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ORIGINAL ARTICLE

THE INCIDENCE OF IMPAIRED RENAL FUNCTIONS TAKING LONG TERM OMEPRAZOLE FOR GASTRIC PROBLEMS

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Abstract

Background: The proton pump inhibitors are principally recommended to treat acid related diseases. There is evidence that long term use of this class may affect the renal functions.

Objective: To determine the incidence of impaired renal functions in patients taking long term Omeprazole for gastrointestinal reflux disease or peptic ulcer disease.

Material and Methods: This case-control study was conducted at the Department of Medicine Public Sector Hospital, Islamabad, from Jul-2023 to Dec-2023. A total of 60 patients using oral Omeprazole at least 20mg tablet daily over a period of 6 months were enrolled in study group. Another 60 patients who were not taking any medication for their gastric problem were included as control group. All the investigations regarding demographics, medical history and laboratory investigations were recorded. The primary outcome was the number of patients with prevalence of chronic kidney disease.

Results: The mean age of study population was 51.08±9.52 years. The mean duration of Omeprazole use was 6.27±0.69 months. The results of primary outcomes showed that significantly higher number of patients developed chronic kidney disease in the study group compared to control group (43.33% Vs 10%, p<0.0001). Similarly, a significant decrease in eGFR was recorded in patients taking Omeprazole in comparison to the control group (64.23±27.16 Vs 85.53±16.7, p<0.0001).

Conclusion: Long term use of Omeprazole significantly increases the risk of impaired renal functions and should be recommended while considering this risk. This study specifically investigated Omeprazole; however, similar renal effects may extend to other proton pump inhibitors as a class.

Keywords: Impaired renal functions, Gastric problems, Omeprazole.
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Introduction:

The proton pump inhibitor (PPI) is a class of drugs principally recommended to prevent and treat acid related diseases which include both gastro esophageal reflux disease and peptic ulcer disease. It is also recommended to prevent bleeding caused by NSAIDs.[1] PPIs are among extensively used drugs as the global data show them in the list of 10 most widely used pharmaceutical agents.[2] Omeprazole was the first PPI available in the pharmaceutical market in 1988 and soon it emerged as ever best-selling product.[3] Different molecules marketed in PPI class include Omeprazole, pantoprazole, esomeprazole, lansoprazole, rabeprazole and dexlansoprazole.[4,5] Generally PPIs were considered very safe and effective drugs that lead to their use worldwide. Lately, it had been noticed that PPIs may impair renal functions in a group of patients in USA. The mechanism proposed for this impairment involves the PPI-induced acute interstitial nephritis which causes chronic inflammation and subsequent decline in glomerular filtration rate, ultimately predisposing to CKD. This has provoked the reservations to find out underlying potential side effects of this highly

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overused drug.

It is important to mention that PPIs are mostly recommended for a duration of 1-2 month but we observe that patients tend to take it over longer periods.[6] Matter of concern arises from the fact that 40-60% patients are using PPIs without any proper indication.[7] A recent study reported even a worse situation in Pakistan where 66.2% of the patients are inappropriately taking PPIs.[8] This unnecessary use of PPIs has causes some serious adverse events in these users including C. difficile infection, fracture and stroke.[1,9,10,11,12] Patients using PPIs are also reported with elevated risk of diabetes and kidney disease.[13,14,15]

The incidence of chronic kidney disease (CKD) as estimated globally is up to 9.1% which accounts for early incidences of morbidity and mortality as the mortality figures due to CKD ranges up to 1.2 million.[16] Although the risk factors of CKD are numerous which include diabetes, hypertension, cardiovascular disease, obesity and life style, however, there is evidence that PPIs may also affect the renal functions.[17] These evidences also suggest that PPI's effect on renal function may result in CKD.[18] A recent meta-analysis by Vengrus including 8 studies shared that PPIs increase the risk of CKD by 35%.[19]

The process of developing the CKD was initially explained to be linked to the incidences of acute interstitial nephritis which further leads to reduced glomerular filtration rate (GFR). [14] In contrast to these previous explanations, it is now found that CKD is even observed in patients using PPIs without any history of acute episodes.

