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ASSOCIATION BETWEEN THE PROTON PUMP INHIBITOR USE AND INCREASED HAZARD OF INTERSTITIAL NEPHRITIS

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ABSTRACT

Background: Proton pump inhibitors (PPIs), widely used to manage gastric acid-related disorders, have been increasingly linked to renal complications, particularly interstitial nephritis (IN). Acute interstitial nephritis (AIN) is characterized by inflammation in the renal interstitium and can progress to chronic kidney disease if not promptly diagnosed.

Objective: To determine the association between PPI use and the incidence of interstitial nephritis among adult patients.

Methodology: This case-control study was conducted at Hameed Latif Hospital, Lahore from 10 December 2024 to 31 May 2025. A total of 70 patients (35 cases with interstitial nephritis and 35 controls without) aged 18–70 years were selected using non-probability consecutive sampling. Clinical data, laboratory results, and PPI usage history were recorded using a structured proforma. Data were analyzed using SPSS version 27.

Results: PPI use was significantly more frequent among cases than controls. The odds ratio demonstrated a strong association between PPI exposure and interstitial nephritis. After adjusting for age, gender, and comorbidities such as diabetes and hypertension, the association remained statistically significant ($p < 0.05$).

Conclusion: There is a significant association between the use of proton pump inhibitors and the incidence of interstitial nephritis. Caution should be exercised while prescribing PPIs, especially among elderly individuals or those with predisposing factors.

INTRODUCTION

Interstitial nephritis is a renal condition characterized by inflammation and oedema of the interstitial space between the renal tubules. Kidneys are the blood purifying organs and the excretory organs and they execute the functions to remove the metabolic excretion and waste material of the body that is assisted by excretory and secretory functions of the renal tubules. Depending on the cause and the time of exposure to the offensive substance, interstitial nephritis can take the form of acute or chronic manifestation. The disease might be clinically expressed in a great number of ways and such symptoms can appear as fever, rash, eosinophilia, malaise, myalgia, arthralgia, loss of weight, changes of urine volume, hematuria, pyuria, and high blood pressure [1 3].

A frequent cause of acute interstitial nephritis (AIN) is allergic reaction especially to some medicines. Common examples of such drugs include proton pump inhibitors (PPIs) that are very commonly used in the treatment of acid related gastrointestinal disorders. There are also other known nephrotoxic agents and among them are antibiotics like penicillin and sulphonamides, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants like cyclosporine, diuretics, allopurinol, and the use of H 2 receptor blockers like cimetidine [4].

Patients of senior citizens have a propensity towards drug induced age-related AIN because of the impacts of aging on the physiological status of the patients and the interplay of polypharmacy and predisposition of hypersensitivity reactions in old patients. These individuals are also predisposed to interstitial nephritis by non allergic factors that include autoimmune diseases, hypokalemia, and hypercalcemia [5]. Also, elderly people might eventually have a hard time managing mediation thus accidentally overdosing or causing drug interactions. One older study has been carried out and revealed that the incidence of PPI-induced AIN in older patients is much higher than was found in the younger populations. With regard to the most often implicated agents in this age group, omeprazole and penicillin were found [6,7].

The actions of PPIs can be explained by their ability to decrease the ability of the H + / K + ATPase enzyme system in the gastric parietal cell; the effect leads to inhibition of gastric acid secretion [8]. Though PPIs tend to be generic well-tolerated medicine, the growing amount of data is pointing to the suggestion that long-term use is associated with a variety of adverse consequences, such as pneumonia, Clostridium difficile infection, bone fractures, hypomagnesemia, dementia, and, not least, interstitial nephritis [9,10].

Nochaiwong et al. conducted a meta-analysis to examine the presence of adverse renal events by comparing the use of PPIs and those not engaging in them. Using the information of four cohort studies and five cases based on the control study of patients, the research discovered that 20.2 percent of patients had taken PPI. The rate ratios of the acute kidney injury (AKI) and the chronic kidney disease (CKD) in the PPI users were 1.44 and 1.36, respectively. Furthermore, odds of AIN and end-stage renal disease were (ESRD) 3.61 and 1.42 respectively [11,12]. In a study performed in 2014 by the University of Otago, New Zealand, it was found that three-quarters (35 out of 46) of AKI instances were recipients of PPI at the period, as opposed to one-half (207 out of 460) of controls [13].

