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Original Research Article

Proton Pump Inhibitors and Renal Disease: a Prospective Observational Study at a Tertiary Care Hospital

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Abstract:

Background: Widespread over-the-counter use of Proton pump inhibitors has raised a concern regarding their safety profile during long-term use. Various retrospective & observational studies have reported the development of chronic kidney disease in individuals on Proton pump inhibitors.

Aims & Objectives: To find an association between the uses of proton pump inhibitors and renal disease

Material & Methods: This prospective observational study was carried out in the Department of Nephrology of our Tertiary care hospital from August 2023 till February 2024 for six months. 200 patients within the age range of 45-65 yrs suffering from gastro-oesophageal reflux disease, peptic ulcers including gastric ulcers and duodenal ulcers, with once / twice daily prescribed PPI (duration between 15 days to 6 months of use) were included in the study. Patients with comorbidities, suffering from renal disease, on nephrotoxic medications, and pregnant women were excluded from the study. The patients were divided into 2 groups: Group A: Patients with users of PPI (n=100); Group B: Patients with non-users of PPI (n=100). Detailed history including socio-demographic details, age at clinical presentation, and medication history was taken. Renal function tests - serum creatinine, blood urea nitrogen, and glomerular filtration rate were measured at baseline, 3- and 6 months of the study.

Results: In Group A, 9 patients while in Group B, 2 patients showed signs of developing renal disease with the usage of PPI. There was a significant increase in the serum creatinine levels, BUN, and reduction in GFR at 6 months follow-up ($p<0.05$). 61.2% of the patients were in the age range 55-60 yrs, 23% in 61-65 yrs, and 16% in the age group of 51-55 yrs. Males were at a greater risk than females.

Conclusion: The use of proton pump inhibitors can contribute to the development of chronic renal disease. These medications should be carefully administered. Further large prospective studies should be conducted to confirm this association.

Keywords: Proton Pump Inhibitors, Chronic Renal Disease, Creatinine, BUN.

Introduction

Kidney diseases are the eighth most common cause of mortality & morbidity worldwide. It has a substantial impact on the quality of life of people. It is estimated that by 2040, kidney diseases will be the fifth leading cause of significant, mortality. [1] The two main types of kidney diseases are acute and chronic disease. [2] The risk of progression of kidney disease is 60% higher in the elderly and the lower socioeconomic group. [3] According to Global Burden of Disease Collaboration CKD is the major etiology behind morbidity and mortality worldwide.4 From 1990 to 2017, the prevalence of CKD increased by 29.3%. [4] In India, the mortality increased by 38% between 2001–03 and 2010–13 due to CKD. [5]

Proton pump inhibitors (PPIs) are widely being in used to treat peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), *and* *Helicobacter pylori* infection. PPIs are massively & long-term used over-the-counter drugs. The side effects of PPI use are rare. The most common are headache, nausea, constipation, flatulence, diarrhea, skin rash, and dizziness. [4] Due to widespread use, its safety concern is raised with regards to causing kidney injuries. Although infrequent, bone fractures, pneumonia, dementia, hypomagnesemia, and renal diseases including acute interstitial nephritis (AIN), acute kidney injury (AKI) & CKD have been evidenced to be associated with PPI use.

AIN is a rare adverse event associated with the use of PPIs. It involves the interstitium and the renal tubules, initiated by autoimmune disease, blood disorders, infection, and medication. Firstly, tubule epithelial cells are injured, and later on, a lymphocytic inflammatory infiltrate containing

predominantly T cells can be seen. the spread of the infiltrate may result in renal scarring & reduced renal function. In cases of drug-induced AIN, if even after the discontinuation of the suspected drug, no improvement is noted then the patients may progress to CKD with interstitial fibrosis and tubular atrophy. [6,7]

Many systemic & retrospective studies have been conducted to associate the renal risk associated with the use of PPIs. A retrospective cohort study conducted by Hart E Dunn et al 2019 stated PPIs were associated with a higher risk of CKD compared with controls. [8] YangY. et al. 2017 conducted a meta-analysis including 2,404,236 participants, out of which 513,696 individuals were PPI users, and observed higher risks of acute kidney injury in individuals with age <60 years. [9] In a large 3-year randomized clinical trial, Moayyedi P. et al evaluated only pantoprazole and could not find any significant association between pantoprazole and CKD. [10]

Thus the present study aimed to find an association between the use of proton pump inhibitors and renal disease

Material & Methods

This prospective observational study was carried out in the Department of Nephrology of our Tertiary care hospital from August 2023 to February 2024 for a period of six months. 200Patients within the age range of 45-65 yrs suffering from Gastro-Oesophageal Reflux Disease (GERD), Peptic ulcers including gastric ulcers, and duodenal ulcers, with once / twice daily prescribed PPI (duration between 15 days to 6 months of use) were included in the study. Patients with comorbidities, suffering from renal disease, on nephrotoxic medications, and pregnant women were excluded from the study. The study was approved by the Institutional Ethical Committee & written informed consent was taken from all the patients.