Despite the importance of these serious findings, very few studies have worked on this topic especially in Pakistan. Selection of Omeprazole for this research was made, as it is the most widely prescribed and utilized PPI in the clinical setting of Pakistan, making it the most relevant agent for population-specific outcomes. In this scenario, this study was planned to determine the incidence of impaired renal functions in patients taking long term Omeprazole (one among the initial and most commonly used PPIs in Pakistan) for gastric problems. The findings of this study will be helpful in developing any clinical guidelines that encourage the prudent use of PPIs while taking into account the advantages and disadvantages of this treatment strategy.

Material and Method:

Place & duration: This prospective case-control study was conducted at the department of medicine of a Public sector Hospital in Islamabad from 1st of July 2023 to 31st of December 2023 over a period of 6 months.

Study design & setting: This case-control study was conducted at the Department of Medicine Public Sector Hospital, Islamabad, from July 2023 to December 2023.

Sample Size: Sample size was calculated using OpenEpi sample size calculator. Assumptions: Alpha = 5% (two-sided), Power = 80%, p_1 = 70.6% (CKD progression in Omeprazole users), p_2 = 10.5% (CKD progression in Omeprazole non-users).20 Estimated sample size: n_1 = 10, n_2 = 10. However, to improve the statistical power and reliability of the results, and to account for considerations such as confounders, small effect sizes, and potential participant dropouts, we enrolled a higher sample size of 60 participants per group.

Inclusion criteria:

The study group included a total of 60 patients aging 18 to 65 years reporting at the outpatient department and already using oral omeprazole at least 20mg tablet daily over a period of 6 months for their gastric problems. The patients were required to have a record of their baseline renal parameters and other related laboratory investigations at the time of Omeprazole recommendations. These baseline renal parameters were obtained from laboratory records at the time of Omeprazole initiation. Standardized automated assays within the hospital laboratory were used, ensuring uniformity of measurement across all participants.

Another 60 patients, not taking any medication for their gastric problem and had their record of concerning laboratory investigations were added as control group.

Exclusion Criteria:

Patients having baseline pre-existing CKD, patients taking regular NSAIDS, ACEIs, ARBs, other nephrotoxic drugs, diseases like CKD, DM of more than 2 years were excluded from the study.

Patient's compliance with Omeprazole use was confirmed through patient self-reporting and available prescription records. However, as the compliance was partly based on self-reporting, minor non-compliance cannot be excluded and may have influenced the results.

The two study groups were then sent to clinical examination and investigations including blood glucose, serum blood urea, serum createnine and eGFR.

The objective of the study was to find out the incidence of impaired renal functions in patients using regular PPIs. The primary outcome was set as the number of patients with prevalence of CKD among both groups.

The renal functions of the patients in the two groups were then tabulated and patients of low eGFR were then documented accordingly. Stages of renal functions were

determined as normal (GFR≥90), mild (GFR=60-89), moderate (GFR=30-59), severe (GFR=15-29) and end stage kidney disease (<15/ dialysis).

Informed consent was taken from the study group individually as required.

Data analysis:

SPSS version 25 was used for the process of data analysis. Quantitative variables were calculated in form of mean and standard deviation. Qualitative variables were expressed in form of frequency and percentage. Independent t-tests and chi-square tests (or Fisher exact test) were employed to assess the statistical significance of differences among outcomes of the 2 groups keeping p≤0.05 as significant. The results were then formed and tabulated accordingly. No additional adjustments were made for potential confounders such as diet or hydration status, which is acknowledged as a limitation of the study.

Results:

The mean age of overall study population was 51.08±9.52 years with age range from 34 to 65 year. Number of male patients was 74 (61.66%) while the number of female patients was 46 (38.33%). The group wise details of demographic are given in Table-I.

