Original Article

# Diabetic Nephropathy and Proton Pump Inhibitors – Pilot Case-Control Study


## Abstract

**Introduction:** Proton pump inhibitors (PPIs) are liberally used over the counter medication and is largely considered safe. Off late, there are many reports that suggest increased incidence of chronic kidney disease with long-term PPI use. PPIs are often prescribed in patients with diabetes mellitus (DM) and one of the well-known complications of DM is diabetic nephropathy (DN). Thus, the aim of our study was to evaluate association between PPI use and DN. **Methods:** It was a case-control study conducted over a 2-year period (April 2017–March 2019). Cases were outpatients with type II DM and associated DN. Controls were age and sex-matched type II DM without DN. **Results:** A total of 200 participants, 100 each in the case and control group, were recruited. The proportion of participants using PPI was 62% in the cases and 42% in the controls ($P$ = 0.005). The most common PPI used was pantoprazole. Increased duration of PPI use was significantly associated with DN [adjusted odds ratio: 1.171; 95% confidence interval: 1.022, 1.341; $P$ = 0.023]. **Conclusion:** There is a significant association between the use of PPIs and DN in patients with type II DM. Since PPIs have other beneficial effects in patients with DM such as glycaemic control and relief from gastro-oesophageal symptoms, need for risk benefit assessment for long-term use of PPIs in DM is warranted.


**Keywords:** *Case control study, chronic kidney disease, diabetic nephropathy, noninsulin dependent diabetes mellitus, proton pump inhibitors*


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## Introduction

Diabetes mellitus (DM) is currently one of the most frequently diagnosed noncommunicable disease in the world with an estimated 462 million individuals (6.28%). Approximately, 1 million deaths were attributed to DM in the year 2017 alone, making it the ninth leading cause of mortality.[1] The long-term effects of DM include various complications such as diabetic retinopathy, nephropathy, neuropathy, and autonomic dysfunction.[2] Proton pump inhibitors (PPIs) are liberally used and is also available over the counter considering its safety profile. Among patients with DM, PPI prescription is common as they are at high risk of gastroesophageal reflux secondary to decreased gastrointestinal (GI) motility.[3] Further, those with diabetic nephropathy (DN) can have GI symptoms such as nausea and/or vomiting that warrants use of a PPI.[4] In 2005, over 43 million prescriptions were written for antiulcer therapy in the United States. It has been estimated that between 25 and 70% of PPI prescriptions have no appropriate indication. The duration of use frequently extended beyond the recommended guidelines.[5] Although generally well-tolerated, there is emerging evidence of association between PPIs and renal dysfunction such as acute interstitial nephritis and CKD. Acute interstitial nephritis (AIN) associated with omeprazole was first published in 1992.[6] In the subsequent 12 years, 29 cases of omeprazole-induced AIN were published, of which 23 were biopsy-proven.[7] In 2004, two large case series revealed that other PPIs, such as lansoprazole and pantoprazole, cause kidney injury.[8] A retrospective data collection from two teaching hospitals from Australia over a period of 10 years between 1993 and 2003 reported 28 cases of biopsy proven AIN, of which 18 were associated with a PPI. The mean time of development of AIN after initiation of PPIs was 11 weeks.[9] The most likely pathogenesis was described as hypersensitivity immune reaction to the drug or one of its metabolites.[6] With this background, the



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current study was aimed at evaluating association between PPI use and DN. The secondary objective was to describe the prescription pattern of ulceroprotective agents (UPA) among diabetic patients.

## Methods

The study was approved by the institutional ethics committee (Study reference number: 173/2016). A written informed consent was obtained from all participants.

### Study design and eligibility criteria

This was a case control study conducted during a 2-year period (April 2017–March 2019) in a tertiary care teaching hospital in Bengaluru, south India. The cases were defined as those patients who visit Medicine, Endocrinology, and Nephrology outpatient departments of our hospital with type II DM, glycemic levels controlled on treatment and are diagnosed by the treating physician with DN as per the American Diabetes Association Guidelines.[10] The controls were defined as those patients with type II DM, glycemic levels controlled on treatment, but with no evidence of DN. The controls were age and sex matched. Participants who were on hemodialysis, critically ill, concomitant heart or liver failure, and those who were not willing to give consent were excluded from the study.

