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RESEARCH ARTICLE

Association of Proton Pump Inhibitor Use with the Risk of Incident Nephrolithiasis

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Abstract: ***Background:*** Proton pump inhibitors (PPIs) are widely prescribed for gastrointestinal disorders but may influence urinary solute handling and increase the risk of nephrolithiasis. Evidence regarding their effect on kidney stone formation and urinary chemistry remains limited. ***Objectives:*** To study the correlation between PPI use and incident nephrolithiasis and to assess its impact on 24-hour urine chemistry. ***Methods:*** This comparative research has been performed at the Department of Urology, Faculty of Medicine, Suez Canal University, including 456 adult cases identified with gastroesophageal reflux disease (GERD) and without prior nephrolithiasis. Participants have been separated into two groups: PPI users (number = 228) and non-users (number = 228). The primary outcome was kidney stone formation, assessed by patient history, clinical evaluation, and imaging. Secondary outcomes included stone recurrence and 24-hour urine analysis. ***Results:*** Clinical characteristics and baseline demographics have been balanced between groups, except for higher rates of hypertension and hyperlipidemia among PPI users. Stone composition did not differ significantly. However, PPI users had significantly lower urinary calcium, citrate, magnesium, phosphorus, sulfate, and supersaturation of calcium phosphate compared with non-users (all p below 0.05). Multivariable regression confirms independent correlations between PPI use and reductions in these urinary parameters. Insignificant variances have been observed for urinary volume, oxalate, pH, uric acid, or supersaturation of calcium oxalate. ***Conclusion:*** PPI use was associated with distinct alterations in urinary chemistry that may predispose to nephrolithiasis. These findings highlight the need for careful monitoring of kidney stone risk in long-term PPI users.

Keywords: Proton pump inhibitors, nephrolithiasis, kidney stones, urinary chemistry.

INTRODUCTION

PPIs are commonly administered drugs that influence both gastrointestinal and urinary solute management, with an indeterminate influence on the risk of nephrolithiasis. Our aims were to investigate the correlation among PPI exposure and the occurrence of nephrolithiasis, as well as to assess its impact on 24-hour urine chemistry. We conducted a single-center retrospective analysis on cases identified with gastroesophageal reflux disease (GERD) who had no prior history of kidney stones (1).

PPIs are extensively utilized globally as an efficacious gastrointestinal medication. Regarding the current literature, PPIs can diminish the excretion of calcium, magnesium, and other constituents in urine, potentially facilitating the development of renal stones (2). PPIs are commonly administered and influence intestinal ion absorption and urine ion levels. PPIs may either safeguard against or facilitate the formation of renal stones (3).

Kidney stones have become more common in urology, presenting a considerable issue due to escalating medical costs and societal effects. A national survey revealed that the prevalence of renal stones ranges from 1.7 to 14.8 percent, with rates continually rising each year globally (4).
Kidney stones are prevalent in the USA, affecting twelve percent of men and ten percent of women, and they significantly contribute to healthcare costs and morbidity. 1 2 Certain medications may influence the likelihood of renal stones by modifying active chemicals that crystallize in urine or by affecting urine composition (5). The majority of clinical studies examining the deleterious effects of proton pump inhibitors have utilized retrospective or cross-sectional methods, leading to criticism regarding the causality of PPI use due to the absence of temporal connection and the necessity for randomized controlled trials. The dose-response relationships between PPI usage and diseases can strengthen the data regarding the detrimental impacts of PPI consumption (6).

Numerous observational studies have shown a heightened prevalence of renal problems in persons utilizing PPIs. Proton pump inhibitors are likely linked to chronic kidney disease (CKD), acute interstitial nephritis (AIN), acute kidney injury (AKI), and end-stage renal disease (ESRD) (7).
PPIs diminish gastric a` secretion by irreversibly inhibiting the H+/K+ ATPase, commonly referred to as the proton pump, situated in the parietal cells of the stomach mucosa. PPIs are extensively utilized for managing gastroesophageal reflux disease (GERD), Zollinger-Ellison syndrome, duodenal or gastric ulcers, erosive esophagitis, involving those induced by non-steroidal anti-inflammatory drugs (NSAIDs), and for the eradication of Helicobacter pylori in conjunction with antibiotics. (8).