Table-I: Demographics n=120

Demographics		Study group n=60	Control group n=60
Age (Mean±SD) years		50.46±9.72	51.7±9.44
Gender	Male n (%)	36 (60)	38 (63.33)
	Female n (%)	24 (40)	22 (36.66)

Baseline clinical characteristics were recorded. Similarly, duration of Omeprazole use was recorded in the study group are shown in Table-II.

Table-II: Baseline clinical characteristic n=120

Baseline clinical characteristic		Study group n=60	Control group n=60
Dyslipidemia n (%)		16 (26.66)	14 (23.33)
Smoking n (%)		14 (23.33)	12 (20)
Duration of Omeprazole use (Mean±SD) months		6.27±0.69	N/A
eGFR (Mean±SD) ml/min/1.73 m2		89.06±16.76	90.9±10.90
CKD stage	Normal n (%)	56 (93.33)	54 (90)
	Mild n (%)	4 (6.66)	6 (10)

A significant decrease in eGFR was recorded in patients taking Omeprazole in comparison to the control group (64.23±27.16 Vs 85.53±16.7, p<0.0001). The results of primary outcomes showed that significantly higher number of patients developed CKD in the study group compared to control group (43.33% Vs 10%, p<0.0001) and patients in the study group had 10.29 times higher odds of developing CKD compared to the control group (95% CI: 3.84–27.52, p<0.0001) as shown in Table-III.

Table-III: Study Outcomes n=120

Study outcomes	Study group n=60	Control group n=60	Odds Ratio (95% CI)	p-value
eGFR (Mean±SD) ml/min/1.73 m²	64.23±27.16	85.53±16.7	-	<0.0001
Patients with CKD				
Mild n (%)	26 (43.33)	6 (10)	6.89 (2.57-18.45)	<0.0001
Moderate n (%)	6 (10)	0 (0.0)	-	0.03
Total	32 (53.3)	6 (10)	10.29 (3.84-27.52)	<0.0001

It is important to mention that no subgroup analysis was performed to assess the association between patient characteristics (age, gender, or duration of using Omeprazole) and CKD severity, which is acknowledged as a limitation of the study. Moreover, patients were not followed up to evaluate progression or resolution of CKD after the discontinuation of Omeprazole, which is also recognized as a limitation of this study.

Discussion:

The topic of correlation between PPI and impaired renal functions has been discussed in international literature; however, this data is sparse in Pakistani population. Moreover, most of the studies have discussed this impact on patients who were renal compromised while our study focused on determining the effect of Omeprazole use over the long term on patients with normal renal functions.

A systemic review done by Parmer M P worked on the comparison on the benefit and risks of PPI usage in view of incidences of decreased eGFR, acute kidney injury (AKI) and progression of CKD. The results mentioned a correlation between the two and asked for extra evaluation before recommending PPIs in patients having pre-existing kidney related risks.[21]

A case-controlled study to find any relation of using PPI and CKD risk was planned in Taiwan by extracting the nation-wide data. The results showed that patients using PPIs had increased risk of developing CKD by 1.4-fold.[22]

Hart E studied the correlation between the PPIs use and the incidences of AKI and CKD. The results of this large scale study confirmed that the patients using PPI had significantly higher risk of AKI (p<0.0001). Similarly the patients using PPIs had significantly elevated risk of CKD compared to non-users (3.43% Vs 0.875%, p<0.0001).[23]

ELSA-Brasil study worked on the data of 13909 patients and assessed their renal functions using the findings of GFR considering < 60 ml/ min/1.73 m2 as CKD. The results of this study showed that patients using PPIs ≥6 months had notable decreased renal functions compared to non-users.[24]

A recently published cross-sectional study by Singh M et al. in an Indian population aimed to find the correlation of PPI use and renal dysfunction. This study included 250 patients using PPIs including Omeprazole, pantoprazole, and rabeprazole. Patients using PPIs for 1 week showed a mild reduction in renal function ($p<0.0001$) and those using PPIs for >1 to 2 weeks developed grade 2 renal dysfunction ($p=0.001$), while use of PPIs for >2-3 weeks resulted in grade 3 dysfunction (a statistically non-significant $p=0.44$). The authors mentioned that this impact of PPIs on renal dysfunction is more prominent in patients aged above 50 years. The study shared important finding that there is 4 fold increases in risk of kidney dysfunction in older patients using PPIs for more than 2 weeks.[25]

