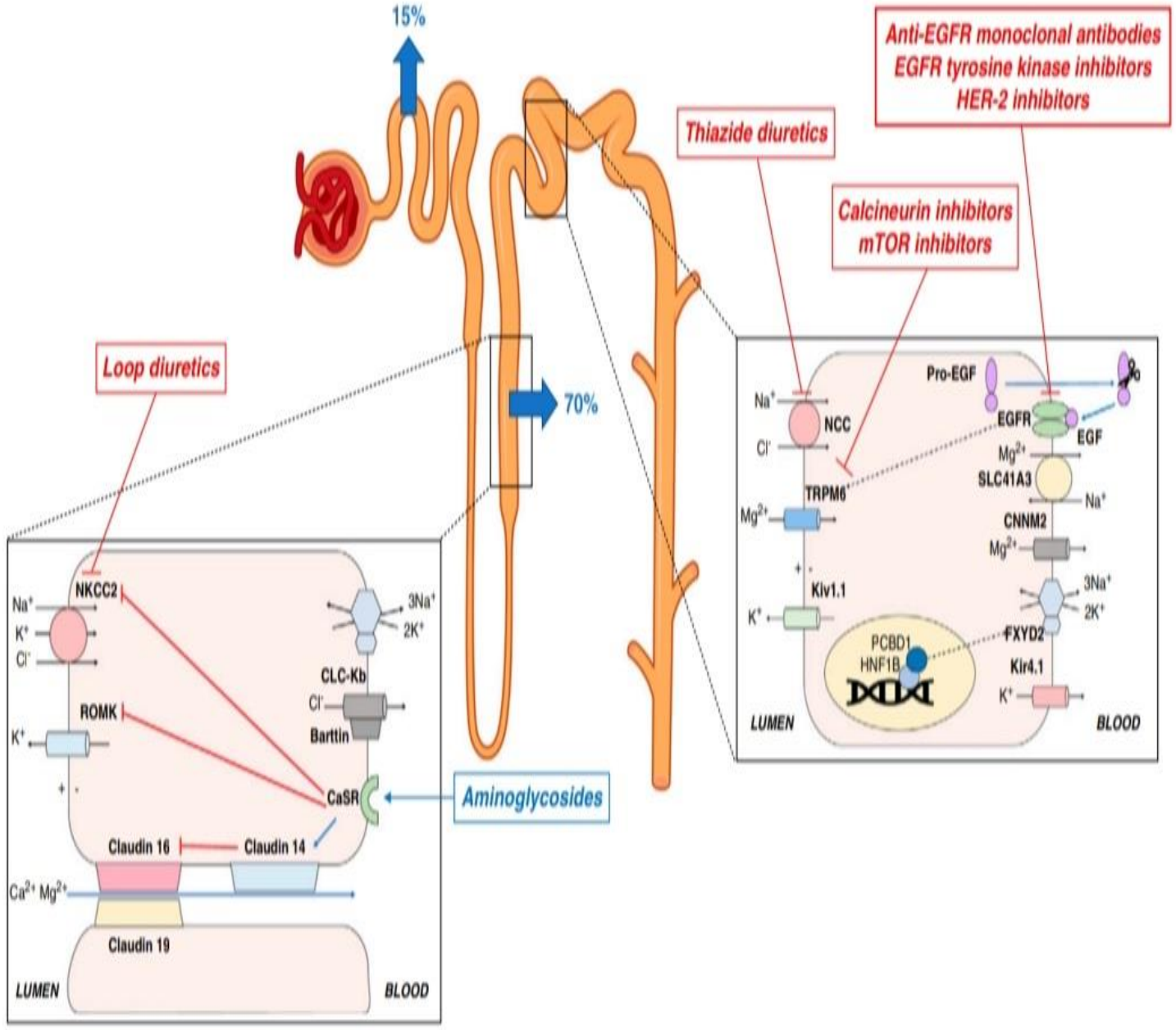
Abbreviation: PPI, proton pump inhibitor.

- Hypomagnesemia is another side effect derived from the use of PPIs.low urinary Mg concentration suggest that Mg-depletion occurs in the GI-tract.evidence indicates that low blood levels of Mg are associated with CKD.this risk is further increased in patients taking diuretics and taking PPIs for extended durations(>1 year).