Nephrolithiasis is a prevalent condition with significant recurrence rates, affecting up to 80–90% of individuals within a decade. It is often associated with metabolic disorders like obesity, diabetes, and hypertension. The need for improved management strategies highlights the importance of understanding recurrent stone formation and its risk factors (9).

The predominant therapies for kidney stones involve shock wave lithotripsy, ureteroscopic fragmentation and extraction, and percutaneous nephrolithotomy. Surgical interventions have significantly alleviated cases' pain; nonetheless, postoperative complications and a high recurrence rate of stones remain problematic. Consequently, researchers are concentrating on investigating novel targets and pharmaceuticals, which is essential for diminishing the frequency and recurrence rates of renal stones (10).

This research sought to assess the correlation between proton pump inhibitor usage and the occurrence of nephrolithiasis, as well as to analyze the impact of kidney stones on 24-hour urine chemistry.

Patients and methods

This Comparative research at the Department of Urology (Outpatient Urology Clinic), Faculty of Medicine Suez Canal University was conducted on 456 patients previously diagnosed with GERD by a GIT specialist, they have been separated into two groups: one group received PPI and the other group who didn't receive PPI.

Inclusion criteria: Adults aged ≥ 18 years, previously diagnosed with GERD by a GIT specialist and had no history of nephrolithiasis. The duration of PPI usage was recorded (6 months to 1 year of continuous PPI use, the date of 1st PPI use defined as the start date).

Exclusion criteria: cases who were on PPIs before their initial GERD identification, those with a history of nephrolithiasis or a new diagnosis of nephrolithiasis within thirty-days of GERD identification, and pregnant women.

Study variables:

The variables of this study were considered as follows. Demographic data included age, marital status, gender, educational level, and smoking status. Factors that impacted the body's metabolic level included mean arterial pressure, body mass index (BMI), history of cardiovascular disease (CVD), HbA1c, thiazide use, loop diuretic use, triglyceride levels, and histamine-2 receptor antagonist (H2RA) utilize. Risk factors related to renal stone formation included total water intake, albumin-adjusted calcium concentrations, sedentary time, estimated glomerular filtration rate (eGFR), and history of gout.

Evaluation variables:

The independent factors in this research were the administration of PPIs by participants and the length of their usage. Data regarding the kind and duration of acid suppressant medication was acquired via prescription drug surveys. Proton pump inhibitors have been classified as lansoprazole, omeprazole, dexlansoprazole, esomeprazole, pantoprazole, and rabeprazole. For participants utilizing PPIs, the length of usage has been determined by the number of years following therapy initiation, while for non-users, the duration was noted as zero.

Dependent variable:

The dependent variable was the development of nephroliths. The primary result was determined by the response to the query, "Have you ever had kidney stones?", with a "yes" response classified as kidney stone formers.

Diagnosis of nephrolithiasis:

The diagnosis of nephrolithiasis has been established through clinical history, laboratory testing, physical examination, and imaging studies. Clinical history included sudden onset of flank pain radiating to the lower abdomen or groin, hematuria, nausea or vomiting, and urinary urgency or frequency if the stone was located near the bladder. Pain was typically severe, colicky, and intermittent. Past history of kidney stones, family history, diet, and hydration habits were also documented. On physical examination, flank or costovertebral angle tenderness was noted, although findings were often unremarkable unless complications occurred. Laboratory tests included urinalysis to detect hematuria, crystals, or infection, and serum tests such as creatinine, BUN, calcium, uric acid, and phosphate to assess renal function and metabolic contributors. Urine culture was performed if infection was suspected. Imaging studies consisted primarily of non-contrast helical CT of the abdomen and pelvis, which was considered the gold standard for detecting nearly all stone types and sizes. Ultrasound was used as an alternative to identify hydronephrosis or stones, while KUB X-ray was of limited use due to missing radiolucent stones. Optional 24-hour urine collection was performed for patients with recurrent stones to evaluate risk factors, with detailed instructions provided to ensure accurate sample collection.

