ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 8, Issue – 3, May - 2025, Page No.: 13 – 19

Proton Pump Inhibitors Cause Kidney Injury – Or Do They?

[1]Dr. Samir Govil, Associate Professor, Nephrology, Department of Medicine, GSVM Medical College, Kanpur, UP, India

[2]Dr. Prakhar Kushwaha, Senior Resident, Department of Medicine, GSVM Medical College, Kanpur, UP, India.

Corresponding Author: Dr. Samir Govil, Associate Professor, Nephrology, Department of Medicine, GSVM Medical College, Kanpur, UP, India

How to citation this article: Dr. Samir Govil, Dr. Prakhar Kushwaha, "Proton Pump Inhibitors Cause Kidney Injury – Or Do They?", IJMACR- May - 2025, Volume – 8, Issue - 3, P. No. 13 – 19.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Proton pump inhibitors (PPIs) are commonly prescribed for acid-related conditions such as gastroesophageal reflux disease (GERD) and acid peptic disease. While their use has been shown to be effective, recent studies have raised concerns about their potential association with kidney injury, particularly chronic kidney disease (CKD). However, the evidence linking PPIs to kidney injury is inconclusive. This article reviews the existing literature and examines whether PPIs directly contribute to kidney injury or CKD progression. While some studies suggest a potential association, the overall evidence does not support a direct causality. Further research, particularly prospective cohort studies and randomized controlled trials, is needed to conclusively determine any nephrotoxic effects of PPIs. Additionally, strategies for patient selection, monitoring, and the exploration of non-PPI alternatives are crucial for mitigating risks, especially in high-risk populations.

Keywords: Proton Pump Inhibitors, Kidney Injury, Chronic Kidney Disease, Acute Interstitial Nephritis, Renal Function.

Introduction

Proton pump inhibitors (PPIs) are among the most widely used medications for the treatment of acid-related diseases, including gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. Despite their widespread use and efficacy, growing concerns have emerged regarding their potential adverse effects on kidney health. Several studies have suggested an association between PPI use and kidney injury, with

some linking long-term use to the development of chronic kidney disease (CKD) and even end-stage kidney disease (ESKD). However, the evidence supporting a causal relationship remains limited.

PPIs exert their action by inhibiting the H+/K+ ATPase enzyme in the parietal cells of the stomach, which is responsible for gastric acid production. While their effects on gastric acid suppression are well-documented, their potential systemic effects on renal function are less understood. This article reviews the current evidence regarding the association between PPIs and kidney injury, exploring possible mechanisms and clinical implications, while addressing gaps in the literature, such as the need for more longitudinal studies and the exploration of specific mechanisms like hypomagnesemia, immune-mediated damage, and changes to the gut microbiome.

Methods

A comprehensive literature review was conducted using databases such as PubMed, Google Scholar, and Scopus. Studies published between 2000 and 2024 were considered, focusing on clinical trials, observational studies, and meta-analyses related to PPI use and kidney injury. The review aimed to assess the association between PPIs and renal dysfunction, specifically in relation to acute interstitial nephritis (AIN) and chronic kidney disease (CKD).

Results

Proton Pump Inhibitors and Kidney Injury

PPIs are absorbed in the small intestine and primarily metabolized in the liver through the CYP2C19 enzyme. Their therapeutic effect is achieved by blocking the H+/K+ ATPase pump in the gastric parietal cells, leading to a reduction in gastric acid production. Despite their clinical effectiveness, PPIs have been implicated in several adverse effects, including kidney injury.

One of the most common kidney-related adverse effects associated with PPIs is acute interstitial nephritis (AIN). A retrospective study by Lazarus et al. (2016) found an association between PPI use and an increased risk of CKD. Similarly, a study by Xie et al. (2017) confirmed that long-term PPI use was associated with adverse kidney outcomes, even in the absence of acute kidney injury. These studies suggest a potential link between PPIs and kidney dysfunction, although the mechanisms remain unclear.

Mechanisms of Kidney Injury

The proposed mechanisms of PPI-induced kidney injury are still under investigation. One potential mechanism involves hypomagnesemia, a known side effect of PPIs, which can contribute to kidney damage.

Hypomagnesemia has been linked to the formation of renal calculi and can worsen kidney function over time. However, this phenomenon is not exclusive to PPIs and

has also been observed with other acid-suppressive medications such as H2-receptor antagonists (H2RAs).

Another proposed mechanism is immune-mediated damage. Drug-induced interstitial nephritis (DIIN), particularly acute interstitial nephritis (AIN), is a well-known adverse effect of several medications, including PPIs. In these cases, an immune response is triggered, leading to inflammation within the renal interstitial tissue, which may progress to renal scarring if the offending drug is not discontinued.