The patients were divided into 2 groups:

Group A: Patients with users of PPI (n=100)

Group B: Patients with non-users of PPI (n=100)

Detailed history including sociodemographic details, age at clinical presentation, and medication history was taken. Renal function tests - serum creatinine, blood urea nitrogen, and glomerular filtration rate were measured at baseline, 3- and 6 months of the study.

Statistical Analysis

The collected data was tabulated and put into statistical analysis using SPSS version 22.0 for Windows (IBM Corp, India). Quantitative data are presented as mean ± SD or proportions. Intergroup comparisons were made using Student's paired t-test. A P-value of 0.05 at a 90% confidence interval was considered to be statistically significant. Values were expressed as number (n) and percentage (%).

Results

A total number of 200 patients were recruited in the study, among them 20 patients were excluded due to the development of other comorbidities & nonavailability of renal function tests during follow-up.

In Group A, out of 90 patients, 9 patients showed signs of developing renal disease with the usage of PPI. 61.2% of the patients were in the age range 55-60 yrs, 23% in 61-65 yrs, and 16% in the age group of 51-55 yrs. Males were at a greater risk than females. In Group B, out of 90 patients, 2 patients showed signs of developing renal disease with the non-usage of PPI.

In Group A, out of 90 patients, 9 patients had a significant increase in the serum creatinine levels, BUN, and reduction in GFR at 6 months follow-up ($p<0.05$). In Group B, out of 90 patients, 2 patients had a significant increase in the serum creatinine levels, BUN and reduction in GFR at 6 months follow up ($p<0.05$).

Table 1

	Group A (n=9)		Group B (n=2)		P value
	At Baseline (Mean±SD)	At 3 months (Mean±SD)	At Baseline (Mean±SD)	At 3 months (Mean±SD)	
Serum creatinine levels	0.78±0.07	1.31±0.13	0.74±0.06	1.2±0.14	<0.05
BUN	18.11 ±1.69	27.05±1.58	16.11 ±1.74	26.03±1.38	<0.05
GFR	97.1 ± 3.37	58 ± 6.82	99.1 ± 2.63	60 ± 5.61	<0.05

Discussion

The present prospective observational study demonstrated that the use of PPIs was associated with a significant increase in serum creatinine which could lead to renal disease. In Group I, 61.2% of the patients were at risk of renal disease as compared to other age groups. Males were at a greater risk than females. Accordingly, a study by Yang Y. et al. 2017 which included 2,404,236 participants, out of which 513,696 individuals were PPI users observed higher risks of acute kidney injury in individuals with age <60 years of age. [9] Wu et al observed that male patients were at a

higher risk than female patients which could be attributed to differences in the renal physiology, signs, symptoms & complications, of CKD. [11]

In the present study, in Group A, 9 patients and in Group B, 2 patients showed a significant increase in the serum creatinine levels, BUN, and reduction in GFR at 6 months follow-up ($p<0.05$). Similarly, the Zhang et al study in 2022, documented 7,031 cases of CKD over a follow-up period of 8.1 years. The study observed that regular PPI users had a 37% higher risk of CKD than non-users. A head-to-head comparison showed that PPI users had a 19% higher risk of CKD than histamine-2 receptor antagonist users. [12]

The plausible mechanism behind this association is unclear. Klatte et al 2017 stated that infection and inflammations could partly contribute to the development of CKD by causing tubulointerstitial damage, among PPI users. [13] Also, PPIs cause an imbalance in the intestinal microbiota & increase the risk of enteric infection. [14,15] Studies have demonstrated that there is an increase in the rates of Enterobacteriaceae and Streptococcaceae among PPI users. The accumulation of gut-derived uremic toxins occurs which ultimately leads to CKD progression. [16] Also, PPI use leads to the development of hypomagnesemia which could also contribute to evolving CKD. [17]

Wu et al 2023, observed that the Asian population with PPI use had a higher risk of CKD people than in the Western population, which may be attributed to clinical, metabolic, socioeconomic, and behavioral factors. [18] Due to a higher prevalence of diabetes and hypertension, the Western population is also at an increased risk of developing CKD. [19] Omeprazole, rabeprazole, and esomeprazole have been shown to be significantly associated with an increased risk of CKD. These medications cause an imbalance in the pH levels of the GI tract & thus decrease the absorption mediated by TRPM6 and TRPM7 transporters. [20] Our findings also showed that male patients had a higher risk than female patients. As in other diseases, gender is a fundamental factor of CKD patients because males and females differ in renal physiology, complications, signs, and symptoms of CKD. Thus in individuals requiring long-term use of PPI, benefits should be carefully weighed with the risks associated with prescribing PPIs.

Conclusion

The present study concluded that the long-term use of proton pump inhibitors is associated with an increased risk of developing chronic renal disease. Healthcare professionals should cautiously use these medications in individuals already suffering from renal diseases & other comorbid conditions. The indiscriminate use of these medications should be stopped.