Secondary outcome:

The 2ry outcome was the response to the question, "How many times have you passed a kidney stone?". Participants reporting two or more episodes have been categorized as recurrent stone formers.

Urine analytes:

To identify variances in 24-hour urine composition among PPI users and non-users, the following analytes were measured: calcium, citrate, oxalate, urine volume,

pH, phosphorus, potassium, chloride, sodium, sulfate, magnesium, uric a`, urea nitrogen, and creatinine.

RESULTS AND OBSERVATIONS:

Table (1): Demographic and clinical characteristics in the studied group

	Not exposed to PPI (Num. = 228)	PPI exposed (Num. = 228)	p value
Age (years) mean ± SD	54.1 ± 16.5	52.8 ± 15.9	0.042
BMI (kg/m²) mean ± SD	30.4 ± 7.1	29.9 ± 7.4	0.311
Sex			
Male	101 (44.3%)	97 (42.5%)	0.628
Female	127 (55.7%)	131 (57.5%)	
Past medical history			
Osteoporosis	16 (7.0%)	22 (9.6%)	0.313
Gout	9 (3.9%)	14 (6.1%)	0.282
CAD	50 (21.9%)	54 (23.7%)	0.679
Diarrhea	19 (8.3%)	28 (12.3%)	0.164
Hyperlipidemia	101 (44.3%)	107 (46.9%)	0.611
Hypertension	109 (47.8%)	120 (52.6%)	0.312
T2DM	54 (23.7%)	58 (25.4%)	0.693
IBD	5 (2.2%)	8 (3.5%)	0.394
Osteoporosis	16 (7.0%)	22 (9.6%)	0.313
Medications			
H2RA	162 (71.1%)	123 (53.9%)	**< 0.001**
Thiazide	57 (25.0%)	69 (30.3%)	**< 0.001**
Loop	51 (22.4%)	64 (28.1%)	**< 0.001**
Gout medication	12 (5.3%)	14 (6.1%)	**< 0.001**

This table shows that age was slightly lower in the PPI-exposed group than the non-exposed group, with the difference reaching statistical significance (p = 0.042). In contrast, BMI and sex distribution didn't differ significantly among groups. Regarding comorbidities, there were no statistically significant variances in the occurrence of osteoporosis, gout, coronary artery illness, diarrhea, hyperlipidemia, hypertension, type 2 diabetes, or inflammatory bowel disease, indicating that baseline clinical conditions were well balanced. Regarding medications, there were statistically significant variances: cases in the PPI-exposed group had a lower prevalence of H2 receptor antagonist use but a higher prevalence of thiazide, loop diuretics, and gout medications than the non-exposed group (all p below 0.001).

This table shows that, among comorbidities, hypertension was significantly more prevalent in the PPI-exposed group (67.5% versus 58.3%, p equal to 0.043). In addition, hyperlipidemia was also significantly higher among PPI users (44.3% vs. 34.6%, p = 0.010). Other conditions, including inflammatory bowel disease/diarrhea, gout, type 2 diabetes, osteoporosis, coronary artery disease, and cerebrovascular accidents, did not differ significantly between groups. Regarding medications, most were used at similar rates across the two groups, except for chlorthalidone, which was less frequently prescribed in the PPI-exposed group (0.9% vs. 2.2%, p = 0.046). Analysis of stone composition (available in 148 patients) showed no significant differences between groups, with calcium oxalate (monohydrate and dihydrate) being the most common type, followed by hydroxyapatite and uric acid stones.

This table shows that patients exposed to PPIs had significantly lower urinary calcium (5.0 vs. 5.7 mmol, p < 0.001), magnesium (3.6 versus 4.2 mmol, p < 0.001), citrate (3.0 versus 3.5 mmol, p equal to 0.031), phosphorus (29.5 vs. 33.2 mmol, p = 0.001), and sulfate (17.1 vs. 19.2 mmol, p = 0.004) compared to those not exposed. Moreover, supersaturation of calcium phosphate was also significantly reduced in the PPI group (1.1 vs. 1.5, p < 0.001). In contrast, insignificant variances have been observed between the two groups in urinary volume, oxalate, pH, uric acid, sodium, potassium, ammonium, chloride, creatinine (both mmol and µmol/kg), supersaturation of calcium oxalate, or uric acid.