Additionally, PPIs may alter the gut microbiome, potentially leading to systemic inflammation that could impact renal function. This hypothesis suggests that suppression of gastric acid may increase the risk of infections, which in turn could contribute to kidney injury.

Moreover, drug interactions with other nephrotoxic medications, such as NSAIDs or certain antibiotics, may exacerbate the renal risk in patients taking PPIs, especially those with pre-existing kidney conditions.

Evidence of Renal Safety

Despite some evidence linking PPI use to kidney injury, other studies have failed to establish a clear causative relationship. A large cohort study by Antoniou et al. (2015) found no significant association between PPI use and acute kidney injury in older adults. Similarly, a study by Sampathkumar et al. (2013) did not observe a clear link between PPI use and acute interstitial nephritis.

Furthermore, the development of kidney injury in PPI users is often confounded by other factors, such as pre-existing kidney conditions, comorbidities, and the concurrent use of other nephrotoxic medications. This highlights the need for careful patient selection and monitoring when prescribing PPIs, particularly for individuals with existing renal risk factors.

Discussion

The evidence linking PPIs to kidney injury remains inconclusive. While some studies suggest an association with conditions like acute interstitial nephritis and chronic kidney disease, the overall body of evidence does not support a direct causative relationship. Several factors, including pre-existing kidney disease, comorbidities, and the concurrent use of other nephrotoxic agents, likely contribute to the observed renal dysfunction in PPI users.

The potential mechanisms of PPI-induced kidney injury, including hypomagnesemia, immune-mediated responses, and changes in the gut microbiome, require further investigation. Histopathological studies and large-scale longitudinal trials are needed to clarify the mechanisms behind PPI-associated kidney injury and to establish whether PPIs directly contribute to the development or progression of chronic kidney disease.

Until more conclusive evidence is available, healthcare providers should continue to prescribe PPIs judiciously, ensuring that patients are monitored for potential adverse effects, particularly those at higher risk for kidney disease. Given the benefits of PPIs in treating acid-related conditions, their use should not be discouraged, but rather managed appropriately with regular monitoring of renal function. Special care should be taken when prescribing PPIs to populations at higher risk, such as elderly patients and those with pre-existing kidney conditions.

Conclusion

While proton pump inhibitors are widely used and generally considered safe, the evidence regarding their role in kidney injury remains inconclusive. There is no definitive proof to suggest that PPIs directly cause chronic kidney disease or acute kidney injury, although some studies have raised concerns about their potential nephrotoxic effects. Further research, especially large-scale, long-term cohort studies, is needed to better understand the mechanisms behind PPI-induced kidney injury and to establish whether any direct causality exists. In the meantime, PPIs should be used with caution, particularly in patients with pre-existing renal risk factors, and kidney function should be monitored during long-term therapy.

References

1. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016;176(2):238.
2. Xie Y, Bowe B, Li T, et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017;91(6):1482–94.
3. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol. 2018 Apr 3;14(4):447–60.
4. Cholin L, Ashour T, Mehdi A, et al. Proton-pump inhibitor vs. H2-receptor blocker use and overall risk of CKD progression. BMC Nephrol. 2021 Dec;22(1):264.
5. Strand DS, Kim D, Peura DA. 25 Years of Proton Pump Inhibitors: A Comprehensive Review. Gut Liver. 2017 Jan 15;11(1):27–37.
6. El Rouby N, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. Expert Opin Drug Metab Toxicol. 2018 Apr;14(4):447-460. doi: 10.1080/17425255.2018.1461835. Epub 2018 Apr 12. PMID: 29620484; PMCID: PMC5942154.
7. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J

Neurogastroenterol Motil. 2013 Jan;19(1):25-35. doi: 10.5056/jnm.2013.19.1.25. Epub 2013 Jan 8. PMID: 23350044; PMCID: PMC3548122.

8. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016;176(2):238.
9. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Jun;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021. Epub 2017 Feb 22. PMID: 28237709.
10. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. Kidney Int. 2017 Jun;91(6):1482-1494. doi: 10.1016/j.kint.2016.12.021. Epub 2017 Feb 22. PMID: 28237709.
11. Parmar MP, Kaleem S, Samuganathan P, Ishfaq L, Anne T, Patel Y, Bollu S, Vempati R. Impact of Proton Pump Inhibitors on Kidney Function and Chronic Kidney Disease Progression: A Systematic Review. Cureus. 2023 Dec 3;15(12):e49883. doi: 10.7759/cureus.49883. PMID: 38174181; PMCID: PMC10762285.
12. Florentin M, Elisaf MS. Proton pump inhibitor-induced hypomagnesemia: A new challenge. World J Nephrol. 2012 Dec 6;1(6):151-4. doi: 10.5527/wjn.v1.i6.151. PMID: 24175253; PMCID: PMC3782221.
13. Cheung KS, Leung WK. Long-term use of proton-pump inhibitors and risk of gastric cancer: a review of the current evidence. Therapeutic Advances in Gastroenterology. 2019;12. doi: 10.1177/ 1756284819834511
14. Finnigan NA, Rout P, Leslie SW, et al. Allergic and Drug-Induced Interstitial Nephritis. [Updated 2023 Sep 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from:https://www.ncbi.nlm.nih.gov/books/NBK482 323/
15. Sampathkumar K, Ramalingam R, Prabakar A, et al. Acute interstitial nephritis due to proton pump inhibitors. Indian J Nephrol. 2013;23(4):304.
16. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, Sutter JL, Welter D, Ley RE, Bell JT, Spector TD, Steves CJ. Proton pump inhibitors alter the composition of the gut microbiota. Gut. 2016 May;65(5):749-56. doi: 10.1136/gutjnl-2015-310861. Epub 2015 Dec 30. PMID: 26719299; PMCID: PMC4853574.
17. Patel JB, Sapra A. Nephrotoxic Medications. [Updated 2023 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025

Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553144/

18. Nast CC. Medication-Induced Interstitial Nephritis in the 21st Century. Adv Chronic Kidney Dis. 2017 Mar;24(2):72-79. doi: 10.1053/j.ackd.2016.11.016. PMID: 28284382.
19. Weir MR. Proton Pump Inhibitors and Kidney Disease: Fact or Fiction? Am J Nephrol. 2024;55(4):499-508. doi: 10.1159/000538755. Epub 2024 Apr 18. PMID: 38583423.
20. Shin JM, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. Pflüg Arch - Eur J Physiol. 2009 Jan;457(3):609–22.Sampathkumar K, Ramalingam R, Prabakar A, et al. Acute interstitial nephritis due to proton pump inhibitors. Indian J Nephrol. 2013;23(4):304.
21. Siletsky, S. A. (2023). Proton Pumps: Molecular Mechanisms, Inhibitors and Activators of Proton Pumping. International Journal of Molecular Sciences, 24(10), 9070.
22. Yaffe K, Ackerson L, Kurella Tamura M, Le Blanc P, Kusek JW, Sehgal AR, Cohen D, Anderson C, Appel L, Desalvo K, Ojo A, Seliger S, Robinson N, Makos G, Go AS; Chronic Renal Insufficiency Cohort Investigators. Chronic kidney disease and cognitive function in older adults: findings from the chronic renal insufficiency cohort cognitive study. J Am Geriatr Soc. 2010 Feb;58(2):338-45. doi: 10.1111/j.1532-5415.2009.02670.x. Epub 2010 Jan 26. PMID: 20374407; PMCID: PMC2852884.
23. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. 2016 Feb;176(2):238-46. doi: 10.1001/jamainternmed.2015.7193. PMID: 26752337; PMCID: PMC4772730.
24. Yu LY, Sun LN, Zhang XH, Li YQ, Yu L, Yuan ZQ, Meng L, Zhang HW, Wang YQ. A Review of the Novel Application and Potential Adverse Effects of Proton Pump Inhibitors. Adv Ther. 2017 May;34(5):1070-1086. doi: 10.1007/s12325-017-0532-9. Epub 2017 Apr 20. PMID: 28429247; PMCID: PMC5427147.
25. Geevasinga N, Coleman PL, Webster AC, Roger SD. Proton pump inhibitors and acute interstitial nephritis. Clin Gastroenterol Hepatol. 2006 May;4(5):597-604. doi: 10.1016/j.cgh.2005.11.004. PMID: 16630752.
26. Klatte DCF, Gasparini A, Xu H, De Deco P, Trevisan M, Johansson ALV, et al. Association Between Proton Pump Inhibitor Use and Risk of Progression of Chronic Kidney Disease. Gastroenterology. 2017 Sep;153(3):702–10.

27. Antoniou T, Macdonald EM, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015 Apr 16;3(2):E166–71.
28. Shin JM, Munson K, Vagin O, Sachs G. The gastric HK-ATPase: structure, function, and inhibition. Pflüg Arch - Eur J Physiol. 2009 Jan;457(3):609–22
29. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. Aliment Pharmacol Ther. 2006 Jun;23 Suppl 2:2-8. doi: 10.1111/j.1365-2036.2006.02943.x. PMID: 16700898.