IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 6 Ser.10 (June 2025), PP 71-78
www.iosrjournals.org

Impact of proton pump inhibitors on kidney function & chronic kidney disease progression

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ABSTRACT
Background: *Proton pump inhibitors (PPIs) are among the most frequently prescribed medications for acid-related gastrointestinal disorders. Although generally considered safe, accumulating evidence suggests that prolonged PPI exposure may contribute to renal dysfunction; however, findings remain inconsistent, particularly in South Asian populations.*
Aim of the study: *To determine the association between proton pump inhibitor use and renal dysfunction among adults attending a tertiary care hospital.*
Methods: *This retrospective comparative cohort study included 300 adults recruited from the Departments of Nephrology and Gastroenterology of a tertiary care hospital in Dhaka, Bangladesh, over one year. Participants were categorized into PPI users (n=150) and non-PPI users (n=150). Baseline demographic and clinical characteristics, PPI exposure patterns, and renal outcomes were extracted from medical records. Primary outcomes included increased serum creatinine (≥0.3 mg/dL), decline in estimated glomerular filtration rate (eGFR ≥30%), acute kidney injury, chronic kidney disease (CKD), CKD progression, and proteinuria. Multivariable logistic regression was performed to identify independent associations, with statistical significance defined as $p<0.05$.*
Result: *Baseline characteristics were comparable between groups. Compared with non-users, PPI users had significantly higher incidences of increased serum creatinine (21.33% vs. 11.33%, p=0.02), mean creatinine change (0.18±0.32 vs. 0.09±0.24 mg/dL, p=0.01), eGFR decline ≥30% (19.33% vs. 9.33%, p=0.02), acute kidney injury (12.00% vs. 5.33%, p=0.04), and CKD progression (14.00% vs. 6.67%, p=0.03). Although new-onset CKD (10.00% vs. 4.67%, p=0.07) and proteinuria (11.33% vs. 6.00%, p=0.11) were more frequent among PPI users, these differences were not statistically significant. Patients receiving PPIs for more than 12 months had significantly greater odds of renal dysfunction (adjusted OR 2.47, 95% CI: 1.26–4.83; p=0.008), while high-dose therapy was independently associated with increased risk (adjusted OR 2.62, 95% CI: 1.18–5.81; p=0.02).*
Conclusion: *Proton pump inhibitor use was significantly associated with an increased risk of renal dysfunction, particularly among patients receiving prolonged or high-dose therapy. Careful patient selection, regular review of treatment necessity, and routine monitoring of renal function should be considered during long-term PPI treatment to minimize preventable kidney injury.*
Keywords: *Proton pump inhibitors; renal dysfunction; chronic kidney disease; acute kidney injury; estimated glomerular filtration rate; nephrotoxicity; proton pump inhibitor exposure.*

I. INTRODUCTION

Proton pump inhibitors (PPIs) are a group of medications that suppress gastric acid secretion by irreversibly inhibiting the hydrogen-potassium adenosine triphosphatase (H^+/K^+-ATPase) enzyme located on gastric parietal cells, and they are widely prescribed for acid-related gastrointestinal disorders such as gastroesophageal reflux disease and peptic ulcer disease [1]. Globally, approximately 23.4% (nearly one in four) of adults have been prescribed a proton pump inhibitor, with higher utilization observed among older adults and individuals with chronic comorbidities [2]. In Bangladesh, approximately 51-71% of prescriptions have been reported to be inappropriate or lacking evidence-based indications, reflecting substantial overuse in both hospital and outpatient settings [3]. This extensive utilization has drawn attention to the possibility of drug-related complications, particularly renal dysfunction, which may remain unrecognized until significant kidney damage has occurred. The proposed association between PPIs and renal dysfunction is biologically plausible. PPIs may trigger immune-mediated acute interstitial nephritis, characterized by inflammatory infiltration of the renal