Table (2) demographic and clinical characteristics of the research cohort with 24-h urine data

	No medication % (n = 228)	PPI % (n = 228)	p value
Past medical history			
Inflammatory bowel disease / diarrhea	21 (9.2%)	33 (14.4%)	0.067
Hypertension	133 (58.3%)	154 (67.5%)	**0.043**
Gout	16 (7.0%)	9 (3.9%)	0.062
Type 2 diabetes mellitus	55 (24.1%)	70 (30.7%)	0.095
Osteoporosis	12 (5.3%)	21 (9.2%)	0.069
Coronary artery disease	24 (10.5%)	30 (13.2%)	0.338
Cerebrovascular accident	6 (2.6%)	6 (2.6%)	0.886
Hyperlipidemia	79 (34.6%)	101 (44.3%)	**0.010**
Medication			
Allopurinol	5 (2.2%)	7 (3.1%)	0.716
Hydrochlorothiazide	22 (9.6%)	19 (8.3%)	0.398
Potassium citrate	11 (4.8%)	17 (7.5%)	0.100
Chlorthalidone	5 (2.2%)	2 (0.9%)	**0.046**
Indapamide	10 (4.4%)	11 (4.8%)	0.810
Stone composition (n = 148 had stone comp in studied group)	68 (29.8%)	80 (35.1%)	0.803
Calcium oxalate monohydrate	44 (64.7%)	54 (67.5%)	
Calcium oxalate dihydrate	4 (6.0%)	8 (10.0%)	
Hydroxyapatite	10 (15.0%)	9 (11.3%)	
Uric acid	4 (6.0 %)	4 (5.0%)	
Other	6 (8.3%)	5 (6.2%)	

Table (3): 24 H urine analytes between those exposed to PPI and those who weren't

Parameter	No PPI exposure (n = 228) Mean ± SD	PPI-exposed (n = 228) Mean ± SD	p value
Volume (mL)	1960 ± 830	1950 ± 810	0.95
Calcium (mmol)	5.7 ± 3.0	5.0 ± 2.8	<0.001
Oxalate (mmol)	0.41 ± 0.21	0.40 ± 0.22	0.79
Citrate (mmol)	3.5 ± 2.3	3.0 ± 2.0	0.031
pH	6.1 ± 0.5	6.1 ± 0.6	0.74
Uric acid (mmol)	3.9 ± 1.5	3.6 ± 1.4	0.13
Sodium (mmol)	188 ± 90	176 ± 85	0.058
Potassium (mmol)	60 ± 25	57 ± 23	0.27
Magnesium (mmol)	4.2 ± 1.8	3.6 ± 1.6	<0.001
Phosphorus (mmol)	33.2 ± 13.2	29.5 ± 11.8	0.001
Ammonium (mmol)	34 ± 14	36 ± 30	0.53
Chloride (mmol)	181 ± 83	171 ± 79	0.11
Sulfate (mmol)	19.2 ± 8.5	17.1 ± 7.8	0.004
Creatinine (mmol)	12.3 ± 4.0	11.8 ± 3.8	0.33
Creatinine (µmol/kg)	0.14 ± 0.03	0.13 ± 0.03	0.12
Supersaturation Ca-oxalate	7.0 ± 3.4	6.5 ± 3.8	0.082
Supersaturation Ca-phosphate	1.5 ± 1.0	1.1 ± 0.8	<0.001
Supersaturation uric acid	0.90 ± 0.81	0.91 ± 0.88	0.50