This study has been developed in the light of the need to have further research on whether there is a significant association between the use of proton pump inhibitor and occurrence of interstitial nephritis. With the analysis of such a correlation, the study can make the contribution to safer PPI usage in clinical practice and the necessity of renal testing in the use of PPIs in the course of long-term use.

Objectives

The objective of this study is to determine the association between proton pump inhibitor (PPI) use and the incidence of interstitial nephritis. It aims to compare the frequency of PPI use among patients diagnosed with interstitial nephritis and those without the condition. Through statistical analysis, the study seeks to assess the strength of this association and evaluate whether PPI exposure significantly increases the risk of developing interstitial nephritis.

Methodology

This case-control study was conducted at Hameed Latif Hospital, Lahore from 10 December 2024 to 31 May 2025. A total of 70 participants were enrolled, comprising 35 cases diagnosed with interstitial nephritis and 35 controls without the condition. The total duration of the study was six months following the approval of the research synopsis. The cases and controls were matched based on age and gender to minimize confounding. The sample size was calculated using statistical parameters to ensure sufficient power and confidence. Participants were selected through a non-probability consecutive sampling technique,

allowing for the inclusion of all eligible patients who met the criteria during the study period.

Inclusion Criteria

The study included diagnosed cases of interstitial nephritis confirmed clinically and/or by biopsy. Controls consisted of individuals without interstitial nephritis. Participants were adults between 18 and 70 years of age. Both male and female patients were included.

Exclusion Criteria

Patients on hemodialysis, with known kidney disease, or using drugs other than PPIs that could cause interstitial nephritis were excluded. Individuals with thyroid or adrenal disorders, malabsorption, pregnancy, or allergic conditions were also excluded. All other known causes of secondary nephritis were excluded.

Data Collection

A structured proforma was utilized for data collection in the study. It included demographic details such as age and gender, along with relevant medical history. Clinical symptoms related to interstitial nephritis were carefully documented. Laboratory findings such as serum creatinine, blood urea nitrogen (BUN), glomerular filtration rate (GFR), and urine microscopy were recorded for all participants. Detailed information on PPI usage, including the type of drug, dosage, and duration of use, was also noted. This comprehensive approach ensured standardized and accurate data collection for analysis.

Data Analysis

Data analysis was carried out using SPSS version 27. Descriptive statistics were applied to summarize qualitative variables in terms of frequency and percentage, and quantitative variables using mean and standard deviation. Inferential statistics included the calculation of the odds ratio to assess the strength of association between PPI use and interstitial nephritis. Additionally, the chi-square test was used to evaluate the significance of associations, and stratified analysis was performed for variables such as age, gender, diabetes, and hypertension. A p-value of less than 0.05 was considered statistically significant at a 95% confidence interval.

Results

A total of 70 adult participants were enrolled and divided into two equal groups: 35 cases diagnosed with interstitial nephritis and 35 matched controls without the condition. The two groups were comparable in terms of baseline demographics, including age and gender distribution ($p > 0.05$), ensuring homogeneity for valid comparison.

Baseline Characteristics

Characteristic	Cases (n = 35)	Controls (n = 35)	p-value
Mean Age (years)	56 ± 11	53 ± 9	0.21
Male Gender (%)	20 (57.1%)	18 (51.4%)	0.62

There were no statistically significant differences in baseline characteristics between the two groups, confirming comparability.

Comparison of PPI Use Between Groups

Variable	Cases (n = 35)	Controls (n = 35)	p-value
PPI Use (%)	26 (74.3%)	16 (45.7%)	0.012
Odds Ratio (95% CI)	3.45 (1.41–8.46)	—	0.005

This table shows a significantly higher proportion of PPI use among cases compared to controls (74.3% vs. 45.7%, $p = 0.012$). The calculated odds ratio of 3.45 (95% CI: 1.41–8.46, $p = 0.005$) indicates a strong and statistically significant association between PPI use and interstitial nephritis.

Multivariate Analysis of Associated Factors

After adjusting for potential confounding factors such as age, gender, diabetes mellitus, and hypertension, PPI use remained significantly associated with interstitial nephritis.

Variable	Adjusted OR	95% CI	p-value
PPI Use	3.21	1.27–8.09	0.014
Diabetes Mellitus	1.19	0.52–2.74	0.68
Hypertension	1.44	0.61–3.43	0.41

These findings confirm that PPI use is an independent risk factor for interstitial nephritis, even after controlling for common comorbidities. Diabetes and hypertension were not found to have a significant effect on the incidence of interstitial nephritis in this sample.