interstitium. If this condition is not detected promptly, persistent inflammation may progress to chronic kidney disease through tubular atrophy, interstitial fibrosis, and irreversible nephron loss [4,5]. In addition, recurrent episodes of subclinical kidney injury, disturbances in magnesium homeostasis, oxidative stress, and endothelial dysfunction have been suggested as potential mechanisms contributing to long-term renal impairment among chronic PPI users. These mechanisms indicate that prolonged exposure may adversely affect renal function even in the absence of overt clinical symptoms [6]. Renal dysfunction associated with PPI therapy has important clinical consequences. Impaired kidney function increases the risk of cardiovascular disease, electrolyte imbalance, hospitalization, progression to end-stage kidney disease, and premature mortality [7]. Because PPIs are frequently prescribed for extended durations, even a modest increase in renal risk may have substantial public health implications. Nevertheless, PPIs remain highly effective medications with proven benefits, including rapid symptom relief, healing of peptic ulcers, prevention of upper gastrointestinal bleeding in high-risk patients, and eradication support for *Helicobacter pylori* infection [8]. Conversely, unnecessary or prolonged use may expose patients to avoidable adverse outcomes, including kidney injury, infections, micronutrient deficiencies, and fractures [9]. The association between proton pump inhibitor exposure and renal dysfunction may facilitate risk stratification, promote evidence-based prescribing, support periodic assessment of renal function, and encourage timely discontinuation of therapy when prolonged treatment is no longer clinically indicated [10]. Although numerous observational studies have examined this association, existing evidence remains inconsistent. Differences in study design, duration of follow-up, patient characteristics, definitions of renal outcomes, and control of confounding factors have produced variable findings [11]. Moreover, data from South Asian populations, including Bangladesh, remain limited despite widespread PPI use and the increasing prevalence of chronic kidney disease [12]. Therefore, the current study is needed to evaluate the association between proton pump inhibitor use and renal dysfunction within the local population. Generating context-specific evidence may help clinicians optimize prescribing practices and improve patient safety. The study aimed to determine the association between proton pump inhibitor use and renal dysfunction among the study population.

II. METHODOLOGY & MATERIALS

This retrospective comparative study was conducted in the Department of National Institute of Kidney Diseases & Urology (NIKDU) of a tertiary care hospital in Dhaka, Bangladesh. The study was carried out over a period of 1 year, from January to December 2024. A total of 300 participants were enrolled using a purposive sampling method and were divided into two groups according to proton pump inhibitor (PPI) exposure.

PPI users (n=150): Patients with documented proton pump inhibitor use for at least three consecutive months before enrollment.

Non-PPI users (n=150): Patients with no documented history of proton pump inhibitor use during the study period.

Inclusion Criteria

- Adult patients aged ≥18 years.
- Patients with baseline serum creatinine and eGFR measurements.
- Patients with at least one year of clinical follow-up.
- For the exposed group, documented use of proton pump inhibitors for at least three consecutive months.

Exclusion Criteria

- Patients with end-stage renal disease requiring dialysis.
- Previous renal transplantation.
- Acute kidney injury at baseline.
- Known primary renal diseases such as glomerulonephritis or nephrotic syndrome.
- Pregnancy.
- Patients receiving nephrotoxic chemotherapy or immunosuppressive agents.

Data Collection

After obtaining approval from the institutional authority, demographic and clinical information was collected from hospital medical records using a structured data collection form. Baseline characteristics including age, sex, body mass index (BMI), hypertension, diabetes mellitus, cardiovascular disease, smoking history, baseline serum creatinine, and baseline estimated glomerular filtration rate (eGFR) were recorded. Details of proton pump inhibitor exposure including type of PPI, duration of therapy, prescribed dose (standard-dose or high-dose), and concomitant non-steroidal anti-inflammatory drug (NSAID) use were documented. Participants were followed for one year, during which renal outcomes including increase in serum creatinine ≥0.3 mg/dL, mean change in serum creatinine, decline in eGFR ≥30%, development of acute kidney injury, new-onset chronic kidney disease, CKD progression, and development of proteinuria were recorded. Dose-response and duration-response analyses were also performed to determine the association between different patterns of PPI

exposure and the risk of renal dysfunction.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequency and percentage. The independent sample *t*-test was used to compare continuous variables between the two groups, while the Chi-square test or Fisher's exact test was applied for categorical variables. Multivariable logistic regression analysis was performed to identify independent factors associated with renal dysfunction after adjusting for potential confounding variables. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value of <0.05 was considered statistically significant.