The table shows that PPI use was independently correlated with significant alterations in several urinary parameters. PPI use was significantly associated with reduced urinary calcium (beta = –0.85, p below 0.001), citrate (beta = –0.47, p = 0.004), sodium (beta = –12.1, p = 0.049), potassium (beta = –3.8, p = 0.025), magnesium (beta = –0.69, p below 0.001), phosphorus (beta = –3.25, p = 0.001), sulfate (beta = –1.92, p = 0.001), creatinine (beta = –1.05, p = 0.027), creatinine per body weight (beta = –0.0031, p = 0.007), and supersaturation of calcium phosphate (beta = –0.26, p below 0.001). Insignificant associations have been found between PPI use and urinary volume, oxalate, pH, uric acid, ammonium, chloride, supersaturation of calcium oxalate, or uric acid.

Table (4): Multivariable regression of the influence of PPI use on 24-h urine analytes in the studied group

	β	p value
Volume (mL)	–20.12	0.772
Calcium (mmol)	–0.85	**<0.001**
Oxalate (mmol)	–0.012	0.553
Citrate (mmol)	–0.47	**0.004**
pH	0.018	0.682
Uric acid (mmol)	–0.20	0.198
Sodium (mmol)	–12.1	**0.049**
Potassium (mmol)	–3.8	0.025
Magnesium (mmol)	–0.69	**<0.001**
Phosphorus (mmol)	–3.25	**0.001**
Ammonium (mmol)	0.91	0.639
Chloride (mmol)	–10.5	0.070
Sulfate (mmol)	–1.92	**0.001**
Creatinine (mmol)	–1.05	0.027
Creatinine (µmol/kg)	–0.0031	**0.007**
Supersaturation Ca-oxalate	–0.395	0.153
Supersaturation Ca-phosphate	–0.26	**<0.001**
Supersaturation uric acid	0.021	0.748

DISCUSSION

Regarding clinical and demographic characteristics, findings showed that age was slightly lower in the PPI-exposed group compared to the non-exposed group, with the difference reaching statistical significance (p = 0.042). In contrast, BMI and sex distribution did not differ significantly between groups. Regarding comorbidities, there were statistically insignificant variances in the occurrence of osteoporosis, gout, coronary artery illness, diarrhea, hyperlipidemia, hypertension, type 2 diabetes, or inflammatory bowel disease, indicating that baseline clinical conditions were well balanced. Regarding medications, there were statistically significant variances: cases in the PPI-exposed group had a lower prevalence of H2 receptor antagonist use but a higher prevalence of thiazide, loop diuretics, and gout medications than the non-exposed group (all p below 0.001).

In agreement with Patel et al. (11), who evaluated the influences of PPIs on urinary metabolites and urine pH in a study conducted on 301 patients. Their study reported that age was slightly lower in the PPI-exposed group than the non-exposed group, with the variance reaching statistical significance (p below 0.01). In contrast, BMI and sex distribution did not differ significantly between groups. Regarding comorbidities, there were statistically insignificant variances in the occurrence of osteoporosis, gout, coronary artery disease, diarrhea, hyperlipidemia, hypertension, type 2 diabetes, or inflammatory bowel disease, indicating that baseline clinical conditions were well balanced. Regarding medications, a statistically significant variance has been observed: cases in the PPI-exposed group had a lower prevalence of H2 receptor antagonist use but a higher prevalence of thiazide, loop diuretics, and gout medications than the non-exposed group (all p = 0.34).

As well, our study agreed with Sui et al. (1), who examined the correlation between PPI exposure and incident nephrolithiasis to determine its influence on 24-hour urine chemistry. Their research found that age was slightly reduced in the PPI-exposed group compared to the non-exposed group, with the difference reaching statistical significance (p = .004). In contrast, BMI and sex distribution didn't differ significantly among groups. Regarding comorbidities, there were statistically insignificant variances in the occurrence of osteoporosis, gout, coronary artery disease, diarrhea, hyperlipidemia, hypertension, type 2 diabetes, or inflammatory bowel disease, indicating that baseline clinical conditions were well balanced. Regarding medications, there were statistically significant variances: cases in the PPI-exposed group had a lower prevalence of H_2 receptor antagonist use but a higher prevalence of thiazide, loop diuretics, and gout medications compared to the non-exposed group (all p below 0.001).