References

1. Li, P.; Garcia-Garcia, G.; Lui, S.-F.; Andreoli, S.; Fung, W.; Hradsky, A.; Kumaraswamy, L.; Liakopoulos, V.; Rakhimova, Z.; Saadi, G. Kidney health for everyone everywhere–from prevention to detection and equitable access to care. Braz. J. Med. Biol. Res. 2020;53: 111–122.
2. Hossain, M.P.; Goyder, E.C.; Rigby, J.E.; El Nahas, M. CKD and poverty: A growing global challenge. Am. J. Kidney Dis. 2009; 53: 16 6–174.
3. Jha, V.; Garcia-Garcia, G.; Iseki, K.; Li, Z.; Naicker, S.; Plattner, B.; Saran, R.; Wang, A.Y.-M.; Yang, C.-W. Chronic kidney disease: Global dimension and perspectives. Lancet. 2013; 382: 260–272.
4. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017 Lancet. 2020; 395:709-733.
5. Dare AJ, Fu SH, Patra J et al.; Million Death Study Collaborators. Renal failure deaths and their risk factors in India 2001–13: nationally representative estimates from the Million Death Study. Lancet Glob Health 2017;5: e89-e95.
6. Nast CC. Medication-Induced Interstitial Nephritis in the 21st Century. Adv Chronic Kidney Dis. 2017; 24:72-9.
7. Perazella MA. Clinical Approach to Diagnosing Acute and Chronic Tubulointerstitial Disease. Adv Chronic Kidney Dis 2017; 24:57-63.
8. Hart, E., Dunn, T. E., Feuerstein, S. & Jacobs, D. M. Proton pump inhibitors and risk of acute and chronic kidney disease: A retrospective cohort study. Pharmacotherapy. 2019; 39: 443–453.
9. Yang, Y. et al. Proton-pump inhibitors use, and risk of acute kidney injury: A meta-analysis of observational studies. Drug Des. Dev. Ther. 2017; 11: 1291–1299.
10. Moayyedi, P. et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology. 2019; 157:682–691.
11. Wu C-C, Liao M-H, Kung W-M, Wang Y-C. Proton Pump Inhibitors and Risk of Chronic Kidney Disease: Evidence from Observational Studies. *Journal of Clinical Medicine*. 2023; 12(6):2262.
12. Zhang XY, He QS, Jing Z, He JX, Yuan JQ, Dai XY. Effect of proton pump inhibitors on the risk of chronic kidney disease: A propensity score-based overlap weight analysis using the United Kingdom Biobank. Front Pharmacol. 2022 Nov 10;13:949699.

13. Klatte, D.C.; Gasparini, A.; Xu, H.; de Deco, P.; Trevisan,M.; Johansson, A.L.;Wettermark, B.; Ärnlöv, J.; Janmaat, C.J.; Lindholm, B.Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology. 2017; 153: 702–710.
14. Levy, E.I.; Hoang, D.M.; Vandenplas, Y. The effects of proton pump inhibitors on the microbiome in young children. Acta Paediatr. 2020; 109: 1531–1538.
15. Minalyan, A.; Gabrielyan, L.; Scott, D.; Jacobs, J.; Pisegna, J.R. The gastric and intestinal microbiome: Role of proton pump inhibitors. Curr. Gastroenterol. Rep. 2017; 19: 42.
16. Dube, P.; DeRiso, A.; Patel, M.; Battepati, D.; Khatib-Shahidi, B.; Sharma, H.; Gupta, R.; Malhotra, D.; Dworkin, L.; Haller, S. Vascular calcification in chronic kidney disease: Diversity in the vessel wall. Biomedicines. 2021; 9: 404.
17. Kieboom, B.C.; Kiefte–de Jong, J.C.; Eijgelsheim, M.; Franco, O.H.; Kuipers, E.J.; Hofman, A.; Zietse, R.; Stricker, B.H.; Hoorn, E.J.Proton pump inhibitors and hypomagnesemia in the general population: A population-based cohort study. Am. J. Kidney Dis. 2015; 66: 775–782.
18. Jang, S.Y.; Kim, I.-H.; Ju, E.Y.; Ahn, S.J.; Kim, D.-K.; Lee, S.W. Chronic kidney disease and metabolic syndrome in a general Korean population: The Third Korea National Health and Nutrition Examination Survey (KNHANES III) Study. J. Public Health. 2010; 32:538–546.
19. Gheith, O.; Farouk, N.; Nampoory, N.; Halim, M.A.; Al-Otaibi, T. Diabetic kidney disease: Worldwide difference of prevalence and risk factors. J. Nephropharmacol. 2016; 5: 49.
20. Toh, J.W.T.; Ong, E.;Wilson, R. Hypomagnesaemia associated with long-term use of proton pump inhibitors. Gastroenterol. Rep. 2015; 3: 243–253.