### Sample size and sampling strategy

Since there were no previous studies available on association between PPI use and DN [PubMed search using keywords ("proton pump inhibitor" OR "PPI") AND ("Renal" OR "Nephropathy")] as on July 15, 2016, a formal sample size calculation was not done. Hence, a pilot study was conducted with 100 cases and 100 controls. Few days in a week were chosen at random and all consenting eligible participants fulfilling the criteria for cases were enrolled.

### Study procedures and data management

After obtaining written informed consent, the participants were assessed for their eligibility to participate in the study. A semi-structured standardized, case record format was used to capture data such as demography, relevant clinical history, prescriptions of antidiabetic agents, and UPAs. Data entry was done Epi info ver. 7 (Publisher: CDC, USA in 2011) and analyzed using statistical package for social sciences (SPSS) ver. 20 (Publisher: IBM Corp., USA, 2011).

### Statistical analysis plan

The demography, clinical characteristics, and prescription patterns of antidiabetic agents and UPAs were summarized using descriptive statistics. The difference in proportions of PPI use between groups was analyzed using Chi-Squared test. The association between increased duration of PPI use and DN was evaluated using the binary logistic regression model. The duration of PPI use along with other hypothesized risk factors of renal dysfunction like hypertension and duration of diabetes besides age and gender were subjected to univariate analysis. All factors except age whose significance value, $P < 0.2$, were subjected to multivariate analysis. The statistical significance was set at $P < 0.05$.

## Results

A total of 145 cases and 121 controls were screened and finally 100 each were recruited. The reasons for exclusions in the cases group include unwillingness to give consent ($n = 12$), on hemodialysis ($n = 27$), and severely ill ($n = 6$). The reasons for exclusion in the control group were unwillingness to give consent ($n = 21$). The mean age in the cases group was 57.48 ± 10.37 and that of the control group was 56.19 ± 11.03. Female participants (70%) were more in both the groups. The other relevant clinical and demographic characteristics are summarized in Table 1. The proportion of participants using PPI in the cases group was 62%, while that in the control group was 42% ($P = 0.005$)

The prescription pattern of antidiabetic medications is summarized in Table 2. The common agents include metformin and sulphonylureas. Insulin replacement therapy (isophane, glargine, and regular insulin) have been prescribed more in participants with DN than the controls. The prescription pattern of UPAs is summarized in Table 3. The agents used were PPIs, $H_2$ receptor antagonists, and antacids. The most common UPA used was pantoprazole (56/69 in cases and 32/49 in controls). A total on 4 participants in the cases and 6 participants in the control group were on fixed dose combinations of a PPI with domperidone. There was 9 participants in the case group and 2 participants in the control group who were on two UPAs (One PPI with ranitidine). Among those receiving a UPA, 49 (71.0%) in the cases group and 40 (81.6%) in the controls group were not aware about the reason why they are on a UPA.

The median (IQR) duration of use of PPIs among cases is 3.00 (0.79, 9.00) years, while for those in the control group, it was 1.83 (0.50, 4.00) years. The results of the univariate and the multivariate analysis evaluating the association between duration of use of PPI and DN is summarized in Table 4. Increased duration of PPI use was significantly associated with DN [adjusted odds ratio: 1.171; 95% CI: 1.022, 1.341; $P = 0.023$].

## Discussion

We report an association between PPI drugs and DN in an Indian diabetic population. There was an increased odd of 17% for a diabetic patient developing DN due to PPI use after adjusting for variables like gender, duration of diabetes treatment, medical history of hypertension, and duration of the diabetes. These results are in line with the findings from studies published very recently from other