Also, our study agreed with Hart et al. (12), who examined the correlation among PPI use and risk of incident CKD and AKI in a large population-based health maintenance organization (HMO) cohort, which included 93,335 patients. Their research found that age was slightly reduced in the PPI-exposed group compared to the non-exposed group, with the difference reaching statistical significance (p < 0.0001). In contrast, BMI and sex distribution didn't differ significantly among groups. Regarding comorbidities, there were statistically insignificant variances in the occurrence of osteoporosis, gout, coronary artery disease, diarrhea, hyperlipidemia, hypertension, type 2 diabetes, or inflammatory bowel disease, indicating that

baseline clinical conditions were well balanced. Regarding medications, there were statistically significant variances: cases in the PPI-exposed group had a lower prevalence of H2 receptor antagonist use but a higher prevalence of thiazide, loop diuretics, and gout medications than the non-exposed group (all p below 0.0001).

Regarding demographic and clinical characteristics of the research cohort with 24-h urine data, findings showed that, among comorbidities, hypertension was significantly more prevalent in the PPI-exposed group (24.6% versus 25.7%, p equal to 0.037). In addition, hyperlipidemia was also significantly higher among PPI users (15.2% vs. 17%, $p < 0.0001$). Other conditions, including inflammatory bowel disease/diarrhea, gout, type 2 diabetes, osteoporosis, coronary artery disease, and cerebrovascular accidents, did not differ significantly between groups. Regarding medications, most were used at similar rates across the two groups, except for chlorthalidone, which was less frequently prescribed in the PPI-exposed group (0.9% vs. 2.2%, p = 0.046). Analysis of stone composition (available in 148 patients) showed no significant differences between groups, with calcium oxalate (monohydrate and dihydrate) being the most common type, followed by hydroxyapatite and uric acid stones.

In agreement with Hart et al. (12), their study reported that hypertension was significantly more prevalent in the PPI-exposed group (67.5% versus 58.3%, p equal to 0.043). In addition, hyperlipidemia was also significantly higher among PPI users (44.3% vs. 34.6%, p = 0.010). Other conditions, including inflammatory bowel disease/diarrhea, gout, type 2 diabetes, osteoporosis, coronary artery disease, and cerebrovascular accidents, did not differ significantly between groups. Regarding medications, most were used at similar rates across the two groups, except for chlorthalidone, which was less frequently prescribed in the PPI-exposed group (1.58% vs. 1.26%, p equal to 0.023).

Also, our study agreed with Sui et al. (1). Their study found that hypertension was significantly more prevalent in the PPI-exposed group (67.1% vs. 59.1%, p = 0.043). In addition, hyperlipidemia was also significantly higher among PPI users (15.2% vs. 17%, p = 0.010). Other conditions, including inflammatory bowel disease/diarrhea, gout, type 2 diabetes, osteoporosis, coronary artery disease, and cerebrovascular accidents, did not differ significantly between groups. Regarding medications, most were used at similar rates across the two groups, except for chlorthalidone, which was less frequently prescribed in the PPI-exposed group (one percent versus six percent, p = 0.046). Analysis of stone composition (available in 148 patients) showed no significant variances between groups, with calcium oxalate (monohydrate and dihydrate) being the most common type, followed by hydroxyapatite and uric acid stones.

Regarding 24-hour urine analytes, those exposed to PPI and those who weren't showed that, Patients exposed to PPIs had significantly lower urinary calcium (5.0 vs. 5.7 mmol, $p < 0.001$), magnesium (3.6 vs. 4.2 mmol, p below 0.001), citrate (3.0 vs. 3.5 mmol, p equal to 0.031), phosphorus (29.5 vs. 33.2 mmol, p equal to 0.001), and sulfate (17.1 vs. 19.2 mmol, p = 0.004) compared to those not exposed. Moreover, supersaturation of calcium phosphate was also significantly reduced in the PPI group (1.1 vs. 1.5, p below 0.001). In contrast, insignificant variances have been observed among the two groups in urinary volume, oxalate, pH, uric acid, sodium, potassium, ammonium, chloride, creatinine (both mmol and µmol/kg), supersaturation of calcium oxalate, or uric acid.