III. RESULT

A total of 300 participants were included, comprising 150 PPI users and 150 non-PPI users. The mean age was
56.8±12.4 years among PPI users and 55.1±11.8 years among non-users (p=0.24), with participants aged ≥65 years accounting for 28.00% and 23.33%, respectively (p=0.36). Male participants represented 61.33% and 58.67% of the two groups (p=0.65). There were no significant differences in BMI (25.7±3.8 vs. 25.3±3.6 kg/m²; p=0.38), hypertension (52.00% vs. 42.00%; p=0.08), diabetes mellitus (42.67% vs. 36.67%; p=0.29), cardiovascular disease
(20.67% vs. 16.00%; p=0.31), smoking history (32.00% vs. 28.00%; p=0.46), baseline serum creatinine (1.02±0.31 vs. 0.98±0.28 mg/dL; p=0.25), or eGFR (78.4±18.6 vs. 80.1±17.9 mL/min/1.73m²; p=0.43) (Table 1). Among PPI users, 44.00% received therapy for >12 months, 30.67% for 6–12 months, and 25.33% for <6 months, with a mean treatment duration of 14.2±8.6 months. Omeprazole was the most commonly prescribed PPI (41.33%), followed by pantoprazole (32.00%), esomeprazole (18.67%), and rabeprazole (8.00%). Standard-dose therapy was used in 79.33% of patients, while 20.67% received high-dose treatment. Concomitant NSAID use was reported in 24.00% of PPI users (Table 2). PPI users had significantly higher rates of increased serum creatinine ≥0.3 mg/dL (21.33% vs. 11.33%; *p*=0.02), greater mean creatinine change (0.18±0.32 vs. 0.09±0.24 mg/dL; *p*=0.01), and eGFR decline ≥30% (19.33% vs. 9.33%; *p*=0.02) than non-users. Acute kidney injury (12.00% vs. 5.33%; *p*=0.04) and CKD progression (14.00% vs. 6.67%; *p*=0.03) were also significantly more common among PPI users. Although new-onset CKD (10.00% vs. 4.67%; *p*=0.07) and proteinuria (11.33% vs. 6.00%; *p*=0.11) occurred more frequently in the PPI group (Table 3). PPI users had significantly higher rates of increased serum creatinine ≥0.3 mg/dL (21.33% vs. 11.33%; *p*=0.02), greater mean creatinine change (0.18±0.32 vs. 0.09±0.24 mg/dL; *p*=0.01), eGFR decline ≥30% (19.33% vs. 9.33%; *p*=0.02), acute kidney injury (12.00% vs. 5.33%; *p*=0.04), and CKD progression (14.00% vs. 6.67%; *p*=0.03) compared with non-PPI users (Table 4). Renal dysfunction increased with longer PPI exposure and higher doses. Compared with non-users (16.00%), renal dysfunction occurred in 26.32% of patients using PPIs for <6 months (aOR 1.54, 95% CI: 0.68–
3.48; *p*=0.29), 32.61% for 6–12 months (aOR 1.82, 95% CI: 0.86–3.86; *p*=0.12), and 39.39% for >12 months (aOR
2.47, 95% CI: 1.26–4.83; *p*=0.008). Similarly, high-dose PPI therapy was associated with a significantly greater risk of renal dysfunction than standard-dose therapy (41.94% vs. 31.93%; aOR 2.62, 95% CI: 1.18–5.81, *p*=0.02 vs. aOR 1.71, 95% CI: 0.96–3.04, *p*=0.07), indicating a significant dose- and duration-dependent association (Table 5).

Table 1: Baseline characteristics of study participants according to proton pump inhibitor exposure.

Variables	PPI Users (n=150)	Non-PPI Users (n=150)	p-value
Age (years), mean ± SD	56.8 ± 12.4	55.1 ± 11.8	0.24
Age ≥65 years, n (%)	42 (28.00)	35 (23.33)	0.36
Gender			
Male sex, n (%)	92 (61.33)	88 (58.67)	0.65
Female, n (%)	58(38.67)	62(41.33)	
BMI (kg/m²), mean ± SD	25.7 ± 3.8	25.3 ± 3.6	0.38
Hypertension, n (%)	78 (52.00)	63 (42.00)	0.08
Diabetes mellitus, n (%)	64 (42.67)	55 (36.67)	0.29
Cardiovascular disease, n (%)	31 (20.67)	24 (16.00)	0.31
Smoking history, n (%)	48 (32.00)	42 (28.00)	0.46
Baseline serum creatinine (mg/dL), mean ± SD	1.02 ± 0.31	0.98 ± 0.28	0.25

Baseline eGFR (mL/min/1.73m²), mean ± SD	78.4 ± 18.6	80.1 ± 17.9	0.43

Table 2: Characteristics of proton pump inhibitor exposure among ppi users.