**Table 1: Descriptive characteristics**

| Variable | | Case (*n*) *n*=100 | Control (*n*) *n*=100 | *P* |
|---|---|---|---|---|
| Age (years) | 30-59 | 56 | 52 | 0.670 |
| | 60 and above | 44 | 48 | |
| Sex | Male | 30 | 30 | 1.000 |
| Hypertension | Present | 84 | 48 | <0.001 |
| Duration of diabetes (years) | <5 | 14 | 34 | <0.001 |
| | 5-10 | 17 | 28 | |
| | 10 and above | 69 | 38 | |
| Number of diabetic medications | 1 | 53 | 54 | 0.500 |
| | 2 | 42 | 46 | |
| | 3 | 5 | 10 | |
| Ulceroprotective agents use | Yes | 69 | 49 | 0.004 |
| Proton pump inhibitor use | Yes | 62 | 42 | 0.004 |

**Table 2: Prescription pattern of diabetes mellitus**

| Medication* | Case *n*=100 | Control *n*=100 |
|---|---|---|
| Metformin | 48 | 86 |
| Glimepride | 14 | 24 |
| Glyburide | 5 | 1 |
| Gliclazide | 9 | 8 |
| Glibenclamide | 4 | 1 |
| Glipizide | 3 | 3 |
| Sitagliptin | 0 | 3 |
| Linagliptin | 4 | 2 |
| Tenegliptin | 0 | 6 |
| Pioglitazone | 2 | 1 |
| Vildagliptin | 0 | 6 |
| Voglibose | 0 | 2 |
| Insulin - Isophane | 33 | 15 |
| Insulin - Glargine | 13 | 3 |
| Insulin - Actrapid | 17 | 5 |

*Few participants have received more than one medication and hence the total medicines do not add up to get *n* in each group

**Table 3: Prescription pattern of ulceroprotective agents**

| Medication* | Case [*n* (%)]; *n*=69 | Control [*n* (%)]; *n*=49 |
|---|---|---|
| Pantoprazole | 56 (81.16) | 32 (65.31) |
| Omeprazole | 2 (2.90) | 4 (8.16) |
| Pantoprazole-Domeperidone | 1 (1.45) | 5 (10.20) |
| Omeprazole-Domeperidone | 3 (4.35) | 1 (2.04) |
| Ranitidine | 15 (21.74) | 8 (16.33) |
| Famotidine | 0 (0.00) | 1 (2.04) |
| Antacids | 1 (1.45) | 0 |

*Few participants have received more than one medication and hence the total medicines do not add up to get *n* in each group

countries. Yang *et al*.[11] from Taiwan have reported that the hazards ratio of incident CKD among individual with DM was 1.52. On a similar note, Xie *et al*.[12] have reported it to be 1.28 (95% CI: 1.23, 1.34). Another study from the USA has reported that individuals with DM have an increased odds of 10% to develop CKD if on a PPI.[13] Davis *et al*.[14] from Australia have reported that patients with DM who start on PPI therapy experience a significant reduction in the estimated glomerular filtration rate when compared to those who have never been treated with a PPI.

The mean age of participants in our study was approximately 57 years, which is similar to those reported in other studies.[15,16] Moreover, it is a known fact that increasing age is a risk factor for onset of DN, thus reflecting the later onset of the disease.[15,16] A large majority (81%) of cases had a history of hypertension and 69% also had a history of DM for a duration longer than 10 years both of which are well-documented risk factors for developing DN.[17] The proportions of participants with a history of DM >10 years or hypertension were much less among participants of the control group.

DM could increase the risk of peptic ulcer disease as reported by Peng *et al*.,[18] where type II DM patients had significantly increased risk of peptic ulcer bleeding (hazard ratio 1.44, 95% CI: 1.11, 1.86; $P < 0.001$) after adjusting for confounders. Thus, the concomitant use of UPA has been very common in diabetic patients as seen in our study. The most common UPA in use was a PPI, and the most common PPI in use was pantoprazole. However, a vast majority of the participants (approximately 70–80%) in our study were not aware of the indication. These findings were similar to other studies reporting irrational use of UPAs. Gamelas *et al*.[19] have reported that among 318 hospital admissions, 148 patients (46.5%) were on PPI at admission and 175 (55%) at discharge; most of them had a PPI without an indication ($n = 91$, 61.5% and $n = 109$, 62.3%, respectively).