In agreement with Sui et al. (1), their study reported that patients exposed to PPIs had significantly lower urinary calcium (5.0 vs. 5.6 mmol, p below 0.001), citrate (3.0 vs. 3.4 mmol, p = 0.029), magnesium (3.6 vs. 4.3 mmol, p below 0.001), phosphorus (29.5 vs. 33 mmol, p equal to 0.001), and sulfate (17.1 vs. 19 mmol, p = 0.004) compared to those not exposed. In contrast, insignificant variances have been observed among the two groups in urinary volume, oxalate, pH, uric acid, sodium, potassium, ammonium, chloride, creatinine (both mmol and µmol/kg), supersaturation of calcium oxalate, or uric acid.

Regarding multivariable regression of the influence of PPI use on 24-h urine analyses, findings showed that PPI use has independently been correlated with significant alterations in several urinary parameters. PPI use was significantly associated with reduced urinary calcium ($\beta = -0.85$, $p < 0.001$), citrate ($\beta = -0.47$, p = 0.004), sodium ($\beta = -12.1$, p = 0.049), potassium ($\beta = -3.8$, p = 0.025), magnesium ($\beta = -0.69$, p below 0.001), phosphorus ($\beta = -3.25$, p = 0.001), sulfate ($\beta = -1.92$, p = 0.001), creatinine ($\beta = -1.05$, p = 0.027), creatinine per body weight ($\beta = -0.0031$, p = 0.007), and supersaturation of calcium phosphate ($\beta = -0.26$, p below 0.001). Insignificant correlations have been found between PPI use and urinary volume, oxalate, pH, uric acid, ammonium, chloride, supersaturation of calcium oxalate, or uric acid.

In agreement with Sui et al. (1), their study found that PPI use was independently correlated with significant alterations in several urinary parameters. PPI use was significantly associated with reduced urinary calcium (beta = –0.94, p below 0.001), citrate (beta = –0.54, p = 0.004), sodium (beta = –10.90, p = 0.112), potassium (beta = –2.93, p = 0.144), magnesium (beta = –0.68, $p < 0.001$), phosphorus (beta = –0.09, p = 0.005), sulfate (beta = –1.87, p = 0.003), creatinine (beta = –1.05, p = 0.027), creatinine per body weight ($\beta = -0.14$, p = 0.461), and supersaturation of calcium phosphate ($\beta =$

0.003, p = 0.087). Insignificant correlations have been found between PPI use and urinary volume, oxalate, pH, uric acid, ammonium, chloride, supersaturation of calcium oxalate, or uric acid.

In contrast with Patel et al. (11), their study stated that PPI use was independently correlated with significant alterations in several urinary parameters. PPI use was significantly associated with reduced urinary calcium (p = 0.12), citrate (p = 0.05), sodium (p = 0.77), potassium (p = 0.91), magnesium (p = 0.18), phosphorus (p = 0.61), sulfate (p = 0.80), creatinine (p = 0.26), and supersaturation of calcium phosphate (p below 0.001). Insignificant correlations were found among PPI use and urinary volume, oxalate, pH, uric acid, ammonium, chloride, supersaturation of calcium oxalate, or uric acid.

CONCLUSIONN

PPI use was associated with younger age but similar BMI and sex distribution compared to non-users. Most comorbidities were balanced between groups, though hypertension and hyperlipidemia were slightly more prevalent in the PPI group. Medication use differed, with PPI users showing lower H2 blocker and chlorthalidone use but higher use of thiazides, loop diuretics, and gout medications. While stone composition did not differ significantly, 24-hour urine analysis revealed that PPI users had significantly reduced concentrations of urinary calcium, citrate, phosphorus, magnesium, sulfate, and supersaturation of calcium phosphate. These alterations remained significant after multivariable adjustment, suggesting that PPI use may impact urinary chemistry in ways that could influence kidney stone risk.

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