- AIN,causes acute inflammation and tubulointerstitial damage,which in the long term lead to interstitial fibrosis and chronic interstitial nephritis.chronic interstitial nephritis may ultimately lead to CKD and in severe cases,to renal failure.

- The literature indicates that PPIs should be prescribed with caution to patients with CKD,accompanied by creatinine level monitoring where needed.

- In clinical practice,authers suggested that the *e.GFR should be monitored annually.*



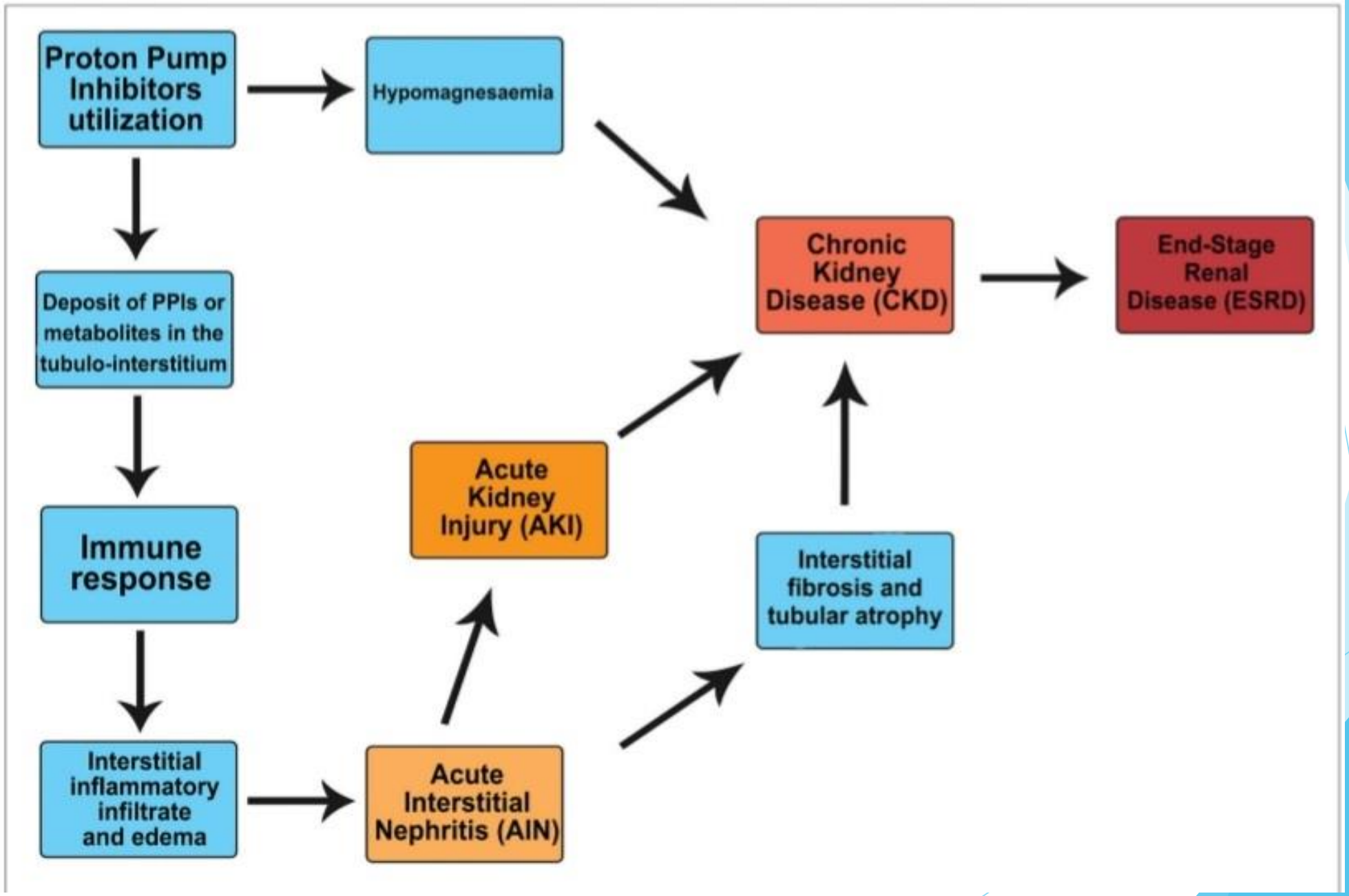
- Hypomagnesemia,in both acute and chronic forms,is associated with poor clinical outcoms.
- Chronic hypomagnesemia is implicated in developing insulin resistance,diabetes,more rapid progression of diabetic nephropathy,nephrolithiasis,fracture and increased risk for cancer and cancer development,possibly in relation to to the induction of chronic inflammation.
- Mg absorption in the gut occurs via two routs:a saturable paracellular route and a nonsaturable transcellular route.
- The paracellular route is a passive mechanism and accounts for the bulk(90%) of tatal Mg reabsorption.the paracellular route is modulated by tight junction proteins called claudins.claudin 2,7 and 12 are expressed in the intestines and might facilitate Mg reabrorption.
- The final segment for Mg reabsorption occurs in the cecum and colon using the transcellular route,which is an active process and accounts for 10% of Mg reabsorption.transcellular Mg transport requires the activity of transient receptor potential melastatin(TRPM6) and (TRPM7) Mg transporters in the entrocyte apical membrane.