Use of PPIs is common in diabetes, and they are particularly effective in reducing risk in patients with upper gastroesophageal reflux disease.[20] In addition to this, PPIs are effective in glycemic control through stimulation of gastrin which in turn activates beta cells of the pancreas and leads to increased insulin release and better diabetes control.[21] However, despite the clinical benefit offered by these drugs, the evidence on development of nephropathy due to PPI is considerable.[22] Most of the

**Table 4: Association between use of proton pump inhibitors and diabetic nephropathy**

| Risk factors | Univariate analysis | | Multivariate analysis* | |
|---|---|---|---|---|
| | OR | *P* | aOR (95 CI) | *P* |
| Male gender | 2.318 | 0.072 | 3.437 (1.075, 10.995) | 0.037 |
| Increasing age | 1.018 | 0.361 | Not included in analysis | |
| Being hypertensive | 10.476 | <0.001 | 15.065 (4.463, 50.847) | <0.001 |
| Increasing duration of diabetes | 1.119 | <0.001 | 1.123 (1.044, 1.208) | 0.002 |
| Increasing duration of PPI use[#] | 1.114 | 0.035 | 1.171 (1.022, 1.341) | 0.023 |

OR - Odds ratio, aOR - Adjusted Odds ratio, CI - Confidence Interval. *Nagelkerke *R*=50.5. [#]Cases: Mean (SD) duration of use of PPIs=5.15 (5.45) years; Median (IQR) = 3.00 (0.79, 9.00) years. Controls: Mean (SD) = 2.99 (3.79) years; Median (IQR) =1.83 (0.50, 4.00)

patients in our study were on Metformin therapy followed by sulfonylureas. The medical history of these patients suggests that they were administered drugs for glycemic control over a long time in addition to the PPIs. Although metformin has always been avoided in patients with renal damage due to the risk of lactic acidosis, recent evidence suggests that the long-term use of metformin in patients with moderate renal failure could result in a decline in renal function in the patients with DM.[23] Also, studies have shown that sulfonylureas, which were the second most commonly prescribed drugs in this case, can cause greater damage to the kidneys relative to metformin.[24] The magnitude of damage could be much higher in patients with other comorbidities. The development of DN, thus, cannot be entirely influenced by the use of PPIs but rather considered as a cumulative outcome of several variables.

In our study, we report that the development of nephropathy was influenced by variables like gender, duration of diabetes, and hypertension besides the long-term use of PPIs. Gender particularly had a significant influence with men having more than three times the odds of developing nephropathy relative to women. This observation is consistent with vast scientific literature that list male sex as a risk factor in the development and progression of nephropathy.[25] The higher probability of development of DN in men could be due to several factors like poor glycemic control, proteinuria, hormonal, and genetic factors.[26] Similarly, hypertensive patients had 15 times higher odds of developing nephropathy relative to those without the disease. The mechanisms involved in the development of nephropathy due to chronic hypertension, although not well elucidated, are believed to be due to oxidative stress and chronic inflammation that play a role in renal damage.[27] Age was not found to have any significant impact although other studies have listed age as a risk factor, probably due to a relatively small sample size in this study. However, the duration of diabetes was found to be a significant factor which is more relevant than the age of the patient in determining risk of development of DN. This is in alignment with a study by Rodriguez-Poncelas A *et al*.[28] who found the risk of CKD to be higher post 3 months of treatment with PPI.

The study has a few limitations. By virtue of the study design, the recall bias on variables such as duration of diabetes or duration of UPA use cannot be ruled out. We were also unable to capture accurate details on use of drugs in the past that have a potential to cause renal damage. These shortcomings could be addressed only by conducting prospective studies. Future research with cohort study designs can not only confirm the association that we have reported in this study but can also evaluate the causation. Despite the shortcomings, the present study is important as it does provide an evidence on the possible role of PPIs in DN.

## Conclusion

We report that there is a significant association between the use of PPIs and DN in patients with type II DM. Also, a vast majority of patients were on UPAs most commonly Pantoprazole. A definite caution must therefore be exercised in patients who have other risk factors for the development of DN, while prescribing a PPI.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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