PPI Exposure Characteristics	Frequency (n)	Percentage (%)
Duration of PPI use		
<6 months	38	25.33
6–12 months	46	30.67
>12 months	66	44.00
Mean duration of use (months), mean ± SD	14.2 ± 8.6	
Type of PPI		
Omeprazole	62	41.33
Pantoprazole	48	32.00
Esomeprazole	28	18.67
Rabeprazole	12	8.00
Daily standard dose use	119	79.33
High-dose PPI therapy	31	20.67
Concomitant NSAID use	36	24.00

Table 3: Comparison of renal outcomes between ppi users and non-ppi users during 1-year follow-up.

Renal Outcomes	PPI Users (n=150)	Non-PPI Users (n=150)	p-value
Increase in serum creatinine ≥0.3 mg/dL, n (%)	32 (21.33)	17 (11.33)	0.02
Mean creatinine change (mg/dL), mean ± SD	0.18 ± 0.32	0.09 ± 0.24	0.01
eGFR decline ≥30%, n (%)	29 (19.33)	14 (9.33)	0.02
Acute kidney injury, n (%)	18 (12.00)	8 (5.33)	0.04
New-onset CKD, n (%)	15 (10.00)	7 (4.67)	0.07
CKD progression, n (%)	21 (14.00)	10 (6.67)	0.03
Proteinuria development, n (%)	17 (11.33)	9 (6.00)	0.11

Table 4: Logistic regression analysis of factors associated with renal dysfunction.

Renal Outcomes	PPI Users (n=150)	Non-PPI Users (n=150)	p-value
Increase in serum creatinine ≥0.3 mg/dL, n (%)	32 (21.33)	17 (11.33)	0.02
Mean creatinine change (mg/dL), mean ± SD	0.18 ± 0.32	0.09 ± 0.24	0.01
eGFR decline ≥30%, n (%)	29 (19.33)	14 (9.33)	0.02
Acute kidney injury, n (%)	18 (12.00)	8 (5.33)	0.04
New-onset CKD, n (%)	15 (10.00)	7 (4.67)	0.07
CKD progression, n (%)	21 (14.00)	10 (6.67)	0.03
Proteinuria development, n (%)	17 (11.33)	9 (6.00)	0.11

Table 5: Dose and duration response relationship between ppi exposure and renal dysfunction.

PPI Exposure Category	Renal Dysfunction n (%)	Adjusted OR (95% CI)	p-value
No PPI exposure	24 (16.00)	Reference	—
PPI use <6 months	10 (26.32)	1.54 (0.68–3.48)	0.29
PPI use 6–12 months	15 (32.61)	1.82 (0.86–3.86)	0.12
PPI use >12 months	26 (39.39)	2.47 (1.26–4.83)	0.008
Standard-dose PPI	38 (31.93)	1.71 (0.96–3.04)	0.07
High-dose PPI	13 (41.94)	2.62 (1.18–5.81)	0.02