Table 3. Drug-induced hypomagnesemia in a patient with cancer: adjunct agents used in patients with cancer

Drug Class or Name	Incidence	Mechanism
PPIs	19% of PPI users	Intestinal loss, malabsorption of magnesium. PPIs interfere with TRPM6 and TRPM7 genes, leading to intestinal malabsorption and possible renal Mg loss
Thiazide diuretics	Unknown	TRPM6 inhibition, leading to increase in renal Mg loss, increase in potassium excretion causes hypokalemia, leading to decrease in passive Mg reabsorption
Loop diuretics	Unknown	Decrease in paracellular reabsorption in thick ascending LOH, increase renal Mg loss, hypokalemia
Pamidronate	Case reports	Renal impairment, increased Mg excretion, and cellular shifting No other bisphosphate has been reported to cause hypomagnesemia
RANKL mAb (denosumab)	Isolated case report	Unknown
Ibuprofen	Isolated case report	Unknown
Aminoglycosides (amikacin, gentamicin, tobramycin, neomycin, streptomycin)	Unknown	Positively charged antibiotics act *via* a polyvalent cation-sensing extracellular receptor in DCT, leading to inhibition of PTH-mediated cAMP formation and Mg uptake in the DCT
Antituberculous agents (viomycin, capreomycin)	Unknown	Proximal tubular dysfunction, secondary hyperaldosteronism with consequent renal Mg loss
Amphotericin B	Unknown	This drug is a polyene antibiotic, and Mg participates in the polyene-sterol binding process, leading to a functional Mg deficiency
Theophylline	Unknown	Renal Mg wasting
Pentamidine	Unknown	Renal Tubular injury
Foscarnet	Up to 70%	Chelates divalent ions, thereby leading to acute reduction in ionized magnesium

PPI, proton-pump inhibitor; TRPM, transient receptor potential melastatin; Mg, magnesium; LOH, loop of Henle; RANKL, receptor activator of NF-κB ligand; DCT, PTH, parathyroid hormone.

Figure 3. Hypothesis explaining the possible correlation between PPIs and renal disease.



The relationship between proton pump inhibitors and renal disease

Inibidores da bomba de prótons e sua relação com a doença renal

Authors
Carine Franco Morschel[1]
Denise Mafra[1]
José Carlos Carraro Eduardo[2]

[1] Universidade Federal Fluminense, Programa de Pós-Graduação em Ciências Médicas, Niterói, RJ, Brasil.
[2] Universidade Federal Fluminense, Faculdade de Medicina, Niterói, RJ, Brasil.

ABSTRACT

Proton pump inhibitors (PPIs) bind to enzyme H^+/K^+-ATPase and inhibit its activity in the stomach, thus decreasing the secretion of gastric acid. PPIs may trigger acute interstitial nephritis, a potentially severe adverse event commonly associated with acute kidney injury. Studies have found that prolonged use of PPIs may increase the risk of chronic kidney disease (CKD). The increase in prescription and inadequate use of this class of medication calls for studies on the effects of prolonged PPI therapy on renal function. Therefore, this review aimed to analyze recent studies on the matter and discuss the possible consequences of the long-term use of PPIs on renal function.