Guedes JVM conducted a retrospective study to determine any relation between regular omeprazole use and the onset of kidney disease. A link of omeprazole use with progression of CKD was established, identifying an elevated risk of disease evolution in patients using omeprazole compared to non-users (70.6% Vs 10.5%, $p>0.05$).[20]

The mean age of total participants of our study was 51.08±9.52 years. Out of these, 74 (61.66%) were males while 46 (38.33%) were females. The mean duration of omeprazole use was 6.27±0.69 months.

In our study, a significant decrease in eGFR was recorded in patients taking omeprazole in comparison to the control group (64.23±27.16 Vs 85.53±16.7, $p<0.0001$). The results of primary outcomes show that the incidence of CKD was significantly higher in the study group compared to controls across all categories. Mild CKD was observed in 43.33% of the study group versus 10% of controls, showing nearly 7 times higher odds of developing mild CKD (OR=6.88, 95% CI: 2.57-18.45, $p<0.0001$). Similarly, moderate CKD occurred exclusively in the study group (10%) with no cases in the control group ($p=0.03$), (odds ratio could not be calculated due to zero events in controls). Overall, 53.3% of the patients in the study group developed CKD compared to only 10% in the control group, representing a 10-fold increased risk associated with omeprazole use (OR=10.29, 95% CI: 3.84-27.52, $p<0.0001$). The underlying mechanisms linking omeprazole use to this renal impairment observed are thought to involve PPI-induced acute interstitial nephritis that can lead to chronic tubulointerstitial inflammation and fibrosis, resulting in a progressive decline in glomerular filtration rate. Additionally, prolonged PPI therapy may cause hypomagnesaemia, oxidative stress, and endothelial dysfunction, all of which can contribute to renal injury and impaired function.[26]

These outcomes of our study are in accordance with the data shared by studies previously conducted on this subject and establish a correlation between long term omeprazole use and incidence of impaired renal function.[20,21, 22, 23,24,25]

As even mild CKD increases the risk of disease progression and CV events, while moderate CKD adds to healthcare burden through frequent monitoring and treatment costs, this risk underscore the need for early detection and cautious regarding long-term use of PPI.

In view of these findings, patients requiring prolonged PPI therapy should undergo periodic monitoring of renal function, particularly eGFR, to enable early detection of renal impairment. Where appropriate, alternative options may be considered such as H_2receptor antagonists for symptom control in patients at risk of kidney dysfunction.

Although we specifically evaluated omeprazole, similar renal effects have been reported with other PPIs. However, variations in pharmacokinetics of different PPIs, such as hepatic metabolism and renal clearance, may influence the degree of renal risk, suggesting that the findings may not be identical across all these agents.

The limitations of our study include the small sample size. Confounders which were not measured like dietary habits or hydration status may also have influenced renal function and were not controlled for in this study. It is important to mention that no subgroup analysis was performed to assess the association between patient characteristics (age, gender, or duration of omeprazole use) and CKD severity. Moreover, patients were not followed up to evaluate progression or resolution of CKD after discontinuation of omeprazole. These all are also recognized as limitations of the study. Future studies covering these aspects will add to this useful data on omeprazole use and renal impairment risk in our local patients.

Conclusion:

Omeprazole is a useful and widely used drug for acid related disorders; however, its long term use significantly elevates the chances of impaired should be monitored every 3–6 months, and prescription should be discontinued once symptoms resolve or when safer alternatives, such as H_2-receptor antagonists, are appropriate. Although this study evaluated only omeprazole, clinicians should consider this as a potential class effect while recognizing that individual PPI pharmacokinetics may modulate risk.

Conflict of interest:

No

Disclaimer:

No

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renal functions. When recommended for the long term, this risk against the benefit must be kept in mind as potential side effect. For patients requiring prolonged therapy, renal function, particularly eGFR

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