IV. DISCUSSION

Proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide for the management of acid-related gastrointestinal disorders. Although they are generally considered safe, increasing evidence has suggested a potential association between long-term PPI use and adverse renal outcomes [13,14]. The present study evaluated the relationship between PPI exposure and renal dysfunction over a one-year follow-up period and demonstrated that PPI use was associated with a significantly greater risk of deterioration in renal function compared with non-PPI use. Furthermore, prolonged duration and high-dose PPI therapy were independently associated with an increased risk of renal dysfunction. The baseline demographic and clinical characteristics of the two groups were comparable, reducing the likelihood that the observed renal outcomes resulted from major baseline differences. The mean age was 56.8±12.4 years among PPI users and 55.1±11.8 years among non-users (p=0.24), while males accounted for 61.33% and 58.67% of the two groups, respectively. Baseline serum creatinine (1.02±0.31 vs. 0.98±0.28 mg/dL; p=0.25) and eGFR (78.4±18.6 vs. 80.1±17.9 mL/min/1.73m²; p=0.43) were also similar. These findings resemble those reported by Lazarus et al., whose prospective cohort included participants with preserved baseline kidney function and comparable demographic characteristics before evaluating the relationship between PPI exposure and incident CKD [15]. One of the principal findings of the present study was the significantly greater deterioration in renal function among PPI users. An increase in serum creatinine of ≥0.3 mg/dL occurred in 21.33% of PPI users compared with 11.33% of non-users (p=0.02), while the mean increase in serum creatinine was also significantly greater among exposed patients (0.18±0.32 vs. 0.09±0.24 mg/dL; p=0.01). These findings are consistent with the large cohort study by Xie et al., which demonstrated that PPI users had a significantly greater risk of serum creatinine doubling and progressive renal function decline than patients receiving H_2-receptor antagonists [16]. The present study also demonstrated that an eGFR decline of at least 30% occurred in 19.33% of PPI users compared with only 9.33% of non-users (p=0.02). This finding closely parallels the observations of Xie et al., who reported that PPI exposure significantly increased the risk of a greater than 30% decline in eGFR during long-term follow-up [16]. Similarly, Klatte et al. found that patients receiving PPIs experienced significantly faster deterioration of kidney function than H_2-blocker users, supporting the hypothesis that chronic PPI exposure contributes to progressive renal impairment. The consistency between these studies and the present findings strengthens the evidence linking long-term PPI therapy with declining renal function [17]. Acute kidney injury developed in 12.00% of PPI users compared with 5.33% of non-users (p=0.04), indicating more than a two-fold higher occurrence among exposed patients. This observation agrees with the population-based cohort study by Antoniou et al., who reported that initiation of PPI therapy was associated with significantly increased risks of both acute interstitial nephritis and acute kidney injury among older adults [18]. Comparable findings were reported by Blank et al., who demonstrated an increased occurrence of biopsy-confirmed acute interstitial nephritis among current PPI users, suggesting that immune-mediated renal injury represents an important mechanism underlying PPI-associated AKI [19]. Regarding chronic renal outcomes, CKD progression occurred in 14.00% of PPI users compared with 6.67% of non-users (p=0.03), whereas new-onset CKD was more frequent among PPI users (10.00% vs. 4.67%), although this difference did not reach statistical significance (p=0.07). These findings are consistent with those of Lazarus et al., who first demonstrated that regular PPI use was independently associated with an increased risk of incident CKD in the Geisinger replication cohort [20]. Likewise, Arora et al. reported significantly greater odds of CKD among patients receiving PPIs than among non-users after adjustment for important clinical confounders [21]. Xie et al. further demonstrated that prolonged PPI therapy increased the risks of CKD, CKD progression, and end-stage kidney disease, supporting the present findings [16]. An important strength of the present study is the evaluation of dose-response and duration-response relationships. Patients receiving PPIs for more than 12 months demonstrated significantly greater odds of renal dysfunction (adjusted OR 2.47, 95% CI: 1.26–4.83; p=0.008), whereas high-dose therapy was associated with an adjusted OR of 2.62 (95% CI: 1.18–5.81; p=0.02). In contrast, shorter durations of therapy (<6 months and 6–12 months) showed increased but statistically non-significant risks. These observations are highly consistent with Xie et al., who demonstrated a graded increase in adverse renal outcomes with increasing cumulative duration of PPI exposure [16]. Similarly, Klatte et al. reported that prolonged PPI use was associated with progressively greater deterioration in renal function, indicating that cumulative exposure plays an important role in renal injury [17].

Limitations of the study: This study has several limitations. Its retrospective single-center design may have introduced selection and information bias, limiting generalizability. Residual confounding from unmeasured factors, including over-the-counter PPI use, medication adherence, dietary habits, and socioeconomic status, could not be completely excluded. Causality cannot be established because of the observational design. Renal biomarkers beyond serum creatinine and eGFR were unavailable, and histopathological confirmation of PPI-induced nephrotoxicity was not performed. Larger prospective multicenter studies are warranted.

V. CONCLUSION

The present study demonstrated a significant association between proton pump inhibitor use and adverse renal outcomes during one year of follow-up. Patients receiving PPIs exhibited significantly higher rates of increased serum creatinine, eGFR decline, acute kidney injury, and chronic kidney disease progression compared with non-users. Furthermore, prolonged therapy exceeding 12 months and high-dose PPI treatment were independently associated with a substantially greater risk of renal dysfunction, suggesting both duration- and dose-dependent effects. These findings support judicious prescribing of PPIs, particularly when long-term therapy is considered. Regular reassessment of treatment indications and periodic monitoring of renal function may facilitate early detection of kidney injury and improve patient safety while preserving the therapeutic benefits of PPIs.

Funding: *No funding sources*
Conflict of interest: *None declared*

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