Keywords: Proton Pump Inhibitors; Renal Insufficiency, Chronic; Nephritis, Interstitial; Acute Kidney Injury.

RESUMO

Os Inibidores da Bomba de Prótons (IBPs) são medicamentos que inibem a enzima H^+/K^+-ATPase no estômago, diminuindo a secreção gástrica. Esses medicamentos podem desencadear nefrite intersticial aguda, evento adverso potencialmente grave e que pode cursar com lesão renal aguda. Além disso, pesquisadores têm observado que o uso prolongado de IBPs pode também aumentar o risco de progressão da doença renal crônica (DRC). Com o crescimento da prescrição e o uso inadequado dessa classe de medicamentos, torna-se importante o estudo dos efeitos do uso prolongado dos IBPs sobre a função renal. Assim, esta revisão pretende abordar os recentes estudos sobre o tema e discutir as possíveis consequências que o uso contínuo dos inibidores da bomba de prótons pode causar na função renal.

Palavras-chave: Inibidores da Bomba de Prótons; Insuficiência Renal Crônica; Nefrite Intersticial; Lesão Renal Aguda.

Proton Pump Inhibitors and the Kidney: Implications of Current Evidence for Clinical Practice and When and How to Deprescribe

Ziyad Al-Aly, Geetha Maddukuri, and Yan Xie

Proton pump inhibitors (PPIs), long thought to be safe, are associated with a number of nonkidney adverse health outcomes and several untoward kidney outcomes, including hypomagnesemia, acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, kidney failure, and increased risk for all-cause mortality and mortality due to chronic kidney disease. PPIs are abundantly prescribed, rarely deprescribed, and frequently purchased over the counter. They are frequently used without medical indication, and when medically indicated, they are often used for much longer than needed. In this In Practice review, we summarize evidence linking PPI use with adverse events in general and adverse kidney outcomes in particular. We review the literature on the association of PPI use and risk for hypomagnesemia, acute kidney injury, acute interstitial nephritis, incident chronic kidney disease, kidney disease progression, end-stage kidney disease, and death. We provide an assessment of how this evidence should inform clinical practice. We review the impact of this evidence on patients' perception of risk, synthesize PPI deprescription literature, and provide our recommendations on how to approach PPI use and deprescription.

Complete author and article information provided before references.

Am J Kidney Dis. 75(4):497-507. Published online October 10, 2019.

doi: 10.1053/j.ajkd.2019.07.012

Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. This is a US Government Work. There are no restrictions on its use.

Review Article

Kidney360

Hypomagnesemia in the Cancer Patient

Biruh T. Workeneh,[1] Nupur N. Uppal,[2] Kenar D. Jhaveri,[2] and Helbert Rondon-Berrios[3]

Abstract

Hypomagnesemia is a common medical problem that contributes to the morbidity and mortality of patients with cancer. This review summarizes magnesium physiology and highlights the mechanisms underlying magnesium disturbances due to cancer and cancer treatment. The causes of hypomagnesemia can be categorized according to the pathophysiologic mechanism: decreased intake, transcellular shift, gastrointestinal losses, and kidney losses. Patients with cancer are at risk for opportunistic infections, frequently experience cardiovascular complications, and often receive classes of medications that cause or exacerbate hypomagnesemia. Also, cancer-specific therapies are responsible for hypomagnesemia, including platinum-based chemotherapy, anti-EGF receptor mAbs, human EGF receptor-2 target inhibitors (HER2), and calcineurin inhibitors. Urinary indices, such as the fractional excretion of magnesium, can provide useful information about the etiology. The management of hypomagnesemia depends on the magnitude of hypomagnesemia and the underlying cause. We recommended checking serum magnesium at the beginning of treatment and as part of routine monitoring throughout cancer treatment. Opportunities exist for potential research and practice improvement, including further characterization of hypomagnesemia regarding the clinical effect on cancer outcomes, preventing hypomagnesemia in patients receiving high-risk anticancer agents, and developing effective therapeutic strategies.