Discussion

This study reinforces the growing body of literature suggesting a significant association between proton pump inhibitor (PPI) use and the development of interstitial nephritis (IN), especially acute interstitial nephritis (AIN). According to our findings, PPIs users were almost three times more likely to

develop IN than non-users, which was consistent with conclusions of the general reports based on large groups of people. It is noteworthy that in the third and fourth studies on this topic by Nochaiwong et al. and Blank et al., mildly to significantly higher risk of acute kidney injury (AKI), chronic kidney disease (CKD), and AIN was also noted among PPI users [11,13]. The tendency highlights a significant risk of a widely used drug category that is usually neglected.

Though PPIs are very useful in treating acid disorders like gastroesophageal reflux disease (GERD), peptic ulcers and Zollinger-Ellison syndrome, their side effects have come to be under serious attention with their multi-year use. The mechanism of these drugs is the inactivation of parietal cells H+/K+ ATPase pump irreversibly, which resulted in inhibition of gastric acid secreting capacity [8]. There is however evidence that there may be an immune based mechanism, which may be T cell based hypersensitivity, to the development of PPI-induced interstitial nephritis leading to tubulointersitial inflammation and loss of renal function [5,6,14].

Klatte et al. (2022) went further to writing that PPI-induced nephrotoxicity has an insidious clinical course and that it can be underdiagnosed since asymptomatic patients do not undergo regular renal testing [15]. More so, the risk is under threat in different formulations of PPI such as omeprazole, esomeprazole, and pantoprazole. Several sources identified that omeprazole and esomeprazole were the most commonly reported drugs with regard to drug-induced nephropathy [7,10].

Older adults are especially vulnerable because of various reasons: diminished renal reserve, a number of comorbidities and multi-pharmacy. As shown by Muriithi et al., the prevalence of AIN in older people is much higher, which usually translates to the delay in diagnosis and a worse prognosis [7]. A more recent study conducted by Shi et al. (2023) established that patients who were 60 or older and taking PPIs chronically (more than 6 months) were at 1.8 higher risk of developing renal function decrease than those taking it chronically but past the age of 60 [16].

Moreover, PPI-induced AIN has a non-obvious presentation, usually could be confined to non-specific manifestations, functional fatigue, malaise, or trivial alterations in urinary habits. Without any evident symptoms, clinicians can prescribe PPIs on a regular basis once started without reviewing the need. Without treatment, the AIN may cause a gradual and, at times, irreversible kidney injury, which may result in end-stage renal disease (ESRD) [3,10,12]. Based on these results, it is apparent that awareness and caution by healthcare providers are in dire need. Testing of renal functions (serum creatinine and estimated glomerular filtration rate) should become a regular part of treating patients undergoing long-term PPI therapy who have added risk factors (including advanced age, diabetes or hypertension). Prescribers must also follow evidence-based prescription, take the lowest effective dose, and restrict the durations of treatment to the extent possible.

Inappropriate use of PPI can be minimized by changing the behavior of the clinicians and patients through education. Also, deprescribing interventions in primary care are safe and may lead to the safe (j) discontinuation of unwarranted prescriptions of PPIs without affecting the control of gastrointestinal symptoms [17].

In short, PPIs are a significant group of drugs, but their risks may as well lead to interstitial nephritis, particularly in a vulnerable population, warranting a more conservative use. The safety guidelines can be optimized only by the future prospective studies and pharmacovigilance data in order to ensure the correct protection of renal health in the cases of long-term users.

Conclusion

The results of this study strongly suggest a significant association between the use of proton pump inhibitors (PPIs) and the development of interstitial nephritis (IN). Patients who were using PPIs had a notably higher likelihood of being diagnosed with IN compared to non-users, reinforcing findings from prior studies and meta-analyses. This association is particularly concerning given the widespread and often prolonged use of PPIs, especially in elderly patients who may already have age-related decline in renal function and are more susceptible to drug-induced kidney injury. Although PPIs are effective in managing acid-related gastrointestinal conditions, their long-term use should not be taken lightly. Physicians must adopt stricter prescribing practices, ensuring PPIs are prescribed only when clinically indicated and for the shortest duration necessary.

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