KIDNEY360 2: 154–166, 2021. doi: https://doi.org/10.34067/KID.0005622020

Critical Care Nephrology and Acute Kidney Injury

Drug-Induced Acute Kidney Injury

Mark A. Perazella[1,2] and Mitchell H. Rosner[3]

Abstract

Medications are a common cause of AKI, especially for patients admitted to hospital wards and the intensive care unit. Although drug-related kidney injury occurs through different mechanisms, this review will focus on three specific types of tubulointerstitial injury. Direct acute tubular injury develops from several medications, which are toxic to various cellular functions. Their excretory pathways through the proximal tubules contribute further to AKI. Drug-induced AKI may also develop through induction of inflammation within the tubulointerstitium. Medications can elicit a T cell–mediated immune response that promotes the development of acute interstitial nephritis leading to AKI. Although less common, a third pathway to kidney injury results from the insolubility of drugs in the urine leading to their precipitation as crystals within distal tubular lumens, causing a crystalline-related AKI. Intratubular obstruction, direct tubular injury, and localized inflammation lead to AKI. Clinicians should be familiar with the pathogenesis and clinical-pathologic manifestations of these forms of kidney injury. Prevention and treatment of AKI relies on understanding the pathogenesis and judiciously using these agents in settings where AKI risk is high.

CJASN 17: 1220–1233, 2022. doi: https://doi.org/10.2215/CJN.11290821

[1]Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut
[2]Veteran's Affairs Medical Center, West Haven, Connecticut
[3]Division of Nephrology, University of Virginia Health System, Charlottesville, Virginia

CLINICAL EPIDEMIOLOGY www.jasn.org

Proton Pump Inhibitors and Risk of Incident CKD and Progression to ESRD

Yan Xie,* Benjamin Bowe,* Tingting Li,† Hong Xian,*‡ Sumitra Balasubramanian,* and Ziyad Al-Aly*†§

*Clinical Epidemiology Center, Veterans Affairs Saint Louis Health Care System, Saint Louis, Missouri; †Department of Medicine, Washington University School of Medicine, Saint Louis, Missouri; ‡Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, Missouri; and §Division of Nephrology, Department of Medicine, Veterans Affairs Saint Louis Health Care System, Saint Louis, Missouri

ABSTRACT

The association between proton pump inhibitors (PPI) use and risk of acute interstitial nephritis has been described. However, whether exposure to PPI associates with incident CKD, CKD progression, or ESRD is not known. We used Department of Veterans Affairs national databases to build a primary cohort of new users of PPI (n=173,321) and new users of histamine H_2-receptor antagonists (H_2 blockers; n=20,270) and followed these patients over 5 years to ascertain renal outcomes. In adjusted Cox survival models, the PPI group, compared with the H_2 blockers group, had an increased risk of incident eGFR<60 ml/min per 1.73 m^2 and of incident CKD (hazard ratio [HR], 1.22; 95% confidence interval [95% CI], 1.18 to 1.26; and HR, 1.28; 95% CI, 1.23 to 1.34, respectively). Patients treated with PPI also had a significantly elevated risk of doubling of serum creatinine level (HR, 1.53; 95% CI, 1.42 to 1.65), of eGFR decline >30% (HR, 1.32; 95% CI, 1.28 to 1.37), and of ESRD (HR, 1.96; 95% CI, 1.21 to 3.18). Furthermore, we detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31–90, 91–180, 181–360, and 361–720 days compared with those exposed for ≤30 days. Examination of risk of renal outcomes in 1:1 propensity score-matched cohorts of patients taking H_2 blockers versus patients taking PPI and patients taking PPI versus controls yielded consistent results. Our results suggest that PPI exposure associates with increased risk of incident CKD, CKD progression, and ESRD.

J Am Soc Nephrol 27: 3153–3163, 2016. doi: 10.1681/ASN.2015121377

Debates in Nephrology

Kidney360

Do Proton-Pump Inhibitors Cause CKD and Progression of CKD?: PRO

Linda Awdishu and Ruben Abagyan

KIDNEY360 3: 1134–1136, 2022. doi: https://doi.org/10.34067/KID.0007622021

Thanks for your attention